BEFORE THE PUBLIC UTILITIES COMMISSION
OF THE STATE OF SOUTH DAKOTA

IN THE MATTER OF THE APPLICATION OF CROWNED RIDGE, LLC FOR A FACILITIES PERMIT TO CONSTRUCTION 300 MEGAWATT WIND FACILITY

Docket No. EL19-003

REBUTTAL TESTIMONY AND EXHIBITS

OF DR. ROBERT MCCUNNEY

May 24, 2019

INTRODUCTION

Q. PLEASE STATE YOUR NAME AND BUSINESS ADDRESS.

A. My name is Dr. Robert McCunney. My business address is PO Box 29077, Charlestown MA 02129.

Q. BY WHOM ARE YOU EMPLOYED AND IN WHAT CAPACITY?

A. Brigham and Women's Hospital, Boston, MA; Staff physician in Pulmonary, Center for Chest Diseases; Role: I perform clinical evaluations and recommend treatment of occupational and environmental illnesses and serve in an educational capacity as part of Harvard Medical School faculty position. My curriculum vitae is attached as Exhibit RM-R-1.

Q. WHAT ARE YOUR RESPONSIBILITIES?

A. I was hired by Crowned Ridge Wind, LLC ("CRW") to submit rebuttal testimony and testify in this proceeding on the health and welfare issues and concerns raised in the testimony of Staff and proposed conditions of the Intervenors.

Q. PLEASE DESCRIBE YOUR BACKGROUND AND QUALIFICATIONS.

A. In summary, I am a licensed practicing physician. I completed training as a specialist in internal medicine and am also board certified in occupational and environmental medicine. My background in noise and health includes post graduate residency training in occupational medicine at Harvard, as an author of peer reviewed publications, such as three book chapters on occupational noise exposure; clinical experience in reviewing audiometric tests of workers exposed to noise and experience related to occupational

hearing conservation programs. With respect to wind turbines and health, I am the lead author of a critical review of the scientific literature on wind turbines and health sponsored by the Massachusetts Institute of Technology and published in the Journal of Occupational and Environmental Medicine in 2014; a co-author of a document entitled "Wind Turbines and Health"; (Colby et al, 2009) and lead author of a mathematical analysis of a proposed case definition related to health and living proximity to wind turbines. (Full citations are set forth in Exhibit RM-R-1). In addition, I have lectured to scientific, professional and lay audiences in numerous settings in the USA and Canada on wind turbines and health. I have also been admitted as an expert to testify in wind turbine hearings in numerous jurisdictions in the USA and Canada.

Q. HAS THIS TESTIMONY BEEN PREPARED BY YOU OR UNDER YOUR DIRECT SUPERVISION?

A. Yes.

Q. HAVE YOU PREVIOUSLY TESTIFIED BEFORE THE SOUTH DAKOTA PUBLIC UTILITIES COMMISSION?

A. No.

Q. PLEASE DESCRIBE THE PURPOSE OF YOUR REBUTTAL TESTIMONY.

A. The purpose of my testimony is to respond to Intervenors' proposed conditions as set forth in Staff witness Darren Kearney's Direct Testimony, Exhibit DK-8.

Sound Study

Intervenors' Proposed Conditions

Q. THE INTERVENORS' PROPOSED CONDITION 1 (KEARNEY EXHIBIT DK-8) WOULD REQUIRE THE FOLLOWING : THAT THERE BE A 2 MILE SETBACK FROM ALL NON-PARTICIPATING LANDOWNERS, BASED ON THE ASSUMPTION THAT THEY SHOULD NOT BE EXPOSED TO THE EFFECTS OF THE PROJECT. IS SUCH A CONDITION NEEDED TO ADDRESS A HEALTH OR WELFARE CONCERN FOR NON-PARTICIPANTS?

A. A two mile setback is not necessary for non-participating landowners. Moreover, the most appropriate scientific measure of potential health impacts from a noise generating source, including wind turbines, is to model or measure the noise levels outside of the home. One can then assess these noise levels in the context of scientific studies and regulations. I am unaware of any scientific peer reviewed study in the world's literature that indicates the necessity of a two mile setback. In fact, to the contrary, results of the largest epidemiology study that evaluated health issues associated with living in proximity to wind turbines noted no adverse health effects, including sleep and stress, among others, at noise levels up to 46 dB. (Michaud et al, 2016 -- Exhibit CO-11). As far as I am aware, no scientific studies indicate that wind turbine operations can generate sound to 46 dB or higher two miles from the source.

Q. THE INTERVENORS' PROPOSED CONDITION 2 (KEARNEY EXHIBIT DK-8) WOULD REQUIRE THAT THERE BE A 2 MILE SETBACK FROM THE WAVERLY SCHOOL TO PROTECT CHILDREN FROM DISTURBANCES

FROM THE PROJECT WHILE IN THEIR LEARNING ENVIRONMENT. IS SUCH A CONDITION NEEDED TO ADDRESS A HEALTH OR WELFARE CONCERN FOR THE STUDENTS AT WAVERLY?

A. No, it is not. As part of my work on this rebuttal, I reviewed the distances and noise levels from the nearest turbines to the school. The modeled sound level at Waverly School was 39 dBA and the closest turbine is 6,207 feet away. In light of these noise levels and the absence of any scientific support that such noise levels would interfere with the children's learning and behavior as well as health, this setback is safe for the school children.

Q. THE INTERVENORS' PROPOSE A NUMBER OF CONDITIONS (KEARNEY EXHIBIT DK-8) RELATED TO MEASUREMENT AND MONITORING OF INFRASOUND. ARE THESE CONDITIONS NEEDED TO ADDRESS A HEALTH OR WELFARE CONCERN?

A. Such conditions are not necessary. It is not necessary to differentiate low frequency sound or infrasound from broad noise level measurements conducted in the A scale. (See, Berger et al, 2015, which is Exhibit CO-6). Further, recent reviews conclude that there is no scientific evidence to support the hypothesis that wind turbine infrasound and low-frequency sound have unique adverse health effects that other sources of noise do not have. (McCunney et al, 2014 – Exhibit CO-8)

In summary, although wind turbines can generate infrasound and low-frequency sound, detectable levels of infrasound and low-frequency sound at residences are not at harmful levels based on studies near wind farms in the United States, the United Kingdom, the Netherlands, Denmark, and Australia. No studies demonstrate harmful effects to humans as a result of exposure to infrasound or low-frequency sound at the noise levels measured in the vicinity of wind turbines or in experimental studies involving noise levels several orders of magnitude higher than those noted in the vicinity of wind turbines.

Q. THE INTERVENORS' PROPOSED CONDITIONS 19, 20, AND 21 (KEARNEY EXHIBIT DK-8) WOULD LIMIT SOUND AT 40 DBA AT THE PROPERTY LINE OF A NON-PARTICIPATING PROPERTY OWNER. IS SUCH A CONDITION NEEDED TO ADDRESS A HEALTH OR WELFARE CONCERN?

A 40 dBA limit outside of a non-participant's home is not necessary to prevent adverse health effects from noise. The Health Canada study, the largest epidemiology study in the world, found no adverse health effects, including sleep, stress, and blood pressure, among others, at noise levels up to 46dB. (Michaud et al, 2016 – Exhibit CO-3).

Q. A NUMBER OF THE INTERVENORS' CONDITIONS (KEARNEY EXHIBIT DK-8) ARE PREMISED ON PEOPLE COMPLAINING ABOUT PHYSICAL CONDITIONS OR HEALTH ISSUES THEY BELIEVE ARE BROUGHT ON BY THE CRW WIND PROJECT. DO YOU HAVE AN OPINION ON WHETHER CONDITIONS SHOULD BE IMPOSED BECAUSE PEOPLE MAY ATTRIBUTE A PHYSICAL OR HEALTH ISSUE TO THE CRW WIND PROJECT?

A. I disagree that such a condition would be appropriate. There is no direct link between wind projects and adverse impact on health. To understand why, it is important to distinguish the process involved in diagnosing symptoms in contrast to determining the cause of symptoms. Below, I outline a well-accepted method to evaluate whether symptoms may be due to exposure to an occupational or environmental hazard and use sleep disturbances as an example.

In determining the cause of a disease or symptoms, the essential first step in the process is forming a diagnosis. It is necessary to establish a diagnosis based on accepted medical criteria. For example, the National Heart Lung and Blood Institute of the USA have proposed objective criteria for the diagnosis of asthma since the disorder is widely recognized to be "over diagnosed". (NHLBI, 2007 – Exhibit RM-R-2). In population surveys, the prevalence of self-reported asthma may be as high as 10%, whereas asthma diagnosed according to widely accepted criteria is about 5%. The point of this example is that any causality assessment needs to begin with an accurate diagnosis of the symptoms, based on well-accepted criteria. Once a diagnosis is made, one can then assess its potential cause. It is critical in this process, however, to conduct a routine procedure performed by physicians known as a differential diagnosis. In short, most symptoms have numerous causes. Headaches, for example, can occur due to a major illness like a brain tumour, as well as stress, and alcohol abuse, among others. A differential diagnosis is the process by which a physician considers these various explanations as the cause of a patient's symptoms through a medical history and appropriate diagnostic studies.

In my experience, patients' own self-assessments of causes of symptoms, although potentially helpful in the evaluation, can often be incorrect. For instance, if sleep disturbance is misattributed to wind turbines, serious treatable illnesses could be overlooked. In fact, recall bias, a well-recognized factor in epidemiological studies, can distort the accuracy of a person's recall. This phenomenon of recall bias has been confirmed in studies of breast cancer, Parkinson's disease and coronary artery disease (Rugbjerg et al, 2011 Zota et al, 2010 and Metcalfe et al, 2008, attached as Exhibit RM-R-3). In fact, Zota et al noted that their "results highlight the difficulty of distinguishing in retrospective self-report studies between valid associations and the influence of recall bias." Further, Metcalfe et al concluded, "Recall is likely to be influenced by present outcome" (Metcalfe et al, 2008). The point of this commentary is to demonstrate the limited utility of recall when evaluating self-reported symptoms. These comments are not intended to discredit or ignore a person's own assessment of causality but in contrast, to place in perspective the shortcomings and uncertainty in relying on recall to document events and timing thereof in the past.

What follows is a summary of the steps involved in forming a causality assessment. A critical component in assessing potential environmental illness is an evaluation of the exposure, which in this case is noise and its components, such as low frequency sound and infra sound, associated with wind turbine operations. A causality assessment where noise exposure may be a factor should also consist of a thorough review of noise measurements conducted in the vicinity of the individual's home along with a comparison of the symptoms, diagnosis and noise levels in light of what has been published in the peer reviewed scientific literature.

In addition, it is equally important to understand that in contrast to a placebo response in which favorable expectations can influence favorable outcomes in clinical practice and pharmaceutical research, a nocebo response refers to new or worsening symptoms produced by negative expectations that being treated with, or exposed to, an external stimuli will cause adverse health effects (Colloca et al, 2012; Hauser et al. 2012; Webster et al, 2016; Dodd et al; 2017 and Chavaria et al, 2017, attached as Exhibit RM-R-4)). A nocebo response is a well-recognized phenomenon in medical practice and can affect the integrity of pharmaceutical research and patient compliance with treatment, among others. For example, in clinical trials, expectations can influence the reporting of symptoms, such as side effects of a medication or a medical procedure involving informed consent (Ruan et al, 2016 – Exhibit RM-R-5), and adherence to treatment, (Tobert et al, 2016 – Exhibit RM-R-6) among others. This matter can have serious clinical and therapeutic impacts if symptoms that are misattributed to the medication lead to poor therapeutic responses, as a result of poor compliance-not taking the medications.

Thus, in trying to understand why some people are more apt to report annoyance in the context of wind turbines, it is important to consider how nocebo effects may contribute to self-reported symptoms. In a nocebo reaction, people expect untoward reactions and develop symptoms in ***anticipation*** of an event, in this case, wind turbine operations. (Dodd et al, 2017 – Exhibit RM-R-4). Indeed, a study analyzed Canadian newspaper coverage of wind turbines and found that media coverage might contribute to nocebo responses. (Deignan et al, 2013 – Exhibit RM-R-7)

Chapman, (et al, 2013 – Exhibit RM-R-8) also explored patterns of formal complaints (health and noise) made in relation to 51 wind farms in Australia from 1993 to 2012.

Very few complaints were formally lodged; only 129 individuals in Australia formally or publicly complained during the time period studied; the majority of wind farms had no complaint made against them. Complaints increased around 2009 when "wind turbine syndrome" was introduced. The authors concluded that nocebo effects likely play an important role in wind farm health complaints. People living near large wind farms filed the most complainants (16 out of 18; r=0.32) Furthermore, the strongest predictor of a formal complaint was the presence of an opposition group in the area of the wind farm. Opposition groups were present in 15 of the 18 sites that filled complaints while only 1 opposition group was present in the 33 areas that did not file a complaint (r=0.82). Accordingly, these studies show that while there may be a perceived health impact from wind farms, the health complaints do not correlate to actual adverse health impacts.

Q. **A NUMBER OF THE INTERVENORS' CONDITIONS (KEARNEY EXHIBIT DK-8) ARE PREMISED ON PEOPLE BEING ANNOYED BY THE WIND PROJECT. DO YOU HAVE AN OPINION ON WHETHER CONDITIONS SHOULD BE IMPOSED BECAUSE PEOPLE COULD BE ANNOYED BY THE CRW WIND PROJECT?**

A. My opinion is that such conditions are inappropriate. Annoyance is one of the most common assessments made in environmental noise studies, including those related to wind turbines. However, many factors can contribute to a person reporting "annoyance" in the context of living near wind turbines, including attitudes towards the turbines, visual aspects of the turbines, and whether a person derives economic benefit and noise from the turbines. (Pedersen et al, 2010 – Exhibit RB-R-9)

Annoyance is an outcome measure that has been used in environmental noise studies, primarily self-completed questionnaires. Noise levels, however, account for only a modest portion of self-reported annoyance in the context of wind turbines. (Knopper & Ollson, 2011 (Exhibit CO-2), McCunney et al, 2014 (Exhibit CO-8) and Michaud et al, 2016 Exhibit CO-11). Further, in the Health Canada study (Exhibit CO-3), annoyance was related to several reported measures of health and well-being, although these associations were statistically weak (R^2< 0.09%), independent of wind turbine noise ("WTN") levels, and not retained as a significant predictive variable in multiple regression models. A correlation coefficient (R^2) of 0.09 is extremely weak and indicates that the wind turbine noise category alone was a weak predictor of whether or not an individual was highly annoyed by WTN or not. The Health Canada study confirmed earlier research in which noise from wind turbines was noted to play a minor-if any- role in people reporting annoyance, in contrast to more significant factors, such as attitudes towards wind turbines, the impact of visual factors on the landscape and finally whether a person derives economic benefit from the turbines, a group that is completely absent of reported annoyance, despite residing in areas with the highest WTN levels. Therefore, sound pressure levels appear to play a limited-role in the experience of annoyance associated with wind turbines, a conclusion similar to that reached by Knopper & Ollson (2011) – Exhibit CO-2.

Further, self-reported annoyance is not coded as a specific diagnosis in the International Classification of Diseases. (ICD, 10th edition) The ICD is used worldwide for diagnostic, insurance and research purposes. Accordingly, I do not view that annoyance is sufficiently supported as a reason to adopt the Intervenors conditions or require a

reduction in the sound and shadow/flicker thresholds proposed by CRW – 30 hours of shadow/flicker a year and 50 dBA at a participant's residence, and 45 dBA at a non-participant's residence.

Q. GIVEN THE INTERVENORS CONDITIONS THAT ARE CRITICAL OF THE PROPOSED CRW SETBACKS FOR TURBINES FOR THE CRW PROJECT, ARE THE PROPOSED TURBINE PLACEMENT AND SETBACKS PROPOSED BY CRW SUFFICIENT TO NOT SUBSTANTIALLY IMPAIR THE HEALTH OR WELFARE OF NON-PARTICIPANTS?

A. Yes. The proposed turbine placement and setbacks proposed by CRW will not substantially impair the health or welfare of non-participants. I based the conclusion on a variety of factors, including the sound and shadow/flicker results developed by CRW witness Jay Haley; my professional experience as a physician addressing health risks from noise; and the scientific peer reviewed literature.

Q. DOES THIS CONCLUDE YOUR REBUTTAL TESTIMONY?

A. Yes, it does.

Harvard Medical School Curriculum Vitae

Date Prepared: March 22, 2019

Name: Robert J. McCunney, M.D., M.P.H., M.S.

Office Address: Brigham and Women's Hospital; Pulmonary Division, 75 Francis Street, Boston, MA 02115

Work Phone: 617-732-6770; 617-251-5152

Work Email: mccunney@mit.edu; rmccunney@bwh.harvard.edu

Place of Birth: Philadelphia, PA

Education

1971	BS	Chemical Engineering	Drexel University, Philadelphia, PA
1972	MS	Environmental Health	University of Minnesota, Minneapolis, MN
1976	MD	Medicine	Thomas Jefferson University Medical School, Philadelphia, PA
1981	MPH	Occupational Medicine	Harvard School of Public Health, Boston, MA

Postdoctoral Training

7/76 – 6/77	Intern	Internal Medicine	Northwestern University Medical Center, Chicago, IL
7/77 – 6/78	Resident	Internal Medicine	Northwestern University Medical Center
1/79- 6/79	Resident	Internal Medicine	Faulkner Hospital, Boston
1/80 – 6/81	Fellow	Occupational Medicine	Peter Bent Brigham Hospital, Boston, MA

Faculty Academic Appointments

1981 – 1983	Instructor	Medicine	Brown University School of Medicine, Providence, RI
1983 – 1993	Adjunct Assistant Professor	Public Health	Boston University School of Medicine, Boston, MA
1989 – 1995	Clinical Assistant Professor	Preventive Medicine	Medical College of Wisconsin, Milwaukee, WI
1996 – present	Lecturer	Medicine	Harvard Medical School, Boston, MA

Appointments at Hospitals/Affiliated Institutions

1983 – 1994	Director	Medicine Occupational Health	Boston University School of Medicine

1996 – 2010	Physician	Medicine Pulmonary Unit	Massachusetts General Hospital
2012-present	Physician	Medicine Pulmonary Division	Brigham and Women's Hospital, Boston
2001 – present	Research Scientist	Biological Engineering	Massachusetts Institute of Technology
2014-2016	Consulting Staff	Dana Farber Cancer Institute	Dana Farber Cancer Institute

Major Administrative Leadership Positions

Local

1981 – 1983	Medical Director, Occupational Health	Sturdy Memorial Hospital, Attleboro, MA
1983 – 1989	Medical Director, Occupational Health	Goddard Memorial Hospital, Stoughton, MA
1989 – 1994	Medical Director, Occupational Health Residency Program	Boston University Medical Center, Boston, MA
1994 – 2000	Director, Environmental Medicine	Massachusetts Institute of Technology

Regional

1982 – 1986	Board Member	New College of Occupational and Environmental Medicine, Boston, MA
1983 – 1985	President	New College of Occupational and Environmental Medicine

Committee Service

Local

2005-present	Member of Residency Advisory Committee for the occupational and environmental medicine training program	Harvard School of Public Health
1994 – 2000	Radiation Protection Committee	Massachusetts Institute of Technology
1994 – 2000	Pharmacy and Therapeutics Committee	Massachusetts Institute of Technology

Professional Societies: Past President of the American College of Occupational and Environmental Medicine. (1999-2000)

1981 -	American College of Occupational and Environmental Medicine	Member
	1983 – 1989	Member, House of Delegates
	1984 – 1986	President, New England Chapter
	1986 – 1994	Member, Publications Committee
	1985 – 1988	Chair, Publications Committee
	1988 – 1993	Member, Residency Director Section
	1989	Chair, Scientific Sessions of Annual Meeting

	1989 – 1993	Member, Government Affairs
	1994	Member, Ethical Practice Committee
	1993 – 1995	Co-Chair, Occupational Medicine Self-Assessment Program
	1996 – 1999	President Elect, 1st VP, 2nd VP
	1999 – 2000	**President**
1981 -	New England College of Occupational and Environmental Medicine	Member
1986 -	Medichem	Member
	1989 – 1993	Secretary
	1995	Chair, Annual Congress
	1999	Honorary Life Membership
1981 – 1991	American Public Health Association	Member
1983 -	American College of Preventive Medicine	Member
	1983 -	Fellow
1983 – 2000	American Medical Association	Member
2008 -	American Thoracic Society	Member
2010 -	American College of Chest Physicians	Member

Grant Review Activities

1996 - 1997	Medical Research Committee	US Department of Energy Member

Editorial Activities (Ad hoc peer reviewer for the journals noted below)

Journal of Occupational and Environmental Medicine
Environmental Research
Journal of the Acoustical Society of America
Epidemiology
Chest
American Journal of Industrial Medicine
International Archives of Occupational and Environmental Medicine
Inhalation Toxicology

Other Editorial Roles

1995	Co-Editor	International Archives of Occupational and Environmental Medicine (special issue: 1996; 6: 349-530)
1996	Co-Editor	Inhalation Toxicology (special issue: 1996; 8 (suppl): 29-39)
2000	Guest Editor	Journal of Occupational and Environmental Medicine (special issue: 2001; 43: 1-55)
2006	Guest Editor	Journal of Occupational and Environmental Medicine (special issue: 2006; 48: 1217-1338)

Honors and Prizes

1971	Phi Beta Epsilon	National Honor Society

1972	Tau Beta Pi	National Engineering Honor Society
1995	Presidential Award	American College of Occupational and Environmental Medicine (ACOEM)
1996	Drexel 100	Drexel University
2000	National Leadership	Central States Occupational Medical Association
2001	Harriet Hardy Leadership Award	New England College of Occupational and Environmental Medicine
2004	Health Achievement Award	ACOEM
2006	Presidential Award	ACOEM

Report of Funded and Unfunded Projects

Funding Information

Past

2000 – 2009 Cabot Corporation foundation for unrestricted work in occupational and environmental medicine
PI
The goal of this gift was to publish and teach in occupational medicine.

Current

International Carbon Black Association
Mortality study of USA carbon black workers
Particle exposure and risk of heart disease: an international meta analysis of German, British and American cohorts

American Wind Energy Association
Health effects of wind turbine operations: a critical review of literature

US Power Gen
Cluster evaluation of apparent cancer elevation among employees: a preliminary assessment
Parkinson's Disease and Environmental Risk Factors

Current Unfunded Projects

2007 - Occupational causes of kidney cancer
PI
The purpose of this project is to evaluate occupational causes of kidney cancer secondary to recognition of a "cluster" of kidney cancer at a manufacturing plant

2007 - Health implications of occupational and environmental mold exposure.
The purpose of this project is to develop a Continuing Medical Education (CME) course for physicians with other MGH colleagues.

Report of Local Teaching and Training

Teaching of Students in Courses

2000 -	Occupational Noise Exposure	Harvard School of Public Health
	Graduate students	1 hr/yr

2007 -	Public Health and Epidemiology Graduate students	Massachusetts Institute of Technology 4 hr/wk x 6 wks

Clinical Supervisory and Training Responsibilities

1994 – 1999	Preceptor, Occupational Medicine, Boston University Medical Center	6-8 hr/wk x 6 wks
1994 – 1999	Preceptor, Occupational Medicine, Harvard School of Public Health	6-8 hr/wk x 6 wks
2000 - 2010	Preceptor, Allergy and Immunology, Massachusetts General Hospital	

Formally Supervised Trainees

1991 – 1993 Cheryl Barbanel, M.D., M.P.H., M.B.A., Prof Occupational Medicine, University of Connecticut; Chair, Residency section, ACOEM
I served as residency director. Trainee published a paper on chest film opacities in workers and noise exposure.

1992 – 1994 Joseph Chern, M.D., M.P.H., Director of Occupational Neurology at University of Taipei, Taiwan
I served as residency director. Trainee published a book chapter on health effects of solvents.

1990 – 1992 Alain Couturier, M.D., M.P.H., Editor: "Occupational Infectious Disease" *deceased*
I served as residency director. Trainee published a paper on medical surveillance.

1988 – 1990 Ross Myerson, M.D., M.P.H., Chair ACOEM Annual Meeting Consultant, 2004
I served as residency director. Trainee published a book chapter on Health effects of cleaning agents and sterilants

1988 – 1990 John Doyle, M.D., M.P.H., Director, Occupational Health, Taunton Hospital
I served as residency director. Trainee published a paper on occupational illness in the arts.

1989 – 1991 Robert Godefroi, M.D., M.P.H., Director, Occupational Health Center, Manchester, NH
I served as residency director. Trainee published a paper on drug screening practices in industry

1991 – 1993 Khalid Kabrum, M.D., M.P.H., Medical Director, Aluminum Company of Bahrain
I served as residency director. Trainee published a book chapter on Health effects of cleaning agents and sterilants

Formal Teaching of Peers (e.g., CME and other continuing education courses)

1987	Managing Occupational Risks in the High Technology Industries Annual Meeting of American Occupational Medical Association	½ day postgraduate seminar Philadelphia, PA
1987	Introduction to Occupational Medicine Annual Meeting of American Occupational Medical Association	½ day postgraduate seminar Philadelphia, PA
1987	Indoor Air Quality and Health Annual Meeting of American Occupational Medical Association	½ day postgraduate seminar Philadelphia, PA
1988	Establishing Health Services for Small Businesses Annual Meeting of American Occupational Medical Association	4 hr postgraduate seminar New Orleans, LA

1988	Occupational Medicine: An Introduction American College of Occupational Medicine	1 presentation San Antonio, TX
1990	Introduction to Occupational Medicine American College of Occupational Medicine	4 hr seminar Pittsburgh, PA
1991	Introduction to Occupational Medicine American College of Occupational Medicine	1 presentation San Francisco, CA
1991	Ethical Issues in Occupational Medicine American College of Occupational Medicine	seminar San Francisco, CA
1991	Publishing in Occupational Medicine American College of Occupational Medicine	1 presentation San Francisco, CA
1994	Introduction to Occupational Medicine American College of Occupational Medicine	Seminar Dallas, TX

Local Invited Presentations

Sponsored Lectures are marked *

1984 Setting Policy for Reproductive Hazards/Invited Talk
Harvard School of Public Health, Boston, MA

1985 Medical Surveillance: Screening for Occupational Illness/ Invited Talk
Harvard School of Public Health and the New England Occupational Medical Association, Boston, MA

1986 Cholesterol and Heart Disease: A Role for Fitness Programs?/Invited Talk
Harvard School of Public Health, Boston, MA

1987 Indoor Pollution. A Look at an Active Problem/Invited Talk
Harvard School of Public Health, Boston, MA

1989 The American Government and Occupational Medicine: New Developments/Invited Talk
New England College of Occupational Medicine, Harvard School of Public Health, Boston, MA

1994 Setting Policy for Reproductive Hazards/Invited Talk
New England Occupational Medical Association and the Harvard School of Public Health, Boston, MA

1998 Occupational Health at a Major Research Institution/Grand Rounds
Harvard School of Public Health, Boston, MA

2001 Noise and Hearing Loss/Grand Rounds
Harvard School of Public Health, Boston, MA

2007 Screening for Lung Cancer/Grand Rounds
Harvard School of Public Health, Boston, MA

2007 Screening for Lung Cancer/Grand Rounds
Pulmonary Unit, Massachusetts General Hospital

2014 Wind Turbines and Health effects; New England College of Occ/Env Med regional meeting

2014 Pulmonary Grand Rounds at BWH: Lung cancer screening

2017 Update on Occupational Medicine: Invited presentation for BWH Pulmonary Medicine Update; Boston, MA

2018 Epidemiology studies of titanium dioxide workers; presented at annual meeting of TDMA; Boston, MA

2019 Pulmonary Grand Rounds at BWH: Pitfalls in interpreting PFTs in the Occupational Setting

2019 Pulmonary Grand Rounds at BWH Uranium Lung Presented to US Indian Health Service

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

Sponsored Lectures are marked *

Regional

1981 A Clinical Approach to the Patient with Exposure to Asbestos/Invited Talk
Medicine/Surgery Sturdy Memorial Hospital, Attleboro, MA

1982 The Health Hazards in the Jewelry Industry/Invited Talk
25th Annual Safety Institute of Rhode Island, University of Rhode Island, Providence, RI

1982 The Health Hazard Evaluation/Invited Talk
Occupational Medicine, Brown University School of Medicine, Providence, RI

1982 Medical Concerns of the Jewelry Industry/Invited Talk
Medicine/Surgery Sturdy Memorial Hospital, Attleboro, MA

1982 Stress and Its Ramifications/Invited Talk
Medicine/Surgery Sturdy Memorial Hospital, Attleboro, MA

1982 The Role of an Occupational Health Service./Invited Talk
Board of Trustees, Goddard Memorial Hospital, Brockton, MA

1983 A Clinical Approach to the Patient Exposed to Asbestos/Invited Talk
Roger Williams Hospital, Brown University School of Medicine affiliate, Providence, RI

1983 Should Your Company Have an Employee Assistance Program?/Invited Talk
Attleboro Chamber of Commerce Personnel Directors monthly meeting, Attleboro, MA

1983 Asbestosis: A Survey of the Health Effects/Medical Grand Rounds
Department of Medicine, Pawtucket Memorial Hospital, Pawtucket, RI

1983 Occupational Medicine in the People's Republic of China/Invited Talk
South Shore Community Hospital, Weymouth, MA

1983 Cost Containment Through Occupational Health/Invited Talk
South Shore Community Hospital, Weymouth, MA

1984 Asbestos, Current Controversies/Invited Talk
Massachusetts American Lung Association, Boston, MA

1984 Does Exercise Reduce the Risk of Heart Disease?/Invited Talk
Goddard Memorial Hospital and Massasoit College, Brockton, MA

1984 Occupational Medicine Today/Invited Talk
Boston University School of Public Health, Boston, MA

1984 Role of Occupational Medicine Today/Medical Grand Rounds
Braintree Hospital, Braintree, MA

1985 Stress, How To Recognize and Control its Effects/Invited Talk
S.E. Mass Chapter of American Society of Inventory Control Specialist, Stoughton, MA

1985 Indoor Air Pollution/Invited Talk
Down East American Industrial Hygiene Association, Portland, ME

1986 Indoor Air Pollution: An Update/Invited Talk
University of Massachusetts Medical Center, Worcester, MA

1986 Clinical Applications of Epidemiology/ 2 3hr Invited Talks
Occupational Nursing Program, Boston, MA

1986 Drug Screening in Industry: An Overview/Invited Talk
New England Occupational Medical Association, Boston, MA

1986 Staying Healthy in Retirement/Invited Talk

Billerica, MA

1986 Indoor Air Pollution: An Update/Invited Talk
University of Massachusetts Medical Center, Worcester, MA.

1986 Clinical Applications of Epidemiology/2 3 hr Invited Talks
Occupational Nursing Program, Simmons College, Boston, MA

1986 Drug Screening in Industry: An Overview/Invited Talk
New England Occupational Medical Association, Boston, MA

1986 AIDS: What are the Occupational Risks?/Invited Talk
Goddard Memorial Hospital, Stoughton, MA

1986 Silicosis: A Disease of the Past or Current Concern/Invited Talk
Goddard Memorial Hospital, Stoughton, MA

1987 Controlling the Health Risks of Asbestos/Invited Talk
Asbestos Information Center of Tufts University Medical Center, Boston, MA

1987 Health Care Hazardous Waste Sites/Invited Talk
Environmental Protection Agency, Boston, MA

1987 Recognition and Treatment of Occupational Skin disease/Invited Talk
Associated Industries of Massachusetts, Boston, MA

1987 Drug Screening. Scientific and Ethical Issues/Invited Talk
New England Chapter of the American Industrial Hygiene Association, Boston, MA

1988 Occupational Medicine: An Introduction/Invited Talk
American College of Occupational Medicine,

1989 When to Suspect the Building as a Cause of Your Patient's Symptoms/Grand Rounds
University Hospital, Boston, MA

1989 Preventing Back Injuries at Work/Invited Talk
Massachusetts Safety Council, Boston, MA

1990 Occupational Health in Cost Containment/Invited Talk
Health Care Financial Management Association, Boston, MA

1990 Emergency Triage Systems for Work Related Injuries/Invited Talk
American College of Rehabilitation Medicine, Boston, MA

1990 Occupational Health and Cost Containment/Invited Talk
Health Care Financial Management Association, Boston, MA

1990 Recognizing Hand Disorders Due to Vibrating Tools/Invited Talk
New England College of Occupational Medicine, Boston, MA

1991 Occupational Health Challenges in Primary Care/Grand Rounds
Carney Hospital, Boston, MA

1991 Occupational Cancer in the 1990s/Invited Talk
National Workers Compensation and Occupational Medicine Seminar, Hyannis, MA

1993 Indoor Air pollution: A Recurring Problem in Occupational Medicine Practice; the Case Report: Recognition of Occupational Disease/Invited Talk
Workers Compensation and Occupational Medicine, Hyannis, MA

1998 Genetics in the Courtroom/Invited Talk
Einstein Institute for Science, Health and the Courts, Orleans, MA

2000 Work Implications of Sedating Antihistamines/Invited to Testify
Boston City Council, Boston, MA

2001 Risk Assessment: Current Issues/Invited Talk
MIT, Cambridge, MA

2006 Future of Occupational and Environmental Medicine/Invited Talk
Cape Cod Conference SEAK, Hyannis, MA

2010 Health Implications of Wind Turbines/Invited Talk
Rutland Medical Center, Rutland, VT

National

1981 The Need for a National Commission in Boxing/Scientific Panel
American Medical Association, Chicago, IL

1982 Health Hazards in the Garment Industry/Invited Talk
International Ladies Garment Workers Union. New York, New York.

1983 A Hospital Develops an Occupational Health Service/Invited Talk
American Occupational Medical Association, Washington, DC

1983 The Role of Fitness in Preventing Heart Disease/Invited Talk
Amateur Athletic Union Annual Meeting, Washington, DC

1983 Diverse Manifestations of Trichloroethylene/Invited Invited Talk
American Academy of Occupational Medicine Annual Meeting, New Orleans, LA

1985 The Effect of Fitness on High Density Lipoproteins and Heart Disease/Panel Moderator
American Occupational Medical Association, Kansas City, MO.

1985 Indoor Air Quality: A Review With Recommended Protocol to Evaluate Complaints/Invited Invited Talk
New York State Medical Society, New York, New York

1986 Staying Healthy in Retirement/Invited Talk
Cabot Corp, Champagne, IL, Indianapolis, MO, Atlanta, GA, Ville Platte, LA, Amarillo and Midland, TX

1986 Environmental Medicine: Setting Policy at Hazardous Waste Sites/Invited Talk
New York State Medical Society, New York, New York

1987 Managing Workers Compensation Costs Through Fitness Programs/Invited Talk
Food Marketing Institute, New Orleans, LA

1988 Pulmonary Alveolar Proteinosis and Cement Dust: A Case Report/Invited Talk
The 7th International conference on Pneumoconiosis, Pittsburgh, PA

1988 Occupational Medicine: An Introduction/Invited Talk
American College of Occupational Medicine, San Antonio, TX

1989 Establishing Health Services for Small Businesses/Seminar Leader
New York Academy of Sciences, Boston, MA

1989 Hand-Arm Vibration Syndrome: Means of Control/Invited Talk
National Safety Council annual meeting, Chicago, IL

1989 Providing High Quality Occupational Medical Services/Invited Invited Talk
Annual Symposium on Delivery of Occupational Health Services, Washington, DC

1990 Current Developments in Occupational Medicine/Invited Invited Talk
Centers for Disease Control, Atlanta, GA

1990 Ethical Issues in Occupational Medicine/Invited Talk
American College of Occupational Medicine, Houston, TX

1992 A Hospital Based Occupational Medicine Residency Program/Moderator and Presenter
American College of Occupational and Environmental Medicine, Washington, DC

1992 The Academic Industry Interface in Occupational Medicine/Invited Talk
American College of Occupational and Environmental Medicine State of the Art Conference, New York City, New York

1993 Advanced Occupational Medicine/Invited Talk
American College of Preventive Medicine, Chicago, IL

1994 The Use of Biomarkers in Clinical Practice/Invited Talk
US Department of Energy, Santa Fe, NM

1995 Health effects of ionizing radiation exposure/Invited Talk
US Department of Energy, Tampa, FL

1995 Preserving Confidentiality in Occupational Medical Practice; The Physician's Role in Emergency Response; The Occupational Medical Self Assessment Program/3 Invited

Talks
American College of Occupational and Environmental Medicine Annual Meeting, Las Vegas, NV

1996 New Directions in Occupational Medical Practice/Invited Talk
American College of Occupational and Environmental Medicine, San Antonio, TX

1996 The International Agency for Research on Cancer (IARC) decision on Evaluating the Carcinogenicity of Carbon Black/Invited Talk
Annual Joint Labor/Management Health and Safety Conference on United Rubber and Steel Workers, Cleveland, Ohio.

1997 The New EPA Standard on Ambient Particulates and Ozone: Implications for the Occupational Physician
American College of Occupational and Environmental Medicine (ACOEM), Nashville, TN

1998 Health and Productivity: A Role for Occupational Health? /Invited Talk
4th Annual Employers Summit, Chicago, IL

1998 The Legacy of the Cold War; Challenges to the Occupational Health Professional/Invited Talk
Annual Department of Energy meeting in Occupational Medicine, Washington, DC

1998 The Flu, A new Medication and Occupational Health; A Look At The Links/Seminar Leader
Naples, Florida (Glaxo Wellcome)

1998 The Future of Occupational and Environmental Medicine/Invited Talk
Annual meeting of the Maryland, Virginia, and Pennsylvania components of the American College of Occupational and Environmental Medicine (ACOEM), Williamsburg, VA.

2000 Health and Productivity/Invited Talk
Annual meeting of American Journal of Health Promotion on Health and Productivity, Colorado Springs, CO

2000 Occupational Health and Productivity/Invited Talk
Central States Occupational Medical Association annual meeting, Chicago, IL

2000 On behalf of ACOEM, gave oral testimony to OSHA on the proposed ergonomics standard/Invited to Testify (April and May)
Washington, DC

2000 Latex Allergy/Invited Talk
Annual meeting of the Michigan College of Occupational Medicine, Ann Arbor, MI

2000 Clinical application of recent research in occupational medicine/Invited Talk
State of the art meeting, American College of Occupational and Environmental Medicine, Nashville, TN

2001 Health and Productivity: A Role for Occupational Health/Invited Talk
Annual meeting of the Health Enhancement Research Organization, (HERO),Washington, DC

2001 The Human Genome Project: Implications on Occupational Medical Practice/Invited Talk
Annual meeting at the American College of Occupational and Environmental Medicine, San Francisco, CA

2001 Health and Productivity Research/Invited Talk
Annual meeting of the Institute of Productivity Management, Orlando, FL

2003 Future of Occupational Medicine/Invited Talk
MIT and the American College of Occupational and Environmental Medicine, San Juan, Puerto Rico

2006 Should we screen for occupational lung cancer with low dose CT?/Invited Talk
Annual meeting of the American College of Occupational and Environmental Medicine,

Atlanta Georgia

2009 Are there health effects of wind turbine operations?/Invited Talk
Annual meeting of American Wind Energy Association
Orlando, FL

2010 thru 2015 Harvard School of Public Health; Graduate students in Public Health; "Health effects of occupational and environmental noise exposure

2012 thru 2015 Evaluating Occupational Lung Disease Part 1; Harvard Medical School Pulmonary Fellows Conference

2013 Evaluating Occupational Lung Disease Part 2; Harvard Medical School Pulmonary Fellows Conference

2014 "Evaluating health effects from exposure to hazardous materials." and "How to critically interpret the scientific literature." State Supreme Court Justices' Conference, sponsored by a grant from the US Department of Justice. Chapel Hill, NC

2014 Grand Rounds: Pulmonary Division. "Radiation risks in lung cancer screening programs." Brigham and Women's Hospital, Boston

2015 Grand Rounds: Harvard School of Public Health. Hypersensitivity Pneumonitis, Boston
Grand Rounds: Pulmonary Division; Brigham and Women's (BWH) Hospital, Boston.

2016 Hypersensitivity Pneumonitis
Occupational Lung Disease: Lecture to Pulmonary Fellows of BWH

2017 Amorphous Silica; A review of a cross sectional study at German plants; Grand Rounds: Pulmonary Division; Brigham and Women's (BWH) Hospital, Boston.
Lung Tumors in Lab Rats: Implications for humans. Grand Rounds: Pulmonary Division; Brigham and Women's (BWH) Hospital, Boston. ;

2018 Epidemiology studies of Titanium Dioxide workers. Annual meeting of titanium dioxide manufacturers. Boston, MA

International Presentations

1982 Sino-American study tour in occupational medicine to hospitals and factories/Invited Participant
People's Republic of China (Peking, Shanghai, Hangzhou and Canton)

1985 Diverse Manifestations of Trichloroethylene/Invited Talk
Kyoto University Hospital, Kyoto, Japan

1985 Fitness and Heart Disease/Seminar Leader
Mahidol University Hospital, Bangkok, Thailand

1985 Indoor Air Pollution: A Summary of an Investigation in an Office Setting/Invited Talk
Society of Occupational Setting, Society of Occupational Medicine, Hong Kong, United Kingdom

1986 Diverse Manifestations of Trichloroethylene/Invited Speaker
Annual meeting of Medichem, Ludwigshafen, West Germany

1987 Annual Health/Safety Meeting of Cabot Corporation/Seminar Leader
Toronto, Canada

1987 Annual Health/Safety Meeting of Cabot Corporation/Educational Leader
Kenya, East Africa

1988 A Cross-cultural Epidemiology Study/Invited Talk
16th Annual Meeting of Medichem, Helsinki, Finland

1989	Occupational Health in the Chemical Industry/Invited Co-Chair International Commission on Occupational Health triennial meeting, Montreal, Canada
1994	Medical Response to Environmental Emergencies/Invited Talk Annual meeting of Medichem, Melbourne, Australia
1995	Health Effects of Carbon Black/Invited Talk Presented in German to the German Automobile Association, Frankfurt, Germany
1997	Biomarkers and the Human Genome: A look at the Clinical Issues/Invited Talk US Department of Energy International Meeting, Charleston, SC.
1997	Particles and Lung Disease: A Look at the Clinical Issues/Invited Talk Health and Safety Executive of the United Kingdom, University of Leicester, Leicester, England
1999	Occupational Health and Productivity/Invited Talk Annual Latin American Conference on Occupational Medicine, Dorado, Puerto Rico
1999	Occupational Health and Productivity/Invited Talk Annual meeting of Medichem, Vienna, Austria
2000	Chemical Sensitivity and Idiopathic Environmental Intolerance/Invited Talk Ottawa, Canada
2001	The Role of the Human Genome in Occupational Medical Practice/Invited Talk Pulmonary Division, University of Bochum, Bochum, Germany
2002	Review of Epidemiology Studies and the Exposure Limit for Carbon Black./Invited Talk Health and Safety Executive Meeting (UK), London, England
2008	Occupational Health Research in the Carbon Black Industry/Invited Talk Carbon Black World Conference, Guilin, China
2015	Health Effects of Carbon Black; Institute of Occupational Medicine; Edinburgh, Scotland
2015	Health Effects of living near wind turbines: An update; annual meeting of the Canadian Wind Energy Association (Toronto, Canada)
2016	Lung tumors in Lab Rats: Implications for Human Risk Assessment; Titanium Dioxide International Meeting; Paris France
2016	Setting Occupational Exposure Limits; German MAK Commission; Berlin, Germany
2017	Role of epidemiology in evaluating Health Risks; presentation to Risk Assessment Committee of European Chemical Agency; Helsinki, Finland

Report of Clinical Activities and Innovations

Current Licensure and Certification

1983 American Board of Preventive Medicine – Occupational and Environmental Medicine

Practice Activities

1996 – 2010	Ambulatory Practice	MGH	1-2 days per week
2010-current	Ambulatory Practice	Brigham and Women's Hospital, Boston	1-2 days per week

Clinical Innovations

Implemented three hospital-based occupational health programs at:

- Sturdy Memorial Hospital, Attleboro, MA
- Goddard Memorial Hospital, Stoughton, MA

- University Hospital of Boston University Medical Center, Boston, MA

Report of Scholarship

Publications

Peer reviewed publications in print or other media

Research Investigations

1. **McCunney RJ**. "Acute and Chronic Brain Injuries in Boxers; Causes and Prevention". Physician and Sports Medicine, 1984;12:52-64.
2. **McCunney RJ**. "A Hospital-Based Occupational Health Service". Journal of Occupational Medicine, 1984;26:375-80.
3. **McCunney RJ**. "Are Stress Management Programs Cost Effective?" Journal of Occupational Medicine, 1984;26:410.
4. **McCunney RJ**. "Confidentiality of Medical Records." Journal of Occupational Medicine. 1984;26:790-91.
5. **McCunney RJ**. "Are Exercise EKG's Needed Prior to a Fitness Program?" Occupational Health and Safety. 1984, 23-24.
6. **McCunney RJ**. "Corporate Medical Programs". (letter) Harvard Business Review, Nov/Dec, 1984; 16-18
7. **McCunney RJ**. "Video display Terminals: What are the Health Risks?" Boston Business Journal, December 24, 1984; 7-9
8. **McCunney RJ**. Acid Rain. (book review) Journal of the American Medical Association, 1985;253: 2291-92.
9. **McCunney RJ**. "The Role of Fitness in Preventing Health Disease". Cardiovascular Reviews and Reports 1985;6:776-78.
10. **McCunney RJ**. "Health Effects of Work at Wastewater Treatment Plants: A review of the literature with guidelines for medical surveillance". American Journal of Industrial Medicine 1986;9:271-79.
11. **McCunney RJ**. Indoor Air Quality. (book review) Journal of the American Medical Association 1986;255:1261-62**.**
12. **McCunney RJ**. "The Patient with Asbestos Exposure". Journal of Family Practice 1986;22:73-78.
13. **McCunney RJ**. "Distilling Questions on Drug Testing". Boston Business Journal, November 17, 1986.; 2-3
14. **McCunney RJ**. "Physical Activity and HDL Levels". Physician and Sports Medicine 1987;15:67-74.
15. **McCunney RJ**. "The Role of Building Construction and Ventilation in Indoor Air Pollution: A Review of a Recurring Problem". New York State Journal of Medicine 1987;87:203-09.
16. **McCunney RJ**. "Effective Drug Screening Programs Should Be Applied Judiciously". Occupational Health and Safety: News Digest, Feature Story, May 1987, 9-10.
17. **McCunney RJ**. "The Role of Fitness in Controlling Workers Compensation Costs". Proceedings of the Annual Food Marketing Institute, 1987, Washington DC.

18. **McCunney RJ**. Cluster Mystery: Epidemic and The Children of Woburn, Mass. (book review). JAMA 1987; 258: 969-71.

19. **McCunney RJ**, Doyle JR, Russo PK. "Occupational Illness in the Arts" American Family Physician. 1987;36:145-53.

20. Godefroi R, **McCunney RJ**. "Drug Screening Practices in Small Businesses: A Survey". Journal of Occupational Medicine 1988;30:300-02.

21. **McCunney RJ**. "Diverse Manifestations of Trichloroethylene", British Journal of Industrial Medicine, 1988; 45:122-26.

22. **McCunney RJ**, Cashins R. "Environmental Tobacco Smoke: A Problem Revisited". Journal of Occupational Medicine 1988;30:540-42.

23. **McCunney RJ**. "Occupational Health: What the Future Holds". Industry, December 1988.

24. **McCunney RJ**, Walter E. "Occupational Medicine Services" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988;3-20.

25. Godefroi R, **McCunney, RJ**, "The Role of Regulatory Agencies" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988; 36-46.

26. Jacknow D, **McCunney RJ**, Jofe M. "Musculoskeletal Disorders" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988;106-29.

27. **McCunney RJ**. "Cardiovascular Disorders" in Handbook of Occupational Medicine (**McCunney 00RJ**, ed.), Little Brown, Boston 1988; 143-58.

28. **McCunney RJ**. "Medical Surveillance" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988; 297-308.

29. McCauley M, **McCunney RJ**, Scofield M. "Health Promotion" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988; 335-49.

30. Melius J, Wallingford RM, **McCunney RJ**. "The Health Hazard Evaluation: Investigating Occupational Health Problems in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988;362-73.

31. Frumkin H, **McCunney RJ**. "Health Effects of Common Substances" in Handbook of Occupational Medicine (**McCunney RJ**, ed.), Little Brown, Boston 1988; 423-39.

32. **McCunney RJ**, Godefroi R. "Pulmonary Alveolar Proteinosis: A Case Report." Journal of Occupational Medicine 1989;31:233-237.

33. **McCunney RJ**. "Drug Screening: Technical Complications of a Complex Social Issue." American Journal of Industrial Medicine; 1989;15:589-600.

34. **McCunney RJ** "Providing High Quality Occupational Medical Services." J Amb Health Care Marketing 1990; 4: 9-18.

35. **McCunney RJ**. Greaves, W, "Addressing the Shortage of Occupational Physicians," Journal of Occupational Medicine 1990:1247-48.

36. Ducatman A, **McCunney RJ**. "What is Environmental Medicine?" Journal of Occupational Medicine 1990;32:1130-32.

37. **McCunney RJ**, Cikins W. "The Effect of Federal Health Policy on Occupational Medicine. Polish Journal of Occupational Medicine, 1990;3:241-56.

38. **McCunney RJ**, Brandt-Rauf P. "Ethical Issues in the Private Practice of Occupational Medicine.

Journal of Occupational Medicine 1991;33:80-82.

39. **McCunney RJ**. "Occupational Noise Exposure," in Rom WM. (Ed) Environmental and Occupational Medicine, Little Brown, Boston, 1992, 2nd edition.
40. **McCunney, RJ**, "Recognizing Hand Disorders caused by Vibrating Tools." Journal of Musculoskeletal Medicine, 1992;9(3): 91-110.
41. **McCunney RJ**, Jetzer T. "Hand Vibration Isolation: A Study of Various Materials" Journal Applied Occupational Hygiene 1992;7:8-12.
42. **McCunney RJ**, Harzbecker J. "The Role of Occupational Medicine in General Medical Practice: A Look at the Journals." Journal of Occupational Medicine, 1992; 34: 279-286.
43. **McCunney RJ**, Boswell R, Harzbecker J. "Environmental Health in the Journals." Environmental Research 1992;59:114-24.
44. **McCunney RJ**, Couturier A. "Where do Occupational Medicine Residency Programs Belong in the Institution?" Journal of Occupational Medicine 1993; 35: 889-890.
45. **McCunney RJ**, Barbanel C. "Auditing Workers Compensation Claims." Occupational Health and Safety 1993;63:75-84.
46. **McCunney RJ**. "The Academic Occupational Physician as Consultant: A Ten Year Perspective." Journal of Occupational and Environmental Medicine 1994;36:438-42.
47. Barbanel C, **McCunney RJ**. "Environmental Surveillance of Respiratory Disorders: The Hazardous Waste Site as an Example" Environmental Respiratory Disease," Cordasco E., Demeter SL, Zene C. (eds.) Yearbook Medical publishers, Chicago 1995; pp 479-504.
48. **McCunney RJ**. "Challenges and Opportunities in Occupational Medicine". Journal of the American Osteopathic Medical Assoc. 1994;95(2):107-14.
49. **McCunney RJ**, Schmitz, S. Cardiovascular disorders, in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;3-19.
50. **McCunney RJ**. Boswell R. Musculoskeletal Disorders, in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;166-86.
51. **McCunney RJ**. Schmitz S. Cardiovascular Disorders, in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;199-213.
52. Harber P, **McCunney RJ**, Monosson I. Medical Surveillance, in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;358-75.
53. McLellan R, **McCunney RJ**. Indoor Air Pollution, in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;633-50.
54. McCauley M, **McCunney RJ**. Health Promotion in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;465-78.
55. **McCunney RJ**, Barbanel C, Frumkin H. Health Effects of Common Substances in A Practical Approach to Occupational and Environmental Medicine, (**McCunney RJ**, ed.) Little Brown, Boston, 1994;709-33.
56. Boswell R, **McCunney RJ**. Bronchiolitis Obliterans from Exposure to Incinerator Fly Ash. Journal of Occupational and Environmental Medicine 1995;37(7):850-55.
57. Shields P, Chase K, **McCunney RJ**. "Confined Space Hazards: Combined Exposures to Styrene,

Fiberglass, and Silica". Journal of Occupational and Environmental Medicine 1995;37(2):185-88.

58. **McCunney RJ**. "Clinical Applications of Biomarkers in Occupational Medicine" in Biomarkers and Occupational Health: Progress and Perspectives. (Mendelsohn, ML, Peeters, JP, Normandy MJ, eds.) Joseph Henry Press, Washington, DC, 1995;148-60.

59. **McCunney RJ**. "From the Lab Bench to the Work Place: Implications of Toxicology Studies on Occupational Medical Practice." Inhalation Toxicology 1996;8(suppl):29-39.

60. **McCunney RJ**. "Preserving Confidentially in Occupational Medical Practice". Am Fam Phys 1996;53(5):1751-56.

61. **McCunney RJ**. "Emergency Response to Environmental Toxic Incidents: The Role of the Occupational Physician." Occupational Medicine 1996;46(6):397-401.

62. Meyer JD, Islam S, Ducatman A, **McCunney RJ**. "Prevalence of Small Lung Opacities in Populations Unexposed to Dusts: A Literature Analysis." Chest 1997;111:404-410.

63. **McCunney RJ,** Burton W, Anstadt G, Gregg D. "The Competitive Advantage of a Healthy Work Force: Opportunities for Occupational Medicine (editorial). J Occup Env Med, 1997;39:611-13.

64. Couturier A, **McCunney RJ**. "Physicians' Role in Emergency Response. Occ Health and Safety Feb 1997:46-52.

65. **McCunney RJ**, Leopold R. "Protecting Employee Privacy" in Genetic Secrets: Privacy, Confidentiality and New Genetic Technology (M. Rothstein (ed), Yale University Press, 1998; 47-54

66. Couturier A, **McCunney RJ**. "Biological Indicators of Chemical Dosage and Burden" in Handbook of Occupational Safety and Health, 2nd Edition. (DiBerardinis, L, ed.) John Wiley & Sons, Boston, MA, 1998;373-413.

67. **McCunney RJ**. "How to Ensure and Maintain Quality in a Medical Surveillance Program" in Handbook of Occupational Safety and Health, 2nd Edition. (DiBerardinis, L, ed.) John Wiley & Sons, Boston, MA, 1998;415-28.

68. **McCunney RJ**, Meyer J. "Occupational Exposure to Noise" in Environmental and Occupational Medicine (ed. Rom Wm, Little Brown, Boston), 1998; 1121-1132.

69. **McCunney RJ**. "Use of Biomarkers in Occupational Medicine." in Biomarkers; medical and Workplace Applications(Mendelsohn, Mohr, Peeters, eds) John Henry Press, Washington, D.C. 1998;377-86.

70. **McCunney RJ**, "Particles and Lung Disease. A Clinical Perspective." Published in IEH Report on Approaches to Predicting Toxicity from Occupational Exposure to Dusts (Report R11), Leicester UK. Institute for Environment and Health ISBN 1 899110 20 8

71. **McCunney RJ**, Masse F, Galanek M. "The Use of Bioassay Data to Estimate Radiation Dose Resulting From Intake of Radioactive Phosphorous (P-32)." J Occup Env Med October 1999;41(10):878-83.

72. Bunn WB, **McCunney RJ**. "Corporate Occupational Health Services in the United States: Services Provided Internally." Encyclopedia of Occupational Health and Safety, 4th Edition. Int. Labor Organization, Geneva, 1998;16.35-16.38.

73. **McCunney RJ**. "EPA Ruling on Environmental Particulates and the Occupational Physician: An Editorial." J Occup Env Med; September 1998;40(9):768-71.

74. **McCunney RJ**. "Key Gaps in Knowledge About the Role of the PNOC/R in the Etiology of

Chronic Airways Disease: Recommended Future Research." Appl Occup Environ Hyg 1998;13(8): 582-85.

75. **McCunney RJ**. "Hodgkin's Disease: Work and the Environment: A Review." J Occup Env Med January 1999;41(1):36-46.
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77. **McCunney RJ**. Health and Productivity: A Role for Occupational Health. J Occup Environ Med 2001; 43:30-35
78. **McCunney RJ**. Opportunities and challenges in leading a professional organization: a president's perspective J Occup Environ Med 2001;43(7)596-600
79. **McCunney RJ**. Medical Surveillance: The role of the Family Physician. Am Family Physician 2001;63:2339-40
80. **McCunney, RJ**. and Okawroski, L. "Occupational cancer" (in Shields, PG (editor). Methods for Cancer Risk Assessment, Taylor & Francis, Boca Raton, FL, 2005; 331-352
81. **McCunney, RJ**. Genetic Testing: Ethical implications in the workplace. Occupational Medicine: State of the Art Reviews. 2002;17:(4)665-72
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87. **McCunney RJ**. Particles and Cancer (editorial) J Occup Environ Med 2006;1217-18
88. **McCunney RJ**, Meyer J. "Occupational Exposure to Noise" in Environmental and Occupational Medicine; 4th edition (Rom WN, ed.), Lippincott Williams and Wilkins, Baltimore), 2007. pp 1295-38
89. Morfeld P, **McCunney RJ**. Carbon black and lung cancer-testing a new exposure metric in a German cohort Am J Ind Med 2007; 50: 565-567
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91. **McCunney RJ,** Morfeld P, Payne, S What component of coal causes coal workers pneumoconiosis J Occup Environ Med 2009; 51: 467-471
92. Valberg PA, Bruch J, **McCunney, RJ** Are rat results from intra-tracheal installation a reliable basis for predicting cancer risk? Reg Tox Pharm 2009; 54: 72-83
93. Morfeld P, **McCunney RJ** Carbon black and lung cancer – testing a novel exposure metric by

multi-model inference Am J Ind Med 2009; 52: 890-899

94. Morfeld P, **McCunney RJ** Bayesian bias adjustments of the lung cancer SMR in a cohort of German carbon black production workers J Occup Med Toxicol. 2010 Aug 11; 5:23.

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97. **McCunney, RJ,** Valberg P, Muranko H, Morfeld, P "Carbon Black" in Patty's Industrial Hygiene and Toxicology 2012; pp 429-453

98. Levy L, Chaudhuri, I Morfeld P, **McCunney R**. Comments on Induction of Inflammasome dependent Pyroptosis by Carbon Black Nanoparticles. J Biol Chem 2011: 286, NO. 38, 17

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101. **McCunney RJ** and Li J. Risks of radiation-associated cancer in lung cancer screening programs compared to nuclear industry workers and atomic bomb survivors. Chest 2014; 145 (3): 618-624

102. Morfeld P … **McCunney RJ** Cross sectional study on respiratory morbidity in workers after exposure to synthetic amorphous silica at five German production plants. Exposure assessment and exposure estimates. J Occup Environ Med 2014; 56: (1): 72-78

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104. **McCunney RJ,** Mundt K, Colby WD, Dobie R, Kaliski K and Blais M. Wind Turbines and Health: A critical Review of the Scientific Literature. J Occup Environ Med 2014; November, e1-e24

105. **McCunney, RJ** (Invited editorial) "Should Radiation Dose from CT Scans be a Factor in Patient Care? Yes." Chest 2015; 147: (4): 872-874

106. **McCunney RJ.** Rebuttal From Dr McCunney. Chest. 2015 Apr 1; 147(4): 877-8

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2. **McCunney RJ**, editor, A Practical Approach to Occupational and Environmental Medicine, third edition, Lippincott, Williams, Wilcox, Baltimore, 2003 *This 60-chapter text includes contributions from 90 authors. It has been peer reviewed by the American College of Occupational and Environmental Medicine (ACOEM). I have donated the royalties to the ACOEM*

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Proceedings of Meetings or Other Non-Peer Reviewed Research Publications

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2. Mauderly J, **McCunney RJ**. co-editors, Particle Overload in the Rat Lung and Lung Cancer: Implications for Human Risk Assessment. Inhalation Toxicology (Special Supplement, Vol 8) Taylor & Francis 1996. 298 pp, ISBN 1-56032-543-7.
3. **McCunney RJ**, Brandt-Rauf P. co editors, The Chemical Industry as a Global Citizen: Balancing Risks and Benefits. Proceedings of 1995 Medichem (International Commission on Occupational Health) Congress held at MIT. Published in Int Arch Occup Environ Health; Vol 68, No. 6, 1996
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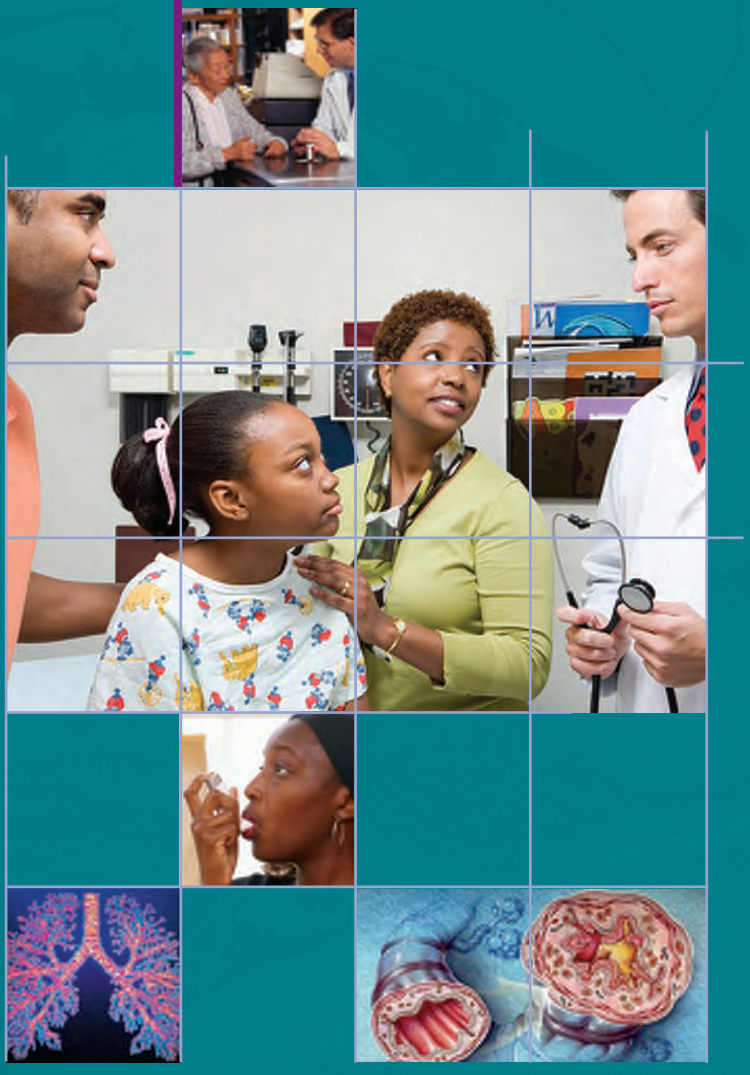
SUMMARY REPORT 2007

National Asthma Education and Prevention Program Expert Panel Report 3

Guidelines for the Diagnosis and Management of Asthma



U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

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Preface

The Expert Panel Report 3 (EPR—3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma was developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

Using the 1997 EPR—2 guidelines and the 2002 update on selected topics as the framework, the expert panel organized the literature review and updated recommendations for managing asthma long term and for managing exacerbations around four essential components of asthma care, namely: assessment and monitoring, patient education, control of factors contributing to asthma severity, and pharmacologic treatment. Subtopics were developed for each of these four broad categories.

The EPR—3 Full Report and the EPR—3 Summary Report 2007 have been developed under the excellent leadership of Dr. William Busse, Panel Chair. The NHLBI is grateful for the tremendous dedication of time and outstanding work of all the members of the expert panel, and for the advice from an expert consultant group in developing this report. Sincere appreciation is also extended to the NAEPP CC and the Guidelines Implementation Panel as well as other stakeholder groups (professional societies, voluntary health, government, consumer/patient advocacy organizations, and industry) for their invaluable comments during the public review period that helped to enhance the scientific credibility and practical utility of this document.

Ultimately, the broad change in clinical practice depends on the influence of local primary care physicians and other health professionals who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. The NHLBI and its partners will forge new initiatives based on these guidelines to stimulate adoption of the recommendations at all levels, but particularly with primary care clinicians at the community level. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for every asthma patient with asthma

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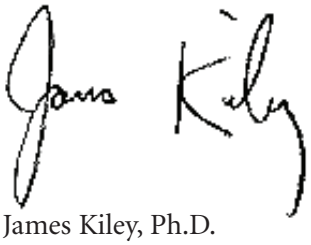

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Introduction

More than 22 million Americans have asthma, and it is one of the most common chronic diseases of childhood, affecting an estimated 6 million children. The burden of asthma affects the patients, their families, and society in terms of lost work and school, lessened quality of life, and avoidable emergency department (ED) visits, hospitalizations, and deaths. Improved scientific understanding of asthma has led to significant improvements in asthma care, and the National Asthma Education and Prevention Program (NAEPP) has been dedicated to translating these research findings into clinical practice through publication and dissemination of clinical practice guidelines. The first NAEPP guidelines were published in 1991, and updates were made in 1997, 2002, and now with the current report. Important gains have been made in reducing morbidity and mortality rates due to asthma; however, challenges remain. The NAEPP hopes that the "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007" (EPR—3: Full Report 2007) will support the efforts of those who already incorporate best practices and will help enlist even greater numbers of primary care clinicians, asthma specialists, health care systems and providers, and communities to join together in making quality asthma care available to all people who have asthma. The goal, simply stated, is to help people with asthma control their asthma so that they can be active all day and sleep well at night.

This EPR—3: Summary Report 2007 presents the key recommendations from the EPR—3: Full Report 2007 (See www.nhlbi.nih.gov/guidelines/asthma/asthgdln. htm). Detailed recommendations, the levels of scientific evidence upon which they are based, citations from the published scientific literature, discussion of the Expert Panel's rationale for the recommendations, and description of methods used to develop the report are included in that resource document. Because EPR—3: Full Report 2007 is an update of previous NAEPP guidelines, highlights of major changes in the update are presented below, and figure 1 presents a summary of recommended key clinical activities.

HIGHLIGHTS OF MAJOR CHANGES IN EPR—3: FULL REPORT 2007

The following are highlights of major changes. Many recommendations were updated or expanded based on new evidence. See EPR—3: Full Report 2007 for key differences at the beginning of each section and for a full discussion.

New focus on monitoring asthma control as the goal for asthma therapy and distinguishing between classifying asthma severity and monitoring asthma control.

- Severity: the intrinsic intensity of the disease process. Assess asthma severity to initiate therapy.
- Control: the degree to which the manifestations of asthma are minimized by therapeutic interventions and the goals of therapy are met. Assess and monitor asthma control to adjust therapy.

New focus on impairment and risk as the two key domains of severity and control, and multiple measures for assessment. The domains represent different manifestations of asthma, they may not correlate with each other, and they may respond differentially to treatment.

- Impairment: frequency and intensity of symptoms and functional limitations the patient is experiencing currently or has recently experienced.
- Risk: the likelihood of either asthma exacerbations, progressive decline in lung function (or, for children, lung growth), or risk of adverse effects from medication.

Modifications in the stepwise approach to managing asthma long term.

- Treatment recommendations are presented for three age groups (0–4 years of age, 5–11 years of age, and youths ≥12 years of age and adults). The course of the disease may change over time; the relevance of different measures of impairment or risk and the potential short- and long-term impact of medications may be age related; and varied levels of scientific evidence are available for these three age groups.
- The stepwise approach expands to six steps to simplify the actions within each step. Previous guidelines had several progressive actions within different steps; these are now separated into different steps.
- Medications have been repositioned within the six steps of care.
  - — Inhaled corticosteroids (ICSs) continue as preferred long-term control therapy for all ages.
  - — Combination of long-acting beta$_2$-agonist (LABA) and ICS is presented as an equally preferred option, with increasing the dose of ICS in step 3 care, in patients 5 years of age or older. This approach balances the established beneficial effects of combination therapy in older children and adults with the increased risk for severe exacerbations, although uncommon, associated with daily use of LABA.
  - — Omalizumab is recommended for consideration for youths ≥12 years of age who have allergies or for adults who require step 5 or 6 care (severe asthma). Clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

New emphasis on multifaceted approaches to patient education and to the control of environmental factors or comorbid conditions that affect asthma.

- Patient education for a partnership is encouraged in expanded settings.
  - — Patient education should occur at all points of care: clinic settings (offering separate self-management programs as well as integrating education into every patient visit), Emergency Departments (EDs) and hospitals, pharmacies, schools and other community settings, and patients' homes.
  - — Provider education should encourage clinician and health care systems support of the partnership (e.g., through interactive continuing medical education, communication skills training, clinical pathways, and information system supports for clinical decisionmaking.
- Environmental control includes several strategies:
  - — Multifaceted approaches to reduce exposures are necessary; single interventions are generally ineffective.
  - — Consideration of subcutaneous immunotherapy for patients who have allergies at steps 2–4 of care (mild or moderate persistent asthma) when there is a clear relationship between symptoms and exposure to an allergen to which the patient is sensitive. Clinicians should be prepared to treat anaphylaxis that may occur.
  - — Potential benefits to asthma control by treating comorbid conditions that affect asthma.

Modifications to treatment strategies for managing asthma exacerbations. These changes:

- Simplify the classification of severity of exacerbations. For the urgent or emergency care setting: <40 percent predicted forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) indicates severe exacerbation and potential benefit from use of adjunctive therapies; ≥70 percent predicted FEV_1 or PEF is a goal for discharge from the emergency care setting.
- Encourage development of prehospital protocols for emergency medical services to allow administration of albuterol, oxygen, and, with medical oversight, anticholinergics and oral systemic corticosteroids.
- Modify recommendations on medications:
  - — Add levalbuterol.
  - — Add magnesium sulfate or heliox for severe exacerbations unresponsive to initial treatments.
  - — Emphasize use of oral corticosteroids. Doubling the dose of ICS for home management is not effective.
  - — Emphasize that anticholinergics are used in emergency care, not hospital care.
  - — Add consideration of initiating ICS at discharge.

Figure 1. SUMMARY OF RECOMMENDED KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA

Clinical Issue	Key Clinical Activities	Action Steps
DIAGNOSIS		
	Establish asthma diagnosis.	Use medical history and physical examination to determine that symptoms of recurrent episodes of airflow obstruction are present. Use spirometry in all patients ≥5 years of age to determine that airway obstruction is at least partially reversible. Consider alternative causes of airway obstruction.
MANAGING ASTHMA LONG TERM	**Goal of asthma therapy is asthma control:** ■ **Reduce impairment (prevent chronic symptoms, require infrequent use of short-acting beta$_2$-agonist (SABA), maintain (near) normal lung function and normal activity levels).** ■ **Reduce risk (prevent exacerbations, minimize need for emergency care or hospitalization, prevent loss of lung function, or for children, prevent reduced lung growth, have minimal or no adverse effects of therapy).**	
Four Components of Care		
Assessment and Monitoring	Assess asthma severity to initiate therapy.	Use severity classification chart, assessing both domains of impairment and risk, to determine initial treatment.
	Assess asthma control to monitor and adjust therapy.	Use asthma control chart, assessing both domains of impairment and risk, to determine if therapy should be maintained or adjusted (step up if necessary, step down if possible). Use multiple measures of impairment and risk: different measures assess different manifestations of asthma; they may not correlate with each other; and they may respond differently to therapy. Obtain lung function measures by spirometry at least every 1–2 years, more frequently for not-well-controlled asthma.
	Schedule followup care.	Asthma is highly variable over time, and periodic monitoring is essential. In general, consider scheduling patients at 2- to 6-week intervals while gaining control; at 1–6 month intervals, depending on step of care required or duration of control, to monitor if sufficient control is maintained; at 3-month intervals if a step down in therapy is anticipated. Assess asthma control, medication technique, written asthma action plan, patient adherence and concerns at every visit.
Education	Provide self-management education.	Teach and reinforce: ■ Self-monitoring to assess level of asthma control and signs of worsening asthma (either symptom or peak flow monitoring shows similar benefits for most patients). Peak flow monitoring may be particularly helpful for patients who have difficulty perceiving symptoms, a history of severe exacerbations, or moderate or severe asthma. ■ Using written asthma action plan (review differences between long-term control and quick-relief medication). ■ Taking medication correctly (inhaler technique and use of devices). ■ Avoiding environmental factors that worsen asthma. Tailor education to literacy level of patient. Appreciate the potential role of a patient's cultural beliefs and practices in asthma management.

Figure 1. SUMMARY OF RECOMMENDED KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA (continued)

Clinical Issue	Key Clinical Activities	Action Steps
Four Components of Care (continued)		
Education (continued	Develop a written asthma action plan in partnership with patient. Integrate education into all points of care where health professionals interact with patients.	Agree on treatment goals and address patient concerns. Provide instructions for (1) daily management (long-term control medication, if appropriate, and environmental control measures) and (2) managing worsening asthma (how to adjust medication, and know when to seek medical care). Involve all members of the health care team in providing/reinforcing education, including physicians, nurses, pharmacists, respiratory therapists, and asthma educators. Encourage education at all points of care: clinics (offering separate self-management education programs as well as incorporating education into every patient visit), Emergency Departments and hospitals, pharmacies, schools and other community settings, and patients' homes. Use a variety of educational strategies and methods.
Control Environmental Factors and Comorbid conditions	Recommend measures to control exposures to allergens and pollutants or irritants that make and asthma worse. Treat comorbid conditions.	Determine exposures, history of symptoms in presence of exposures, and sensitivities (In patients who have persistent asthma, use skin or in vitro testing to assess sensitivity to perennial indoor allergens.). Advise patients on ways to reduce exposure to those allergens and pollutants, or irritants to which the patient is sensitive. Multifaceted approaches are beneficial; single steps alone are generally ineffective. Advise all patients and pregnant women to avoid exposure to tobacco smoke. Consider allergen immunotherapy, by specifically trained personnel, for patients who have persistent asthma and when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive. Consider especially: allergic bronchopulmonary aspergillosis; gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis and sinusitis, and stress or depression. Recognition and treatment of these conditions may improve asthma control. Consider inactivated influenza vaccine for all patients over 6 months of age.
Medications	Select medication and delivery devices to meet patient's needs and circumstances.	Use stepwise approach (See below.) to identify appropriate treatment options. Inhaled corticosteroids (ICSs) are the most effective long-term control therapy. When choosing among treatment options, consider domain of relevance to the patient (impairment, risk, or both), patient's history of response to the medication, and patient's willingness and ability to use the medication.

Figure 1. SUMMARY OF RECOMMENDED KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA (continued)

Clinical Issue	Key Clinical Activities	Action Steps
Stepwise Approach		
General Principles for All Age Groups	Incorporate four components of care.	Include medications, patient education, environmental control measures, and management of comorbidities at each step. Monitor asthma control regularly (See above, assessment and monitoring.).
	Initiate therapy based on asthma severity.	For patients not taking long-term control therapy, select treatment step based on severity (See figures on stepwise approach for different age groups.). Patients who have persistent asthma require daily long-term control medication.
	Adjust therapy based on asthma control.	Once therapy is initiated, monitor the level of asthma control and adjust therapy accordingly: step up if necessary and step down if possible to identify the minimum amount of medication required to maintain asthma control. Refer to an asthma specialist for consultation or comanagment if there are difficulties achieving or maintaining control; step 4 care or higher is required (step 3 care or higher for children 0–4 years of age); immunotherapy or omalizumab is considered; or additional testing is indicated; or if the patient required 2 bursts of oral systemic corticosticosteroids in the past year or a hospitalization.
Ages 0–4 Years	Consider daily long-term control therapy.	Young children may be at high risk for severe exacerbations, yet have low levels of impairment between exacerbations. Initiate daily long-term control therapy for: ■ Children who had ≥4 episodes of wheezing the past year that lasted >1 day and affected sleep AND who have a positive asthma risk profile, either (1) one of the following: parental history of asthma, physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens OR (2) two of the following: sensitization to foods, ≥4 percent blood eosinophilia, or wheezing apart from colds. Consider initiating daily long-term control therapy for: ■ Children who consistently require SABA treatment >2 days per week for >4 weeks. ■ Children who have two exacerbations requiring oral systemic corticosteroids within 6 months.
	Monitor response closely, and adjust treatment.	If no clear and positive response occurs within 4–6 weeks and the patient's/caregiver's medication technique and adherence are satisfactory, stop the treatment and consider alternative therapies or diagnoses. If clear benefit is sustained for at least 3 months, consider step down to evaluate the continued need for daily therapy. Children this age have high rates of spontaneous remission of symptoms.

Figure 1. SUMMARY OF RECOMMENDED KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA (continued)

Clinical Issue	Key Clinical Activities	Action Steps
Stepwise Approach (continued)		
Ages 5–11 Years	Involve child in developing a written asthma action plan.	Address child's concerns, preferences, and school schedule in selecting treatments. Encourage students to take a copy of written asthma action plan to school/ afterschool activities.
	Promote physical activity.	Treat exercise-induced bronchospasm (EIB) (See below.) Step up daily therapy if the child has poor endurance or symptoms during normal play activities.
	Monitor for disease progression and loss of lung growth.	Treatment will not alter underlying progression of the disease, but a step up in therapy may be required to maintain asthma control.
Ages 12 and Older	Involve youths in developing written asthma action plan.	Address youth's concerns, preferences, and school schedule in selecting treatment. Encourage students to take a copy of written asthma action plan to school/afterschool activities.
	Promote physical activity.	Treat EIB. Step up daily therapy if the child has poor endurance or symptoms during normal daily activities.
	Assess possible benefit of treatment in older patients.	Establish reversibility with a short course of oral systemic corticosteroids.
	Adjust medications to address coexisting medical conditions common among older patients.	Consider, for example: calcium and vitamin D supplements for patients who take ICS and have risk factors for osteoporosis; increased sensitivity to side effects of bronchodilators with increasing age; increased drug interactions with theophylline; medications for arthritis (NSAIDs), hypertension, or glaucoma (beta blockers) may exacerbate asthma.
Exercise-Induced Bronchospasm (EIB)	Prevent EIB	Treatment strategies to prevent EIB include: ■ Long-term control therapy. ■ Pretreatment before exercise with SABA, leukotriene receptor antagonists (LTRAs), cromolyn or nedocromil; frequent or chronic use of long acting beta$_2$-agonist (LABA) for pretreatment is discouraged, as it may disguise poorly controlled persistent asthma. ■ Warmup period or a mask or scarf over the mouth for cold-induced EIB.
Pregnancy	Maintain asthma control through pregnancy.	Monitor asthma control during all prenatal visits; asthma worsens in one-third of women during pregnancy and improves in one-third; medications should be adjusted accordingly. It is safer to be treated with asthma medications than to have poorly controlled asthma. Maintaining lung function is important to ensure oxygen supply to the fetus. Albuterol is the preferred SABA. ICS is the preferred long-term control medication (Budesonide is preferred because more data are available on this medication during pregnancy.).
Surgery	Reduce risks for complications during and after surgery.	Assess asthma control prior to surgery. If lung function is not well controlled, provide medications to improve lung function. A short course of oral systemic corticosteroids may be necessary. For patients receiving oral systemic corticosteroids during 6 months prior to surgery, and for selected patients on high dose ICS, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period, and reduce the dose rapidly within 24 hours after surgery.

Figure 1. SUMMARY OF RECOMMENDED KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA (continued)

Clinical Issue	Key Clinical Activities	Action Steps
Managing Exacerbations		
Home Management	Incorporate four components of care. Develop a written asthma action plan.	Include assessment and monitoring, patient education, environmental control, and medications. Instruct patients how to: ■ Recognize early signs, symptoms, peak expiratory flow (PEF) measures that indicate worsening asthma. ■ Adjust medications (increase SABA and, in some cases, add oral systemic corticosteroids) and remove or withdraw from environmental factors contributing to the exacerbation. ■ Monitor response and seek medical care if there is serious deterioration or lack of response to treatment.
Management in the Urgent or Emergency Care Setting	Assess severity. Treat to relieve hypoxemia and airflow obstruction; reduce airway inflammation. Monitor response. Discharge with medication and patient education	Treatment strategies include: ■ Assessing initial severity by lung function measures (for ages ≥5 years) and symptom and functional assessment ■ Supplemental oxygen ■ Repetitive or continuous SABA ■ Oral systemic corticosteroids ■ Monitoring response with serial assessment of lung function measures, pulse oximetry, and symptoms ■ Considering adjunctive treatments magnesium sulfate or heliox in severe exacerbations (e.g., forced expiratory volume in 1 second (FEV_1) or PEF <40 percent predicted) unresponsive to initial treatment ■ Providing at discharge: — Medications: SABA, oral systemic corticosteroids; consider initiating ICS — Referral to followup care — An emergency department asthma discharge plan — Review of inhaler technique and, whenever possible, environmental control measures

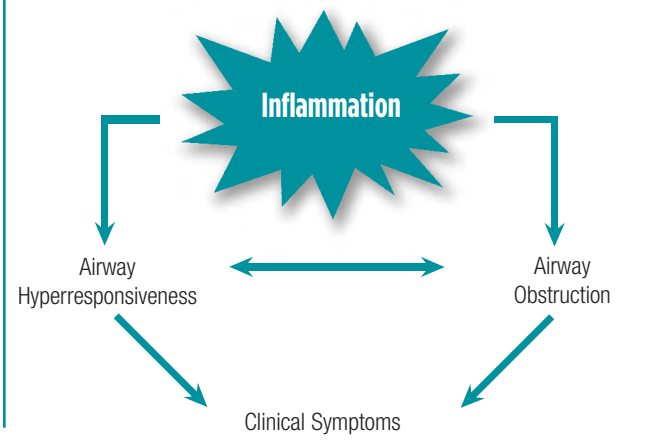
Asthma Definition and Implications for Treatment

Definition and Pathophysiology

Asthma is a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features determines the clinical manifestations and severity of asthma (See figure 2, "The Interplay and Interaction Between Airway Inflammation and the Clinical Symptoms and Pathophysiology of Asthma.") and the response to treatment. The working definition of asthma is as follows:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Figure 2. THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA



Airflow limitation is caused by a variety of changes in the airway, all in influenced by airway inflamation:

- Bronchoconstriction—bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli, including allergens or irritants.
- Airway hyperresponsiveness—an exaggerated bronchoconstrictor response to stimuli.
- Airway edema—as the disease becomes more persistent and inflammation becomes more progressive, edema, mucus hypersecretion, and formation of inspissated mucus plugs further limit airflow.

Remodeling of airways may occur. Reversibility of airflow limitation may be incomplete in some patients. Persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.

Recent studies provide insights on different phenotypes of asthma that exist. Different manifestations of asthma may have specific and varying patterns of inflammation (e.g., varying intensity, cellular mediator pattern, and therapeutic response). Further studies will determine if different treatment approaches benefit the different patterns of inflammation.

Causes of Asthma

The development of asthma appears to involve the interplay between host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system. A definitive cause of the inflammatory process leading to asthma has not yet been established.

- Innate immunity. Numerous factors may affect the balance between Th1-type and Th2- type cytokine responses in early life and increase the likelihood that the immune response will downregulate the Th1 immune response that fights infection and instead will be dominated by Th2 cells, leading to the expression of allergic diseases and asthma. This is known as the "hygiene hypothesis," which postulates that certain infections early in life, exposure to other children (e.g., presence of older siblings and early enrollment in childcare, which have greater likelihood of exposure to respiratory infection), less frequent use of antibiotics, and "country living" is associated with a Th1 response and lower incidence of asthma, whereas the absence of these factors is associated with a persistent Th2 response and higher rates of asthma. Interventions to prevent the onset of this process (e.g., with probiotics) are under study, but no recommendations can yet be made.
- Genetics. Asthma has an inheritable component, but the genetics involved remain complex. As the linkage of genetic factors to different asthma phenotypes becomes clearer, treatment approaches may become directed to specific patient phenotypes and genotypes.
- Environmental factors.
  - Two major factors are the most important in the development, persistence, and possibly the severity of asthma: airborne allergens (particularly sensitization and exposure to house-dust mite and Alternaria) and viral respiratory infections (including respiratory syncytial virus [RSV] and rhinovirus).
  - Other environmental factors are under study: tobacco smoke (exposure in utero is associated with an increased risk of wheezing, but it is not certain this is linked to subsequent development of asthma), air pollution (ozone and particular matter) and diet (obesity or low intake of antioxidants and omega-3 fatty acids). The association of these factors with the onset of asthma has not been clearly defined. A number of clinical trials have investigated dietary and environmental manipulations, but these trials have not been sufficiently long term or conclusive to permit recommendations.

Implications for Treatment

Knowledge of the importance of inflammation to the central features of asthma continues to expand and underscores inflammation as a primary target of treatment. Studies indicate that current therapeutic approaches are effective in controlling symptoms, reducing airflow limitation, and preventing exacerbations, but currently available treatments do not appear to prevent the progression of asthma in children. As various phenotypes of asthma are defined and inflammatory and genetic factors become more apparent, new therapeutic approaches may be developed that will allow even greater specificity to tailor treatment to the individual patient's needs and circumstances.

Diagnosis of Asthma

To establish a diagnosis of asthma, the clinician should determine that symptoms of recurrent episodes of airflow obstruction or airway hyperresponsiveness are present; airflow obstruction is at least partially reversible; and alternative diagnoses are excluded.

KEY SYMPTOM INDICATORS FOR CONSIDERING A DIAGNOSIS OF ASTHMA

The presence of multiple key indicators increases the probability of asthma, but spirometry is needed to establish a diagnosis.

- Wheezing—high-pitched whistling sounds when breathing out—especially in children. A lack of wheezing and a normal chest examination do not exclude asthma.
- History of any of the following:
  - — Cough (worse particularly at night)
  - — Recurrent wheeze
  - — Recurrent difficulty in breathing
  - — Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - — Exercise
  - — Viral infection
  - — Inhalant allergens (e.g., animals with fur or hair, house-dust mites, mold, pollen)
  - — Irritants (tobacco or wood smoke, airborne chemicals)
  - — Changes in weather
  - — Strong emotional expression (laughing or crying hard)
  - — Stress
  - — Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient.

- Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present.
- Airflow obstruction is at least partially reversible, measured by spirometry. Reversibility is determined by an increase in FEV_1 of >200 mL and ≥12 percent from baseline measure after inhalation of short-acting $beta_2$-agonist (SABA). Some studies indicate that an increase of ≥10 percent of the predicted FEV_1 after inhalation of a SABA may have higher likelihood of separating patients who have asthma from those who have chronic obstructive pulmonary disease (COPD).
- Alternative diagnoses are excluded. See discussion below.

Recommended methods to establish the diagnosis are:

- **Detailed medical history.** See figure 3, "Suggested Items for Medical History," for questions to include.
- **Physical examination** may reveal findings that increase the probability of asthma, but the absence of these findings does not rule out asthma, because the disease is variable and signs may be absent between episodes. The examination focuses on:
  - — upper respiratory tract (increased nasal secretion, mucosal swelling, and/or nasal polyp;
  - — chest (sounds of wheezing during normal breathing or prolonged phase of forced exhalation, hyperexpansion of the thorax, use of accessory muscles, appearance of hunched shoulders, chest deformity); and
  - — skin (atopic dermatitis, eczema).
- **Spirometry** can demonstrate obstruction and assess reversibility in patients ≥5 years of age. Patients' perceptions of airflow obstruction are highly variable. Spirometry is an essential objective measure to establish the diagnosis of asthma,

DIFFERENTIAL DIAGNOSTIC POSSIBILITIES FOR ASTHMA

Infants and Children

Upper airway diseases

- Allergic rhinitis and sinusitis

Obstructions involving large airways

- Foreign body in trachea or bronchus
- Vocal cord dysfunction (VCD)
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor

Obstructions involving small airways

- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease

Other causes

- Recurrent cough not due to asthma
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux

Adults

- Chronic obstructive pulmonary disease (COPD) (e.g., chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors)
- Vocal cord dysfunction (VCD)

because the medical history and physical examination are not reliable means of excluding other diagnoses or of assessing lung status. Spirometry is generally recommended, rather than measurements by a peak flow meter, due to wide variability in peak flow meters and reference values. Peak flow meters are designed for monitoring, not as diagnostic tools.

A differential diagnosis of asthma should be considered. Recurrent episodes of cough and wheezing most often are due to asthma in both children and adults; however, other significant causes of airway obstruction leading to wheeze must be considered both in the initial diagnosis and if there is no clear response to initial therapy.

- **Additional studies are not routinely necessary but may be useful when considering alternative diagnoses.**
  - — **Additional pulmonary function studies** will help if there are questions about COPD (diffusing capacity), a restrictive defect (measures of lung volumes), or VCD (evaluation of inspiratory flow-volume loops).
  - — **Bronchoprovocation** with methacholine, histamine, cold air, or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal. For safety reasons, bronchoprovocation should be carried out only by a trained individual. A positive test is diagnostic for airway hyperre sponsiveness, which is a characteristic feature of asthma but can also be present in other conditions. Thus, a positive test is consistent with asthma, but a negative test may be more helpful to rule out asthma.
  - — **Chest x ray** may be needed to exclude other diagnoses.
  - — **Biomarkers of inflammation** are currently being evaluated for their usefulness in the diagnosis and assessment of asthma. Biomarkers include total and differential cell count and mediator assays in sputum, blood, urine, and exhaled air.
- **Common diagnostic challenges include the following:**
  - — **Cough variant asthma.** Cough can be the principal—or only—manifestation of asthma, especially in young children.

FIGURE 3. SUGGESTED ITEMS FOR MEDICAL HISTORY*

A detailed medical history of the new patient who is known or thought to have asthma should address the following items

1. Symptoms
- Cough
- Wheezing
- Shortness of breath
- Chest tightness
- Sputum production

2. Pattern of symptoms
- Perennial, seasonal, or both
- Continual, episodic, or both
- Onset, duration, frequency (number of days or nights, per week or month)
- Diurnal variations, especially nocturnal and on awakening in early morning

3. Precipitating and/or aggravating factors
- Viral respiratory infections
- Environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and outdoor (e.g., pollen)
- Characteristics of home including age, location, cooling and heating system, wood-burning stove, humidifier, carpeting over concrete, presence of molds or mildew, presense of pets with fur or hair, characteristics of rooms where patient spends time (e.g., bedroom and living room with attention to bedding, floor covering, stuffed furniture)
- Smoking (patient and others in home or daycare)
- Exercise
- Occupational chemicals or allergens
- Environmental change (e.g., moving to new home; going on vacation; and/or alterations in workplace, work processes, or materials used)
- Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)
- Emotions (e.g., fear, anger, frustration, hard crying or laughing)
- Stress (e.g., fear, anger, frustration)
- Drugs (e.g., aspirin; and other nonsteroidal anti-inflammatory drugs, beta-blockers including eye drops, others)
- Food, food additives, and preservatives (e.g., sulfites)
- Changes in weather, exposure to cold air
- Endocrine factors (e.g., menses, pregnancy, thyroid disease)
- Comorbid conditions (e.g. sinusitis, rhinitis, gastroesophageal reflux disease (GERD)

4. Development of disease and treatment
- Age of onset and diagnosis
- History of early-life injury to airways (e.g., bronchopulmonary dysplasia, pneumonia, parental smoking)
- Progression of disease (better or worse)
- Present management and response, including plans for managing exacerbations
- Frequency of using short-acting beta$_2$-agonist (SABA)
- Need for oral corticosteroids and frequency of use

5. Family history
- History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives

6. Social history
- Daycare, workplace, and school characteristics that may interfere with adherence
- Social factors that interfere with adherence, such as substance abuse
- Social support/social networks
- Level of education completed
- Employment

7. History of exacerbations
- Usual prodromal signs and symptoms
- Rapidity of onset
- Duration
- Frequency
- Severity (need for urgent care, hospitalization, intensive care unit (ICU) admission.)
- Life-threatening exacerbations (e.g., intubation, intensive care unit admission)
- Number and severity of exacerbations in the past year.
- Usual patterns and management (what works?)

8. Impact of asthma on patient and family
- Episodes of unscheduled care (emergency department (ED), urgent care, hospitalization)
- Number of days missed from school/work
- Limitation of activity, especially sports and strenuous work
- History of nocturnal awakening
- Effect on growth, development, behavior, school or work performance, and lifestyle
- Impact on family routines, activities, or dynamics
- Economic impact

9. Assessment of patient's and family's perceptions of disease
- Patient's, parent's, and spouse's or partner's knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment
- Patient's perception and beliefs regarding use and long-term effects of medications
- Ability of patient and parents, spouse, or partner to cope with disease
- Level of family support and patient's and parents', spouse's, or partner's capacity to recognize severity of an exacerbation
- Economic resources
- Sociocultural beliefs

* This list does not represent a standardized assessment or diagnostic instrument. The validity and reliability of this list have not been assessed.

Monitoring of PEF or bronchoprovocation may be helpful. Diagnosis is confirmed by a positive response to asthma medications.

- — **VCD** can mimic asthma, but it is a distinct disorder. VCD may coexist with asthma. Asthma medications typically do little, if any thing, to relieve VCD symptoms. Variable flattening of the inspiratory flow loop on spirometry is strongly suggestive of VCD. Diagnosis of VCD is from indirect or direct vocal cord visualization during an episode, during which the abnormal adduction can be documented. VCD should be considered in difficult-to-treat, atypical asthma patients and in elite athletes who have exercise-related breathlessness unresponsive to asthma medication.
- — **Gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), and allergic bronchopulmonary aspergillosis (ABPA)** may coexist with asthma and complicate diagnosis. See the section on "Comorbid Conditions," for further discussion.
- — **Children ages 0–4 years.** Diagnosis in infants and young children is challenging and is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Caution is needed to avoid giving young children inappropriate prolonged asthma therapy. However, it is important to avoid underdiagnosing asthma, and thereby missing the opportunity to treat a child, by using such labels as "wheezy bronchitis," "recurrent pneumonia," or "reactive airway disease" (RAD). The chronic airway inflammatory response and structural changes that are characteristic of asthma can develop in the preschool years, and appropriate asthma treatment will reduce morbidity.

- **Consider referral to an asthma specialist if signs and symptoms are atypical, if there are problems with a differential diagnosis, or if additional testing is indicated.**

Managing Asthma Long Term

GOAL OF THERAPY: CONTROL OF ASTHMA

Reduce Impairment

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion).
- Require infrequent use (≤2 days a week) of inhaled SABA for quick relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]).
- Maintain (near) normal pulmonary function.
- Maintain normal activity levels (including exercise and other physical activity and attendance at school or work).
- Meet patients' and families' expectations of and satisfaction with asthma care.

Reduce Risk

- Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations.
- Prevent loss of lung function; for children, prevent reduced lung growth.
- Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.

Achieving and maintaining asthma control requires four components of care: assessment and monitoring, education for a partnership in care, control of environmental factors and comorbid conditions that affect asthma, and medications. A stepwise approach to asthma management incorporates these four components, emphasizing that pharmacologic therapy is initiated based on asthma severity and adjusted (stepped up or down) based on the level of asthma control. Special considerations of therapeutic options within the stepwise approach may be necessary for situations such as exercise-induced bronchospasm (EIB), surgery, and pregnancy.

Four Components of Asthma Care

Component 1: Assessing and Monitoring Asthma Severity and Asthma Control

The functions of assessment and monitoring are closely linked to the concepts of severity, control, and responsiveness to treatment:

- **Severity:** the intrinsic intensity of the disease process. Severity is most easily and directly measured in a patient who is not receiving long-term control therapy. Severity can also be measured, once asthma control is achieved, by the step of care (i.e., the amount of medication) required to maintain control.
- **Control:** the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals of therapy are met.
- **Responsiveness:** the ease with which asthma control is achieved by therapy.

Asthma severity and asthma control include the domains of current impairment and future risk.

- **Impairment:** frequency and intensity of symptoms and functional limitations the patient is currently experiencing or has recently experienced.

- **Risk:** the likelihood of either asthma exacerbations, progressive decline in lung function (or, for children, reduced lung growth), or risk of adverse effects from medication.

This distinction emphasizes the multifaceted nature of asthma and the need to consider separately asthma's current, ongoing effects on the present quality of life and functional capacity and the future risk of adverse events. The two domains may respond differentially to treatment. For example, evidence demonstrates that some patients can have adequate control of symptoms and minimal day-to-day impairment, but still be at significant risk of exacerbations; these patients should be treated accordingly.

The specific measures used to assess severity and control are similar: symptoms, use of SABAs for quick relief of symptoms, limitations to normal activities due to asthma, pulmonary function, and exacerbations. Multiple measures are important, because different measures assess different manifestations of the disease and may not correlate with each other.

The concepts of severity and control are used as follows for managing asthma:

- **Assess severity to initiate therapy.** See section on "Stepwise Approach for Managing Asthma" for figures on classifying asthma severity and initiating therapy in different age groups. During a patient's initial presentation, if the patient is not currently taking long-term control medication, asthma severity is assessed to guide clinical decisions for initiating the appropriate medication and other therapeutic interventions.
- **Assess control to adjust therapy.** See section on "Stepwise Approach for Managing Asthma" for figures on assessing asthma control and adjusting therapy in different age groups. Once therapy is initiated, the emphasis for clinical management thereafter is changed to the assessment of asthma control. The level of asthma control will guide decisions either to maintain or to adjust therapy (i.e., step up if necessary, step down if possible).
- **For assessing a patient's overall asthma severity, once the most optimal asthma control is achieved and maintained,** or for population-based evaluations or clinical research, asthma severity can be inferred by correlating the level of severity with the lowest level of treatment required to maintain control.

Lowest level of treatment required to maintain control

(See "Stepwise Approach for Managing Asthma" for treatment steps.)

Classification of Asthma Severity When Asthma Is Well Controlled

	Persistent		
Intermittent	Mild	Moderate	Severe
Step 1	Step 2	Step 3 or Step 4	Step 5 or Step 6

However, the emphasis for clinical management is to assess asthma severity prior to initiating therapy and then to assess asthma control for monitoring and adjusting therapy.

For the initial assessment to characterize the patient's asthma and guide decisions for initiating therapy, use information from the diagnostic evaluation to:

- **Classify asthma severity.**
- **Identify precipitating factors** for episodic symptoms (e.g., exposure at home, work, daycare, or school to inhalant allergens or irritants).
- **Identify comorbid conditions** that may impede asthma management (e.g., sinusitis, rhinitis, GERD, OSA, obesity, stress, or depression).
- **Assess the patient's knowledge and skills** for self-management.

For periodic monitoring of asthma control to guide decisions for maintaining or adjusting therapy:

- **Instruct patients to monitor their asthma control in an ongoing manner. All patients should be taught how to recognize inadequate asthma control.**
  - — Either symptom or peak flow monitoring is appropriate for most patients; evidence suggests the benefits are similar.
  - — Consider daily peak-flow monitoring for patients who have moderate or severe persistent asthma, patients who have a history of severe exacerbations, and patients who poorly perceive airway obstruction or worsening asthma.
- **Monitor asthma control periodically in clinical visits,** because asthma is highly variable over time and therapy may need to be adjusted (stepped up if necessary, stepped down if possible). **The frequency of monitoring is a matter of clinical judgment. In general:**

FIGURE 4. SAMPLE PATIENT SELF-ASSESSMENT SHEET FOR FOLLOWUP VISITS*

Name:_____ Date:_____

Your Asthma Control

How many days in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?

_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7

How many nights in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?

_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7

Do you perform peak flow readings at home? _____ yes _____ no

If yes, did you bring your peak flow chart? _____ yes _____ no

How many days in the past week has asthma restricted your physical activity?

_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7

Have you had any asthma attacks since your last visit? _____ yes _____ no

Have you had any unscheduled visits to a doctor, including to the emergency department, since your last visit? _____ yes _____ no

How well controlled is your asthma, in your opinion? ____ very well controlled

____ somewhat controlled

____ not well controlled

Average number of puffs per day of quick-relief medication (short acting beta$_2$-agonist) _____

Taking your medicine

What problems have you had taking your medicine or following your asthma action plan?

Please ask the doctor or nurse to review how you take your medicine.

Your questions

What questions or concerns would you like to discuss with the doctor?

How satisfied are you with your asthma care? ____ very satisfied

____ somewhat satisfied

____ not satisfied

* These questions are examples and do not represent a standardized assessment instrument. Other examples of asthma control questions: Asthma Control Questionnaire (Juniper); Asthma Therapy Assessment Questionnaire (Volmer); Asthma Control Test (Nathan); Asthma Control Score (Boulet)

— Schedule visits at 2- to 6-week intervals for patients who are just starting therapy or who require a step up in therapy to achieve or regain asthma control.

— Schedule visits at 1- to 6-month intervals, after asthma control is achieved, to monitor whether asthma control is maintained. The interval will depend on factors such as the duration of asthma control or the level of treatment required.

— Consider scheduling visits at 3-month intervals if a step down in therapy is anticipated.

- **Assess asthma control, medication technique, the written asthma action plan, adherence, and patient concerns at every patient visit.** See figure 4 for a sample patient self-assessment of overall asthma control and asthma care.
- Use spirometry to obtain objective measures of lung function.

  — Perform spirometry at the following times:

    • At the initial assessment.

    • After treatment is initiated and symptoms and PEF have stabilized.

    • During periods of progressive or prolonged loss of asthma control.

    • At least every 1–2 years; more frequently depending on response to therapy.

  — Low FEV_1 indicates current obstruction (impairment) and risk for future exacerbations (risk). For children, FEV_1/forced vital capacity (FVC) appears to be a more sensitive measure of severity and control in the impairment domain. FEV_1 is a useful measure of risk for exacerbations, although it is emphasized that even children who have normal lung function experience exacerbations.
- **Minimally invasive markers** (called biomarkers) such as fractionated exhaled nitric oxide (FeNO) and sputum eosinophils may be useful, but bio markers require further evaluation before they can be recommended as clinical tools for routine management.

Component 2: Education for a Partnership in Care

A partnership between the clinician and the person who has asthma (and the caregiver, for children) is required for effective asthma management. By working together, an appropriate treatment can be selected, and the patient can learn self-management skills necessary to control asthma. Self-management education improves patient outcomes (e.g., reduced urgent care visits, hospitalizations, and limitations on activities as well as improved health status, quality of life, and perceived control of asthma) and can be cost-effective. Self-management education is an integral component of effective asthma care and should be treated as such by health care providers as well as by health care policies and reimbursements.

KEY EDUCATIONAL MESSAGES: TEACH AND REINFORCE AT EVERY OPPORTUNITY

Basic Facts About Asthma

- The contrast between airways of a person who has and a person who does not have asthma; the role of inflammation.
- What happens to the airways during an asthma attack.

Role of Medications: Understanding the Difference Between:

- Long-term control medications: prevent symptoms, often by reducing inflammation. Must be taken daily. Do not expect them to give quick relief.
- Quick-relief medications: SABAs relax airway muscles to provide prompt relief of symptoms. Do not expect them to provide long-term asthma control. Using SABA >2 days a week indicates the need for starting or increasing long-term control medications.

Patient Skills

- Taking medications correctly
  - — Inhaler technique (demonstrate to the patient and have the patient return the demonstration).
  - — Use of devices, as prescribed (e.g., valved holding chamber (VHC) or spacer, nebulizer).
- Identifying and avoiding environmental exposures that worsen the patient's asthma; e.g., allergens, irritants, tobacco smoke.
- Self-monitoring
  - — Assess level of asthma control.
  - — Monitor symptoms and, if prescribed, PEF measures.
  - — Recognize early signs and symptoms of worsening asthma.
- Using a written asthma action plan to know when and how to:
  - — Take daily actions to control asthma.
  - — Adjust medication in response to signs of worsening asthma.
- Seeking medical care as appropriate.

Develop an active partnership with the patient and family by:

- Establishing open communications that consider cultural and ethnic factors, as well as language and health care literacy needs, of each patient and family.
- Identifying and addressing patient and family concerns about asthma and asthma treatment.
- Developing treatment goals and selecting medications together with the patient and family, allowing full participation in treatment decision making.
- Encouraging self-monitoring and self-management by reviewing at each opportunity the patient's reports of asthma symptoms and response to treatment.

Provide to all patients a written asthma action plan that includes instructions for both daily management (long-term control medication, if appropriate, and environmental control measures) and actions to manage worsening asthma (what signs, symptoms, and PEF measurements (if used) indicate worsening asthma; what medications to take in response; what signs and symptoms indicate the need for immediate medical care). Written asthma action plans are particularly recommended for patients who have moderate or severe persistent asthma (i.e., requiring treatment at step 4, 5, or 6), a history of severe exacerbations, or poorly controlled asthma. See figures 5 and 6 for samples of written asthma action plans.

Integrate asthma self-management education into all aspects of asthma care. Asthma self management requires repetition and reinforcement. It should:

- Begin at the time of diagnosis and continue through followup care. See figure 7, "Delivery of Asthma Education by Clinicians During Patient Care Visits," for a sample of how to incorporate teaching into routine clinic visits.
- Involve all members of the health care team, including physicians, nurses, pharmacists, respiratory therapists, and asthma educators, as well as other health professionals who come in contact with asthma patients and their families.
- Occur at all points of care where health care professionals interact with patients who have asthma. The strongest evidence supports self-management education in the clinic setting. Evidence also supports education provided in patients' homes, pharmacies, targeted education in EDs and hospitals, and selected programs in schools and other community sites. Proven community programs should be considered because of their potential to reach large numbers of people who have asthma and encourage "asthma-friendly" support from their families and community environments.
- Use a variety of educational strategies to reach people who have varying levels of health literacy or learning styles. Individual instruction, group programs, written materials (at a 5th grade reading level or below), video- or audiotapes, and computer and Internet programs all provide effective educational opportunities. See figure 8, "Asthma Education Resources," for a sample of available resources.
- Incorporate individualized case/care management by trained health care professionals for patients who have poorly controlled asthma and have recurrent visits to the emergency department or hospital. This will provide tailored self-management education and skills training.

Encourage patients' adherence to the written asthma action plan by:

- Choosing treatment that achieves outcomes and addresses preferences that are important to the patient, and reminding patients that adherence will help them achieve the outcomes they want.
- Reviewing with the patient at each visit the success of the treatment plan to achieve asthma control and make adjustments as needed.
- Reviewing patients' concerns about their asthma or treatment at every visit. Inquire about any difficulties encountered in adhering to the written asthma action plan.
- Assessing the patient's and family's level of social support, and encouraging family involvement.
- Tailoring the self-management approach to the needs and literacy levels of the patient, and maintaining sensitivity to cultural beliefs and ethnocultural practices.

Encourage health care provider and health care system support of the therapeutic partnership by:

- Incorporating effective clinician education strategies,

FIGURE 5. SAMPLE ASTHMA ACTION PLAN—ADULT

ENGLISH

My Asthma Action Plan

Patient Name: _____

Medical Record #: _____

Physician's Name: _____ DOB: _____

Physician's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines	How Much To Take	How Often	Other Instructions
		____ times per day EVERY DAY!	
		____ times per day EVERY DAY!	
		____ times per day EVERY DAY!	
		____ times per day EVERY DAY!	

Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Take ONLY as needed	NOTE: If this medicine is needed frequently, call physician to consider increasing long-term-control medications.

Special instructions when I feel ● *good,* ○ *not good,* and ● *awful.*

GREEN ZONE

I feel *good.*

(My peak flow is in the GREEN zone.)

PREVENT asthma symptoms everyday:

- ☐ Take my long-term-control medicines (above) every day.
- ☐ Before exercise, take ____ puffs of _____
- ☐ Avoid things that make my asthma worse like: _____

YELLOW ZONE

I do *not* feel *good.*

(My peak flow is in the YELLOW zone.)

My symptoms may include one or more of the following:

- Wheeze
- Tight chest
- Cough
- Shortness of breath
- Waking up at night with asthma symptoms
- Decreased ability to do usual activities
- _____

CAUTION. I should continue taking my long-term-control asthma medicines every day AND:

- ☐ Take _____

If I still do not feel good, or my peak flow is not back in the *Green Zone* within 1 hour, then I should:

- ☐ Increase _____
- ☐ Add _____
- ☐ Call _____

RED ZONE

I feel *awful.*

(My peak flow is in the RED zone.)

Warning signs may include one or more of the following:

- It's getting harder and harder to breathe
- Unable to sleep or do usual activities because of trouble breathing

MEDICAL ALERT! Get help!

- ☐ Take _____ until I get help immediately.
- ☐ Take _____
- ☐ Call _____

Danger! Get help immediately! Call 9–1–1 if you have trouble walking or talking due to shortness of breath or lips or fingernails are gray or blue.

Adapted and reprinted with permission from the Regional Asthma Management and Prevention (RAMP) Initiative, a program of the Public Health Institute, to include terms used in the EPR—3: Full Report 2007.

Source: http://www.calasthma.org/uploads/resources/actionplanpdf.pdf; San Francisco Bay Area Regional Asthma Management Plan, http://www.rampasthma.org

FIGURE 6. SAMPLE ASTHMA ACTION PLAN—CHILD

ENGLISH

Child Asthma Action Plan

0–5 years of age

Patient Name: _____

Medical Record #: _____

Health Care Provider's Name: _____ DOB: _____

Health Care Provider's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines (Use Every Day To Stay Healthy)	How Much To Take	How Often	Other Instructions (such as spacers/masks, nebulizers)
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	

Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Give ONLY as needed	NOTE: If this medicine is needed often (_____ times per week), call physician.

GREEN ZONE

Child is ***well*** and has no asthma symptoms, even during active play.

PREVENT asthma symptoms every day:

- Give the above long-term-control medicines every day.
- Avoid things that make the child's asthma worse:

☑ Avoid tobacco smoke; ask people to smoke outside.

☐ _____

☐ _____

YELLOW ZONE

Child is ***not well*** and has asthma symptoms that may include:

- Coughing
- Wheezing
- Runny nose or other cold symptoms
- Breathing harder or faster
- Awakening due to coughing or difficulty breathing
- Playing less than usual
- _____
- _____

Other symptoms that could indicate that your child is having trouble breathing may include: difficulty feeding (grunting sounds, poor sucking), changes in sleep patterns, cranky and tired, decreased appetite.

CAUTION. Take action by continuing to give regular asthma medicines **every day** AND:

☐ Give _____

(include dose and frequency)

If the child is not in the ***Green Zone*** and still has symptoms after 1 hour, then:

☐ Give more _____

(include dose and frequency)

☐ _____

(include dose and frequency)

☐ Call _____

RED ZONE

Child ***feels awful!*** Warning signs may include:

- Child's wheeze, cough, or difficulty breathing continues or worsens, even after giving yellow zone medicines.
- Child's breathing is so hard that he/she is having trouble walking/talking/eating/playing.
- Child is drowsy or less alert than normal.

Danger! Get help immediately!

MEDICAL ALERT! Get help!

☐ Take the child to the hospital or call 9–1–1 immediately!

☐ Give more _____ until you get help. (include dose and frequency)

☐ Give _____ (include dose and frequency)

Call 9–1–1 if:

- The child's skin is sucked in around neck and ribs, or
- Lips and/or fingernails are grey or blue, or
- Child doesn't respond to you.

Adapted and reprinted with permission from "The Asthma Action Plan" developed by a committee facilitated by the Regional Asthma Management and Prevention (RAMP) Initiative, a program of the Public Health Institute.

Source: http://www.calasthma.org/uploads/resources/actionplanpdf.pdf; San Francisco Bay Area Regional Asthma Management Plan, http://www.rampasthma.org

FIGURE 7. DELIVERY OF ASTHMA EDUCATION BY CLINICIANS DURING PATIENT CARE VISITS

Assessment Questions	Information	Skills
Recommendations for Initial Visit		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life **Ask relevant questions** "What worries you most about your asthma?" "What do you want to accomplish at this visit?" "What do you want to be able to do that you can't do now because of your asthma?" "What do you expect from treatment?" "What medicines have you tried?" "What other questions do you have for me today?" "Are there things in your environment that make your asthma worse?"	**Teach in simple language:** ■ What is asthma? Asthma is a chronic lung disease. The airways are very sensitive. They become inflamed and narrow; breathing becomes difficult. ■ The definition of asthma control: few daytime symptoms, no nighttime awakenings due to asthma, able to engage in normal activities, normal lung function. ■ Asthma treatments: two types of medicines are needed: — Long-term control: medications that prevent symptoms, often by reducing inflammation. — Quick relief: short-acting bronchodilator relaxes muscles around airways. ■ Bring all medications to every appointment. ■ When to seek medical advice. Provide appropriate telephone number.	**Teach or review and demonstrate:** ■ Inhaler and spacer or valved holding chamber (VHC) use. Check performance. ■ Self-monitoring skills that are tied to a written asthma action plan: — Recognize intensity and frequency of asthma symptoms. — Review the signs of deterioration and the need to reevaluate therapy: ♦ Waking at night or early morning with asthma ♦ Increased medication use ♦ Decreased activity tolerance ■ Use of a written asthma action plan (See figures 5 and 6.) that includes instructions for daily management and for recognizing and handling worsening asthma.
Recommendations for First Followup Visit (2 to 4 Weeks or Sooner as Needed)		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patient's goals of treatment ■ Medications ■ Patient's treatment preferences ■ Quality of life **Ask relevant questions from previous visit and also ask:** "What medications are you taking?" "How and when are you taking them?" "What problems have you had using your medications?" "Please show me how you use your inhaled medications."	**Teach in simple language:** ■ Use of two types of medications. ■ Remind patient to bring all medications and the peak flow meter, if using, to every appointment for review. ■ Self/assessment of asthma control using symptoms and/or peak flow as a guide.	**Teach or review and demonstrate:** ■ Use of written asthma action plan. Review and adjust as needed. ■ Peak flow monitoring if indicated ■ Correct inhaler and spacer or VHC technique.
Recommendations for Second Followup Visit		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life **Ask relevant questions from previous visits and also ask:** "Have you noticed anything in your home, work, or school that makes your asthma worse?" "Describe for me how you know when to call your doctor or go to the hospital for asthma care." "What questions do you have about the asthma action plan?" "Can we make it easier?" "Are your medications causing you any problems?" "Have you noticed anything in your environment that makes your asthma worse?" "Have you missed any of your medications?"	**Teach in simple language:** ■ Self-assessment of asthma control, using symptoms and/or peak flow as a guide. ■ Relevant environmental control/avoidance strategies: — How to identify home, work, or school exposures that can cause or worsen asthma — How to control house-dust mites, animal exposures if applicable — How to avoid cigarette smoke (active and passive) ■ Review all medications.	**Teach or review and demonstrate:** ■ Inhaler/spacer or VHC technique. ■ Peak flow monitoring technique. ■ Use of written asthma action plan. Review and adjust as needed. ■ Confirm that patient knows what to do if asthma gets worse

FIGURE 7. DELIVERY OF ASTHMA EDUCATION BY CLINICIANS DURING PATIENT CARE VISITS (continued)

Assessment Questions	Information	Skills
Recommendations for All Subsequent Visits		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life **Ask relevant questions from previous visits and also ask:** "How have you tried to control things that make your asthma worse?" "Please show me how you use your inhaled medication."	**Teach in simple language:** ■ Review and reinforce all: — Educational messages — Environmental control strategies at home, work, or school — Medications — Self-assessment of asthma control, using symptoms and/or peak flow as a guide	**Teach or review and demonstrate:** ■ Inhaler/spacer or VHC technique. ■ Peak flow monitoring technique, if appropriate. ■ Use of written asthma action plan. Review and adjust as needed. ■ Confirm that patient knows what to do if asthma gets worse.

Sources: Adapted from Guevara et al. 2003; Janson et al. 2003; Powell and Gibson 2003; Wilson et al. 1993.

such as interactive formats, practice-based case studies, and multidimensional teaching approaches that reinforce guideline-based care.

- Providing communication skills training to clinicians to enhance competence in caring for all patients, especially multicultural populations.
- Using systems approaches, such as clinical pathways and clinical information system prompts, to improve the quality of asthma care and to support clinical care decisionmaking.

Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma

If patients who have asthma are exposed to irritants or inhalant allergens to which they are sensitive, their asthma symptoms may increase and precipitate an asthma exacerbation. Substantially reducing exposure to these factors may reduce inflammation, symptoms, and need for medication. Several comorbid conditions can impede asthma management. Recognition and treatment of these conditions may improve asthma control. See questions in figure 3, "Suggested Items for Medical History," above, for questions related to environmental exposures and comorbid conditions.

Allergens and Irritants

Evaluate the potential role of allergens (particularly inhalant allergens) and irritants.

- Identify allergen and pollutants or irritant exposures. The most important allergens for both children and adults appear to be those that are inhaled.
- For patients who have persistent asthma, use skin testing or in vitro testing to assess sensitivity to perennial indoor allergens. Assess the significance of positive tests in the context of the person's history of symptoms when exposed to the allergen.

Advise patients who have asthma to reduce exposure to allergens and pollutants or irritants to which they are sensitive.

- See figure 9, "How To Control Things That Make Your Asthma Worse," for a sample patient information sheet.
- Effective allergen avoidance requires a multifaceted, comprehensive approach; single steps alone are generally ineffective. Multifaceted allergen-control education programs provided in the home setting can help patients reduce exposures to cockroach, dust-mite, and rodent allergens and, consequently, improve asthma control.
- Advise patients who have severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) about their risk of severe and even fatal exacerbations from using these drugs.
- Indoor air-cleaning devices (high-efficiency particulate air [HEPA] and electrostatic precipitating filters), cannot substitute for more effective dust-mite and cockroach control measures because

FIGURE 8. ASTHMA EDUCATION RESOURCES

Allergy & Asthma Network Mothers of Asthmatics 2751 Prosperity Avenue, Suite 150 Fairfax, VA 22030 www.breatherville.org	1–800–878–4403 1–703–641–9595
American Academy of Allergy, Asthma and Immunology 555 East Wells Street, Suite 100 Milwaukee, WI 53202-3823 www.aaaai.org	1–414–272–6071
American Association For Respiratory Care 9125 North MacArthur Boulevard, Suite 100 Irving, TX 75063 www.aarc.org	1–972–243–2272
American College of Allergy, Asthma, and Immunology 85 West Algonquin Road Suite 550 Arlington Heights, IL 60005 www.Acaai.Org	1–800–842–7777 1–847–427–1200
American Lung Association 61 Broadway New York, NY 10006 www.lungusa.org	1–800–586–4872
Association of Asthma Educators 1215 Anthony Avenue Columbia, SC 29201 www.asthmaeducators.org	1–888–988–7747
Asthma and Allergy Foundation of America 1233 20th Street, NW., Suite 402 Washington, DC 20036 www.aafa.org	1–800–727–8462
Centers for Disease Control and Prevention 1600 Clifton Road Atlanta, GA 30333	1–800–311–3435
Food Allergy & Anaphylaxis Network 11781 Lee Jackson Highway, Suite 160 Fairfax, VA 22033 www.foodallergy.org	1–800–929–4040
National Heart, Lung, and Blood Institute Information Center P.O. Box 30105 Bethesda, MD 20824-0105 www.nhlbi.nih.gov	1–301–592–8573
National Jewish Medical and Research Center (Lung Line) 1400 Jackson Street Denver, CO 80206 www.njc.org	1–800–222–Lung
U.S. Environmental Protection Agency **National Center for Environmental Publications** P.O. Box 42419 Cincinnati, OH 45242-0419 www.airnow.gov	1–800–490–9198

these particles do not remain airborne. The devices can reduce airborne dog and cat allergens, mold spores, and particulate tobacco smoke; however, most studies do not show an effect on symptoms or lung function.

- Use of humidifiers or evaporative (swamp) coolers is not generally recommended in homes of patients who are sensitive to dust mites or mold.

Consider subcutaneous allergen immunotherapy for patients who have persistent asthma when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive. Evidence is strongest for use of subcutaneous immunotherapy for single allergens, particularly house dust mites, animal dander, and pollen. The role of allergy in asthma is greater in children than in adults. If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur.

Consider inactivated influenza vaccination for patients who have asthma. This vaccine is safe for administration to children over 6 months of age and adults, and the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) recommends vaccination for persons who have asthma because they are considered to be at risk for complications from influenza. However, the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season.

Dietary factors have an inconclusive role in asthma. Food allergenies are rarely an aggravating factor in asthma. An exception is that sulfites in foods (e.g., shrimp, dried fruit, processed potatoes, beer, and wine) can precipitate asthma symptoms in people who are sensitive to these food items. Furthermore, individuals who have both food allergy and asthma are at increased risk for fatal anaphylactic reactions to the food to which they are sensitized.

Comorbid Conditions

Identify and treat comorbid conditions that may impede asthma management. If these conditions are treated appropriately, asthma control may improve.

- **Allergic Bronchopulmonary Aspergillosis (ABPA)** may be considered in patients who have asthma and a history of pulmonary infiltrates, immunoglobulin E (IgE) sensitization to Aspergillus, and/or are corticosteroid dependent. Diagnostic criteria include: positive immediate skin test and elevated serum IgE and/or IgG to Aspergillus, total serum IgE >417 IU (1,000 ng/mL), and central bronchiectasis. Treatment is prednisone, initially 0.5 mg per kilogram with gradual tapering. Azole antifungal agents as adjunctive therapy may also be helpful.
- **Gastroesophageal Reflux (GERD)** treatment may benefit patients who have asthma and complain of frequent heartburn or pyrosis, particularly those who have frequent nighttime asthma symptoms. Even in the absence of suggestive GERD symptoms, consider evaluation for GERD in patients who have poorly controlled asthma, especially with nighttime symptoms. Treatment includes: avoiding heavy meals, fried foods, caffeine, and alcohol; avoiding food and drink within 3 hours of retiring; elevating the head of the bed on 6- to 8-inch blocks; using proton pump inhibitor medication.
- **Obese or overweight patients** who have asthma may be advised that weight loss, in addition to improving overall health, might also improve asthma control.
- **Obstructive Sleep Apnea (OSA)** may be considered in patients who have not well controlled asthma, particularly those who are overweight or obese. Treatment for OSA is nasal continuous positive air way pressure (CPAP). However, this treatment may disrupt the sleep of asthma patients who do not also have OSA. Accurate diagnosis is important.
- **Rhinitis or sinusitis** symptoms or diagnosis should be evaluated in patients who have asthma, because the interrelationship of the upper and lower airway suggests that therapy for the upper airway will improve asthma control. Treatment of allergic rhinitis includes intranasal corticosteroids, antihistamine therapy, and the consideration of immunotherapy. Treatment of sinusitis includes intranasal corticosteroids and antibiotics. Evidence is inconclusive regarding the effect on asthma of sinus surgery in patients who have chronic rhinosinusitis.
- **Stress and depression** should be considered in patients who have asthma that is not well controlled. Additional education to improve self-management and coping skills may be helpful.

FIGURE 9. HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE

You can help prevent asthma episodes by staying away from things that make your asthma worse. This guide suggests many ways to help you do this.

You need to find out what makes your asthma worse. Some things that make asthma worse for some people are not a problem for others. You do not need to do all of the things listed in this guide.

Look at the things listed below. Put a check next to the ones that you know make your asthma worse, particularly if you are allergic to these things. Then, decide with your doctor what steps you will take. Start with the things in your bedroom that bother your asthma. Try something simple first.

Tobacco Smoke

- ☐ If you smoke, ask your doctor for ways to help you quit. Ask family members to quit smoking, too.
- ☐ Do not allow smoking in your home, car or around you.
- ☐ Be sure no one smokes at a child's daycare center or school.

Dust Mites

Many people who have asthma are allergic to dust mites. Dust mites are like tiny "bugs" you cannot see that live in cloth or carpet.

Things that will help the most:

- ☐ Encase your mattress in a special dust-mite proof cover.*
- ☐ Encase your pillow in a special dust-mite proof cover* or wash the pillow each week in hot water. Water must be hotter than 130 °F to kill the mites. Cooler water used with detergent and bleach can also be effective.
- ☐ Wash the sheets and blankets on your bed each week in hot water.

Other things that can help:

- ☐ Reduce indoor humidity to or below 60 percent, ideally 30–50 percent. Dehumidifiers or central air conditioners can do this.
- ☐ Try not to sleep or lie on cloth-covered cushions or furniture.
- ☐ Remove carpets from your bedroom and those laid on concrete, if you can.
- ☐ Keep stuffed toys out of the bed, or wash the toys weekly in hot water or in cooler water with detergent and bleach. Placing toys weekly in a dryer or freezer may help. Prolonged exposure to dry heat or freezing can kill mites but does not remove allergen.

***To find out where to get products mentioned in this guide, call:**

Asthma and Allergy Foundation of America (800–727–8462)

Allergy & Asthma Network Mothers of Asthmatics (800–878–4403)

American Academy of Allergy, Asthma, and Immunology (800–822–2762)

National Jewish Medical and Research Center (Lung Line) (800–222–5864)

American College of Allergy, Asthma, and Immunology (800–842–7777)

Animal Dander

Some people are allergic to the flakes of skin or dried saliva from animals.

The best thing to do:

- ☐ Keep pets with fur or hair out of your home.

If you can't keep the pet outdoors, then:

- ☐ Keep the pet out of your bedroom, and keep the bedroom door closed.
- ☐ Remove carpets and furniture covered with cloth from your home. If that is not possible, keep the pet out of the rooms where these are.

Cockroach

Many people with asthma are allergic to the dried droppings and remains of cockroaches.

- ☐ Keep all food out of your bedroom.
- ☐ Keep food and garbage in closed containers (Never leave food out).
- ☐ Use poison baits, powders, gels, or paste (for example, boric acid). You can also use traps.
- ☐ If a spray is used to kill roaches, stay out of the room until the odor goes away.

Vacuum Cleaning

- ☐ Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- ☐ If you vacuum, use a dust mask (from a hardware store), a central cleaner with the collecting bag outside the home, or a vacuum cleaner with a HEPA filter or a double-layered bag.*

Indoor Mold

- ☐ Fix leaking faucets, pipes, or other sources of water.
- ☐ Clean moldy surfaces.
- ☐ Dehumidify basements if possible.

Pollen and Outdoor Mold

During your allergy season (when pollen or mold spore counts are high):

- ☐ Try to keep your windows closed.
- ☐ If possible, stay indoors with windows closed during the midday and afternoon, if you can. Pollen and some mold spore counts are highest at that time.
- ☐ Ask your doctor whether you need to take or increase anti-inflammatory medicine before your allergy season starts.

Smoke, Strong Odors, and Sprays

- ☐ If possible, do not use a wood-burning stove, kerosene heater, fireplace, unvented gas stove, or heater.
- ☐ Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, paints, new carpet, or particle board.

Exercise or Sports

- ☐ You should be able to be active without symptoms. See your doctor if you have asthma symptoms when you are active—such as when you exercise, do sports, play, or work hard.
- ☐ Ask your doctor about taking medicine before you exercise to prevent symptoms.
- ☐ Warm up for a period before you exercise.
- ☐ Check the air quality index and try not to work or play hard outside when the air pollution or pollen levels (if you are allergic to the pollen) are high.

Other Things That Can Make Asthma Worse

- ☐ **Sulfites in foods:** Do not drink beer or wine or eat shrimp, dried fruit, or processed potatoes if they cause asthma symptoms.
- ☐ **Cold air:** Cover your nose and mouth with a scarf on cold or windy days.
- ☐ **Other medicines:** Tell your doctor about all the medicines you may take. Include cold medicines, aspirin, and even eye drops.

Key: HEPA, high-efficiency particulate air

Component 4: Medications

Medications for asthma are categorized into two general classes: long-term control medication and quick-relief medication. Selection of medications includes consideration of the general mechanisms and role of the medication in therapy, delivery devices, and safety.

General Mechanisms and Role in Therapy

Long-term control medications are used daily to achieve and maintain control of persistent asthma. The most effective are those that attenuate the underlying inflammation characteristic of asthma. Long-term control medications include the following (listed in alphabetical order):

- **Corticosteroids** are anti-inflammatory medications that reduce airway hyperresponsiveness, inhibit inflammatory cell migration and activation, and block late phase reaction to allergen. Inhaled Corticosteriods (ICSs) are the most consistently effective long-term control medication at all steps of care for persistent asthma, and ICSs improve asthma control more effectively in both children and adults than leukotriene receptor antagonists (LTRAs) or any other single, long-term control medication do. ICSs reduce impairment and risk of exacerbations, but ICSs do not appear to alter the progression or underlying severity of the disease in children. Short courses of oral systemic corticosteroids are often used to gain prompt control of asthma. Oral systemic corticosteroids are used long term to treat patients who require step 6 care (for severe persistent asthma).
- **Cromolyn sodium and nedocromil** stabilize mast cells and interfere with chloride channel function. They are used as alternative, but not preferred, medication for patients requiring step 2 care (for mild persistent asthma). They also can be used as preventive treatment before exercise or unavoidable exposure to known allergens.
- **Immunomodulators.** Omalizumab (anti-IgE) is a monoclonal antibody that prevents binding of IgE to the high-affinity receptors on basophils and mast cells. Omalizumab is used as adjunctive therapy for patients 12 years of age who have sensitivity to relevant allergens (e.g., dust mite, cockroach, cat, or dog) and who require step 5 or 6 care (for severe persistent asthma). Clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- **Leukotriene modifiers** interfere with the pathway of leukotriene mediators, which are released from mast cells, eosinophils, and basophils. These medications include LTRAs (montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). LTRAs are alternative, but not preferred, therapy for the treatment of patients who require step 2 care (for mild persistent asthma). LTRAs also can be used as adjunctive therapy with ICSs, but for youths 12 years of age and adults, they are not preferred adjunctive therapy compared to the addition of LABAs. LTRAs can attenuate EIB. Zileuton can be used as alternative, but not preferred, adjunctive therapy in adults; liver function monitoring is essential.
- **LABAs** (salmeterol and formoterol) are inhaled bronchodilators that have a duration of bronchodilation of at least 12 hours after a single dose.
  - — LABAs are not to be used as monotherapy for long-term control of asthma.
  - — LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma (Step 3 care or higher in children ≥5 years of age and adults and Step 4 care or higher in children 0–4 years of age, although few data are available for 0–4-year-olds.).
  - — Of the adjunctive therapies available, LABA is the preferred therapy to combine with ICS in youths ≥12 years of age and adults.
  - — A LABA may be used before exercise to prevent EIB, but duration of action does not exceed 5 hours with chronic, regular use. Frequent or chronic use before exercise is discouraged, because this may disguise poorly controlled persistent asthma. See also the section "Safety Issues for Inhaled Corticosteroids and Long-Acting Beta$_2$-Agonists."
- **Methylxanthines.** Sustained-release theophylline is a mild to moderate bronchodilator used as alternative, not preferred, therapy for step 2 care (for mild persistent asthma) or as adjunctive therapy with ICS in patients ≥5 years of age. Theophylline may have mild anti-inflammatory effects. Monitoring of serum theophylline concentration is essential.

Quick-relief medications are used to treat acute symptoms and exacerbations. They include the following (listed in alphabetical order):

- **Anticholinergics** inhibit muscarinic cholinergic receptors and reduce intrinsic vagal tone of the airway. Ipratropium bromide provides additive benefit to SABA in moderate or severe exacerbations in the emergency care setting, not the hospital setting. Ipratropium bromide may be used as an alternative bronchodilator for patients who do not tolerate SABA, although it has not been compared to SABAs.
- **SABAs**—albuterol, levalbuterol, and pirbuterol—are bronchodilators that relax smooth muscle. They are the treatment of choice for relief of acute symptoms and prevention of EIB. Increasing use of SABA treatment or the use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate asthma control and the need for initiating or intensifying anti-inflammatory therapy. Regularly scheduled, daily, chronic use of SABA is not recommended.
- **Systemic corticosteroids.** Although not short-acting, oral systemic corticosteroids are used for moderate and severe exacerbations in addition to SABA to speed recovery and to prevent recurrence of exacerbations.

Complementary and alternative medications (CAMs) and interventions generally have insufficient evidence to permit recommendations. Because as much as one-third of the U.S. population uses complementary alternative healing methods, it is important to discuss their use with patients.

- **Ask patients about all the medications and interventions they are using.** Some cultural beliefs and practices may be of no harm and can be integrated into the recommended asthma management strategies, but it is important to advise patients that alternative healing methods are not substitutes for recommended therapeutic approaches. Clinical trials on safety and efficacy are limited, and their scientific basis has not been established.
- **Evidence is insufficient to recommend or not recommend most CAMs or treatments for asthma.** These include chiropractic therapy, homeopathy and herbal medicine, and breathing or relaxation techniques. Acupuncture is not recommended for the treatment of asthma.
- **Patients who use herbal treatments for asthma should be cautioned** about the potential for harmful ingredients and for interactions with recommended asthma medications.

Delivery Devices for Inhaled Medications

Patients should be instructed in the use of inhaled medications, and patients' technique should be reviewed at every patient visit. The major advantages of delivering drugs directly into the lungs via inhalation are that higher concentrations can be delivered more effectively to the airways and that systemic side effects are lessened. Inhaled medications, or aerosols, are available in a variety of devices that differ in the technique required. See figure 10, "Aerosol Delivery Devices," for a summary of issues to consider for different devices.

Safety Issues for Inhaled Corticosteroids and Long-Acting Beta$_2$-Agonists

Inhaled Corticosteroids

- ICSs are the preferred long-term control therapy in children of all ages and adults. In general, ICSs are well tolerated and safe at the recommended dosages.
- Most benefits of ICS for patients who have mild or moderate asthma occur at the low- to medium-dose ranges. Data suggest higher doses may further reduce the risk of exacerbations. Furthermore, higher doses are beneficial for patients who have more severe asthma. The risk of adverse effects increases with the dose.
- High doses of ICS administered for prolonged periods of time (e.g., >1 year) have significantly less potential than oral systemic corticosteroids for having adverse effects. High doses of ICS used for prolonged periods of time (e.g., >1 year), particularly in combination with frequent courses of oral corticosteroids, may be associated with risk of posterior subcapsular cataracts or reduced bone density. Slit-lamp eye exam and bone densitometry may be considered. For adult patients, consider supplements of calcium and vitamin D, particularly in perimenopausal women. For children, age-appropriate dietary intake of calcium and vitamin D should be reviewed with parents or caregivers.
- To reduce the potential for adverse effects, the following measures are recommended.
  - Advise patients to use spacers or VHCs with nonbreath-activated metered-dose inhalers

(MDIs) to reduce local side effects. There are no clinical data on use of spacers with ultrafine particle hydrofluoroalkane (HFA) MDIs.

— Advise patients to rinse the mouth (rinse and spit) after inhalation.

— Use the lowest dose of ICS that maintains asthma control. Evaluate the patient's inhaler technique and adherence, as well as environmental control measures, before increasing the dose.

— Consider adding a LABA, or alternative adjunctive therapy, to a low or medium dose of ICS rather than using a higher dose of ICS to maintain asthma control.

Inhaled Corticosteroids and Linear Growth in Children

- The potential risks of ICSs are well balanced by their benefits.
- Poorly controlled asthma may delay growth. Children who have asthma tend to have longer periods of reduced growth rates before puberty.
- Growth rates are highly variable in children. Short-term evaluation may not be predictive of final adult height attained.
- The potential for adverse effects on linear growth from ICS appear to be dose dependent. In treatment of children who have mild or moderate persistent asthma, low-to medium-dose ICS therapy may be associated with a possible, but not predictable, adverse effect on linear growth (approximately 1 cm). The effect on growth velocity appears to occur in the first several months of treatment and is generally small and not progressive. The clinical significance of this potential systemic effect has yet to be determined.
- In general, the efficacy of ICSs is sufficient to out weigh any concerns about growth or other systemic effects. However, ICSs should be titrated to as low a dose as needed to maintain good control of the child's asthma, and children receiving ICSs should be monitored for changes in growth by using a stadiometer.

Long-Acting Beta2-Agonists

- The addition of LABA (salmeterol or formoterol) to the treatment of patients who require more than low-dose ICS alone to control asthma improves lung function, decreases symptoms, reduces exacerbations and use of SABA for quick relief in most patients to a greater extent than doubling the dose of ICSs.
- A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy resulted in an increased risk of asthma-related deaths in patients treated with salmeterol (13 deaths among 13,176 patients treated for 28 weeks with salmeterol versus 3 deaths among 13,179 patients treated with placebo). In addition, increased numbers of severe asthma exacerbations were noted in the pivotal trials submitted to the U.S. Food and Drug Administration (FDA) for formoterol approval, particularly in the arms of the trials with higher dose formoterol. Thus, the FDA determined that a Black Box warning was warranted on all preparations containing a LABA.
- The established beneficial effects of LABA for the great majority of patients who require more therapy than low-dose ICS alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk for severe exacerbations, although uncommon, associated with the daily use of LABAs.
- Daily use of LABA generally should not exceed 100 mcg salmeterol or 24 mcg formoterol.
- It is not currently recommended that LABA be used for treatment of acute symptoms or exacerbations.
- LABAs are not to be used as monotherapy for long-term control. Patients should be instructed not to stop ICS therapy while taking LABA, even though their symptoms may significantly improve.

Stepwise Approach for Managing Asthma

Principles of The Stepwise Approach

A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains. These domains may respond differentially to treatment.

For children, see:

Figure 11, "Classifying Asthma Severity and Initiating Therapy in Children"

FIGURE 10. AEROSOL DELIVERY DEVICES

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	≥5 years old (<5 with spacer or valved holding chamber (VHC) or mask)	Actuation during a slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. This technique, however, has not been shown to enhance clinical benefit consistently compared to closed-mouth technique (inserting MDI mouthpiece between lips and teeth).	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 50–80 percent of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically. Lung delivery under ideal conditions varies significantly between MDIs due to differences in formulation (suspension versus solution), propellant (chlorofluorocarbon [CFC] versus hydrofluoralkane [HFA]), and valve design. For example, inhaled corticosteroid (ICS) delivery varies from 5–50 percent.
Breath-actuated MDI Beta$_2$-agonist	≥5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI (see above) followed by 10-second breathhold.	May be particularly useful for patients unable to coordinate inhalation and actuation. May also be useful for elderly patients. Patients may incorrectly stop inhalation at actuation. Cannot be used with currently available spacer/valved holding chamber (VHC) devices.
Dry powder inhaler (DPI) Beta$_2$-agonists Corticosteroids Anticholinergics	≥4 years old	Rapid (60 L/min or 1–2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent. Most children <4 years of age may not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Delivery is more flow dependent in devices with highest internal resistance. Rapid inhalation promotes greater deposition in larger central airways. Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed.
Spacer or valved holding chamber (VHC)	≥4 years old <4 years old VHC with face mask	Slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold immediately following actuation. Actuate only once into spacer/VHC per inhalation. If face mask is used, it should have a tight fit and allow 3–5 inhalations per actuation. Rinse plastic VHCs once a month with low concentration of liquid household dishwashing detergent (1:5,000 or 1–2 drops per cup of water) and let drip dry.	Indicated for patients who have difficulty performing adequate MDI technique. May be bulky. Simple tubes do not obviate coordinating actuation and inhalation. The VHCs are preferred. Face mask allows MDIs to be used with small children. However, use of a face mask reduces delivery to lungs by 50 percent. The VHC improves lung delivery and response in patients who have poor MDI technique. The effect of a spacer or VHC on output from an MDI depends on both the MDI and device type; thus data from one combination should not be extrapolated to all others. Spacers and/or VHCs decrease oropharyngeal deposition and thus decrease risk of topical side effects (e.g., thrush). Spacers will also reduce the potential systemic availability of ICSs with higher oral absorption. However, spacer/VHCs may increase systemic availability of ICSs that are poorly absorbed orally by enhancing delivery to lungs. No clinical data are available on use of spacers or VHCs with ultrafine-particle-generated HFA MDIs. Use anti-static VHCs or rinse plastic non-anti-static VHCs with dilute household detergents to enhance delivery to lungs and efficacy. This effect is less pronounced for albuterol MDIs with HFA propellant than for albuterol MDIs with CFC propellant. As effective as nebulizer for delivering SABAs and anticholinergics in mild- to moderate-exacerbations; data in severe exacerbations are limited.

FIGURE 10. AEROSOL DELIVERY DEVICES (continued)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Nebulizer Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	Patients of any age who cannot use MDI with VHC and face mask.	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece. Using the "blow by" technique (i.e., holding the mask or open tube near the infant's nose and mouth) is not appropriate.	Less dependent on patient's coordination and cooperation. Delivery method of choice for cromolyn sodium in young children. May be expensive; time consuming; bulky; output is dependent on device and operating parameters (fill volume, driving gas flow); internebulizer and intranebulizer output variances are significant. Use of a face mask reduces delivery to lungs by 50 percent. Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in the ED for mild to moderate exacerbations; data in severe exacerbations are limited. Choice of delivery system is dependent on resources, availability, and clinical judgment of the clinician caring for the patient. Potential for bacterial infections if not cleaned properly.

Key: ED, emergency department; SABAs, inhaled short-acting beta$_2$-agonists

*See figures in component 2—Education for a Partnership in Asthma Care for description of MDI and DPI techniques.

Figure 12, "Assessing Asthma Control and Adjusting Therapy in Children"

Figure 13, "Stepwise Approach for Managing Asthma Long Term in Children, 0–4 Years of Age and 5–11 Years of Age"

For adults, see:

Figure 14, "Classifying Asthma Severity and Initiating Treatment in Youths 12 Years of Age and Adults"

Figure 15, "Assessing Asthma Control and Adjusting Therapy in Youths ≥ 12 Years of Age and Adults"

Figure 16, "Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults"

For medication dosages, see:

Figure 17, "Usual Dosages for Long-Term Control Medications"

Figure 18, "Estimated Comparative Daily Dosages for Inhaled Corticosteroids"

Figure 19, "Usual Dosages for Quick-Relief Medications"

- The stepwise approach incorporates all four components of care: assessment of severity to initiate therapy or assessment of control to monitor and adjust therapy; patient education; environmental control measures, and management of comorbid conditions at every step; and selection of medication.
- The type, amount, and scheduling of medication is determined by the level of asthma severity or asthma control.
  - — Therapy is increased (stepped up) as necessary and decreased (stepped down) when possible.
  - — Because asthma is a chronic inflammatory disorder, persistent asthma is most effectively controlled with daily long-term control medication directed toward suppressing inflammation. ICSs are the most consistently effective anti-inflammatory therapy for all age groups, at all steps of care for persistent asthma.
  - — Selection among alternative treatment options is based on consideration of treatment effectiveness for the domain of particular relevance to the patient (impairment, risk, or both), the individual patient's history of previous response to therapies (sensitivity and responsiveness to different asthma medications can vary among patients), and the willingness and ability of the patient and family to use the medication.
- Once asthma control is achieved, monitoring and followup are essential, because asthma often varies over time. A step up in therapy may be needed, or a step down may be possible, to identify the minimum medication necessary to maintain control.

The stepwise approach and recommended treatments are meant to assist, not replace, the clinical decisionmaking necessary to determine the most appropriate treatment to meet the individual patient's needs and circumstances.

Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma, if the patient required >2 bursts of oral systemic corticosteriods in 1 year or has an exacerbation requiring hospitalization, if step 4 care or higher is required (step 3 care or higher for children 0–4 years of age), if immunotherapy or omalizumab is considered, or if additional testing is indicated.

To achieve control of asthma, the following sequence of activities is recommended:

- For patients who are not already taking long-term control medications, assess asthma severity and initiate therapy according to the level of severity.
- For patients who are already taking long-term control medications, assess asthma control and step up therapy if the patient's asthma is not well controlled on current therapy. Before stepping up, review the patient's adherence to medications, inhaler technique, and environmental control measures.
- Evaluate asthma control in 2–6 weeks (depending on level of initial severity or control).
  - — In general, classify the level of asthma control by the most severe indicator of impairment or risk.
  - — The risk domain is usually more strongly associated with morbidity in young children than the impairment domain because young children are often symptom free between exacerbations.
  - — If office spirometry suggests worse control than other measures of impairment, consider fixed obstruction and reassess the other measures. If fixed obstruction does not explain the lack of control, step up therapy, because low FEV_1 is a predictor of exacerbations.
  - — If the history of exacerbations suggests poorer control than does assessment of impairment, reassess impairment measures, and consider a step up in therapy. Review plans for handling exacerbations and include the use of oral systemic corticosteroids, especially for patients who have a history of severe exacerbations.
- If asthma control is not achieved with the above actions:
  - — Review the patient's adherence to medications, inhaler technique, environmental control measures (or whether there are new exposures), and management of comorbid conditions.
  - — If adherence and environment control measures are adequate, then step up one step (if not well controlled) or two steps (if very poorly controlled).
  - — If an alternative treatment was used initially, discontinue its use and use the preferred treatment option before stepping up therapy.
  - — A short course of oral systemic corticosteroids may be considered to gain more rapid control for patients whose asthma frequently interrupts sleep or normal daily activities or who are experiencing an exacerbation at the time of assessment.
  - — If lack of control persists, consider alternative diagnoses before stepping up further.
  - — If the patient experiences side effects, consider different treatment options.

To maintain control of asthma, regular followup contact is essential because asthma often varies over time.

- Schedule patient contact at 1- to 6-month intervals; the interval will depend on such factors as the level or duration of asthma control and the level of treatment required.
- Consider a step down in therapy once asthma is well controlled for at least 3 months. A step down is necessary to identify the minimum therapy required to maintain good control. A reduction in therapy should be gradual and must be closely monitored. Studies are limited in guiding therapy reduction. In general, the dose of ICS may be reduced 25 percent to 50 percent every 3 months to the lowest possible dose.
- Consider seasonal periods of daily long-term control therapy for patients who have asthma

symptoms only in relation to certain seasons (e.g., seasonal pollens, allergens, or viral respiratory infections) and who have intermittent asthma the rest of the year. This approach has not been rigorously evaluated; close monitoring for 2–6 weeks after therapy is discontinued is essential to assure sustained asthma control.

Stepwise Treatment Recommendations for Different Ages

Recommendations for treatments in the different steps are presented in three different age groups (0–4 years, 5–11 years, and 12 years and older) because the course of the disease may change over time, the relevance of measures of impairment or risk and the potential short- and long-term impact of medications may be age related, and varied levels of scientific evidence are available for the different ages.

Steps for Children 0–4 Years of Age

See figure 13, for recommended treatments in the different steps and figures 17–19 for recommended medication dosages. In addition to the general principles of the stepwise approach, special considerations for this age group include initiating therapy, selecting among treatment options, and monitoring response to therapy.

The initiation of daily long-term control therapy in children ages 0–4 years is recommended as follows:

- It is recommended for reducing impairment and risk of exacerbations in infants and young children who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have a positive asthma predictive index (either (1) one of the following: a parental history of asthma, a physician's diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens; OR (2) two of the following: evidence of sensitization to foods, >4 percent peripheral blood eosinophilia, or wheezing apart from colds).
- It should be considered for reducing impairment in infants and young children who consistently require symptomatic treatment >2 days per week for a period of more than 4 weeks.
- It should be considered for reducing risk in infants and young children who have two exacerbations requiring systemic corticosteroids within 6 months.
- It may be considered for use only during periods, or seasons, of previously documented risk (e.g., during seasons of viral respiratory infections).

The decision about when to start long-term daily therapy is difficult. The chronic airway inflammatory response in asthma can develop in the preschool years; for example, between 50–80 percent of children who have asthma developed symptoms before their fifth birthday. Adequate treatment will reduce the burden of illness, and underdiagnosis and undertreatment are key problems in this age group. Not all wheeze and cough are caused by asthma, however, and caution is needed to avoid giving inappropriate, prolonged therapy.

Initiating long-term control therapy will depend on consideration of issues regarding diagnosis and prognosis.

- — Viral respiratory infections are the most common cause of asthma symptoms in this age group, and many children who wheeze with respiratory infections respond well to asthma therapy even though the diagnosis of asthma is not clearly established. For children who have exacerbations with viral infections, exacerbations are often severe (requiring emergency care or hospitalization), yet the child has no significant symptoms in between these exacerbations. These children have a low level of impairment but a high level of risk.
- — Most young children who wheeze with viral respiratory infection experience a remission of symptoms by 6 years of age, perhaps due to growing airway size.
- — However, two-thirds of children who have frequent wheezing AND also have a positive asthma predictive index (see above) are likely to have asthma throughout childhood. Early identification of these children allows appropriate treatment with environmental control measures and medication to reduce morbidity.

Select medications with the following considerations for young children:

- Asthma treatment for young children, especially infants, has not been studied adequately. Most recommendations are based on limited data and extrapolations from studies in older children and adults. Preferred treatment options are based on

individual drug efficacy studies in this age group; comparator trials are not available.

- The following long-term control medications are FDA approved for the following ages in young children: ICS budesonide nebulizer solution (1–8 years of age); ICS fluticasone dry power inhaler (DPI) (>4 years of age); LABA salmeterol DPI, alone or in combination with ICS (>4 years of age); LTRA montelukast (chewable tablets, 2–6 years of age; granules, down to 1 year old).
- Several delivery devices are available, and the doses received may vary considerably among devices and age groups. In general, children <4 years of age will have less difficulty with a face mask and either (1) a nebulizer or (2) an MDI with a VHC. (See figure 10 above.)
- ICSs are the preferred long-term control medication for initiating therapy. The benefits of ICSs out weigh any concerns about potential risks of a small, nonprogressive reduction in growth velocity or other possible adverse effects. ICSs, as with all medications, should be titrated to as low a dose as needed to maintain control.
- For children whose asthma is not well controlled on low-dose ICS, few studies are available on stepup therapy in this age group, and the studies have mixed findings. Some data on children ≤4 years old and younger show dose-dependent improvements in the domains of impairment and risk of exacerbation from taking ICS. Data from studies on LABA combined with ICS have only small numbers of 4-year-old children, and these data show improvement in the impairment but not risk domain. Adding a noncorticosteroid long-term control medication to medium-dose ICS may be considered before increasing the dose of ICS to high dose to avoid potential risk of side effects with high doses of medication.

Monitor response to therapy closely, because treatment of young children is often in the form of a therapeutic trial.

- **If a clear and beneficial response is not obvious within 4–6 weeks and the patient's/family's medication technique and adherence are satisfactory, treatment should be stopped. Alternative therapies or alternative diagnoses should be considered.**
- **If a clear and beneficial response is sustained for at least 3 months, consider a step down to evaluate the need for continued daily long-term control therapy.** Children in this age group have high rates of spontaneous remission of symptoms.

Steps for Children 5–11 Years of Age

See figure 13, "Stepwise Approach for Managing Asthma Long Term in Children, 0–4 Years of Age and 5–11 Years of Age," for recommended treatments in different steps and figures 17, 18, and 19 for recommended medication dosages. Special considerations for this age group include the following:

Promote active participation in physical activities, exercise, and sports because physical activity is an essential part of a child's life. Treatment immediately before vigorous activity usually prevents EIB (see section on "Exercise-Induced Bronchospasm"). However, if the child has poor endurance or has symptoms during usual play activities, a step up in therapy is warranted.

Directly involve children ≥10 years of age (and younger children as appropriate) in developing their written asthma action plans and reviewing their adherence. This involvement may help address developmental issues of emerging independence by building the children's confidence, increasing personal responsibility, and gaining problem-solving skills.

Encourage parents to take a copy of the written asthma action plan to the student's school, or childcare or extended care setting, or camp.

Consider the following when selecting treatment options:

- ICSs are the preferred long-term control therapy. The benefits of ICSs outweigh any concerns about potential risks of a small, nonprogressive reduction in growth velocity or other possible adverse effects. ICSs, as with all medications, should be titrated to as low a dose as needed to maintain control. High-quality evidence demonstrates the effectiveness of ICS in children 5–11 years of age, and comparator studies demonstrate improved control with ICS on a range of asthma outcomes compared to other long-term control medications.
- Step up treatment options for children whose asthma is not well controlled on low-dose ICS have not been adequately studied or compared in this age group. The selection will depend on the domain

SAMPLE RECORD FOR MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY

Patient name: **Date**							
Long-term control medication							
ICS daily dose*							
LTRA							
LABA							
Theophylline							
Other							
Significant exacerbations							
Exacerbations (number/month)							
Oral systemic corticosteroids (number/year)*							
Hospitalization (number/year)							
Long-term control medication							
Prebronchodilator FEV_1/FVC							
Prebronchodilator FEV_1 percent predicted							
Postbronchodilator FEV_1 percent predicted							
Percent bronchodilator reversibility							
Potential risk of adverse corticosteroid effects (as indicated by corticosteroid dose and duration of treatment)							
Height, cm							
Percentile Plots of growth velocity							

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$ agonist; LTRA, leukotriene receptor antagonist

*Consider ophthalmologic exam and bone density measurement in children using high doses of ICS or multiple courses of oral corticosteroids.

of particular relevance (impairment, risk, or both) and clinician–patient preference.

— For the impairment domain:

- Children who have low lung function and >2 days per week impairment may be better served by adding a LABA to a low dose of ICS (based on studies in older children and adults).
- Increasing the dose of ICS to medium dose can improve symptoms and lung function in those children who have greater levels of impairment (based on studies in children).
- One study in children suggests some benefit in the impairment domain with adding LTRA.

— For the risk domain:

- Studies have not demonstrated that adding LABA or LTRA reduces exacerbations in children. Adding LABA has the potential risk of rare life-threatening or fatal exacerbations.
- Studies in older children and adults show that increasing the dose of ICS can reduce the risk of exacerbations, but this may require up to a four-fold increase in the dose. This dose may increase the potential risk of systemic effects, although the risk is small within the medium-dose range.

- The need for step 4 care usually involves children who have a low level of lung function contributing to their impairment. The combination of ICS and LABA is preferred, on the basis of studies in older children and adults.
- Before maintenance dose of oral corticosteroids is initiated in step 6, consider a 2-week course of oral corticosteroids to confirm clinical reversibility, measured by spirometry, and the possibility of an effective response to therapy. If the response is poor, a careful review for other pulmonary conditions or comorbid conditions should be conducted to ensure that the primary diagnosis is severe asthma.

Monitor asthma progression. Declines in lung function or repeated periods of worsening asthma impairment may indicate a progressive worsening of the underlying severity of asthma. Although there is no indication that treatment alters the progression of the underlying disease in children, adjustments in treatment may be necessary to maintain asthma control.

Steps for Youths 12 Years of Age and Adults

See figure 16, "Stepwise Approach for Managing Asthma in Youths 12 Years of Age and Adults," for recommended treatment options in different steps and figures 18 and 19, for recommended medication dosages for youths 12 years of age and adults.

Special considerations for this age group include the following:

For youths:

- Involve adolescents in the development of their written asthma action plans and reviewing their adherence.
- Encourage students to take a copy of their plan to school, after school programs, and camps.
- Encourage adolescents to be physically active.

For older adults:

- Consider a short course of oral systemic corticosteroids to establish reversibility and the extent of possible benefit from asthma treatment. Chronic bronchitis and emphysema may coexist with asthma.
- Adjust medications as necessary to address coexisting medical conditions. For example, consider calcium and vitamin D supplements for patients who take ICS and have risk factors for osteoporosis. Consider increased sensitivity to side effects of bronchodilators, especially tremor and tachycardia with increasing age, and increased possibilities for drug interactions with theophylline. Consider also that NSAIDs prescribed for arthritis and the beta-blockers prescribed for hypertension or glaucoma may exacerbate asthma.
- Review the patient's technique and adherence in using medications, and make necessary adjustments. Physical or cognitive impairments may make proper technique difficult.

Consider the following when selecting treatment options:

- Recommended treatment for step 3 weighs the high-quality evidence demonstrating the benefits of adding LABA to low-dose ICS against the potential risk of rare life-threatening or fatal exacerbations with the use of LABA. The selection will depend on the domain of particular relevance (impairment, risk, or both) and clinician–patient preference.

- — Adding LABA more consistently results in improvements in the impairment domain compared to increasing the dose of ICS.
- — If the risk domain is of particular concern, then a balance of potential risks needs to be considered.
  - Adding LABA to low-dose ICS reduces the frequency of exacerbations to a greater extent than doubling the dose of ICS, but adding LABA has the potential risk of rare life-threatening or fatal exacerbations.
  - Increasing the dose of ICS can significantly reduce the risk of exacerbations, but this benefit may require up to a fourfold increase in the ICS dose. This dose may increase the potential risk of systemic effects, although the risk is small within the medium-dose range.

- Comparator studies demonstrate significantly greater improvements with adding LABA to ICS compared to other adjunctive therapies.
- Clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each omalizumab injection (the optimal length of the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency self treatment, and seeking immediate medical care).

Managing Special Situations

Patients who have asthma may encounter situations that will require adjustments to their asthma management to keep their asthma under control, such as EIB, pregnancy, and surgery.

Exercise-Induced Bronchospasm

EIB should be anticipated in all asthma patients. A history of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercises suggests EIB. An exercise challenge, in which a 15 percent decrease in PEF or FEV_1 (measured before and after exercise at 5-minute intervals for 20–30 minutes) will establish the diagnosis.

An important dimension of adequate asthma control is a patient's ability to participate in any activity he or she chooses without experiencing asthma symptoms. EIB should not limit either participation or success in vigorous activities.

Recommended treatments for EIB include:

- **Long-term control therapy, if appropriate.** Frequent or severe EIB may indicate the need to initiate or step up long-term control medications.
- **Pretreatment before exercise:**
  - — Inhaled $beta_2$-agonists will prevent EIB for more than 80 percent of patients. SABA used shortly before exercise may be helpful for 2–3 hours. LABA can be protective up to 12 hours, but there is some shortening of the duration of protection when LABA is used on a daily basis. Frequent or chronic use of LABA as pretreatment for EIB is discouraged, as it may disguise poorly controlled persistent asthma.
  - — LTRAs, with an onset of action generally hours after administration, can attenuate EIB in up to 50 percent of patients.
  - — Cromolyn or nedocromil taken shortly before exercise is an alternative treatment, but it is not as effective as SABAs.
  - — A warmup period before exercise may reduce the degree of EIB.
  - — A mask or scarf over the mouth may attenuate cold-induced EIB.

Pregnancy

Maintaining asthma control during pregnancy is important for the health and well-being of both the mother and her baby. Maintaining lung function is important to ensure oxygen supply to the fetus. Uncontrolled asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants. It is safer for pregnant women to be treated with asthma medications than to have asthma symptoms and exacerbations.

- **Monitor the level of asthma control and lung function during prenatal visits.** The course of asthma improves in one-third of women and worsens for one-third of women during pregnancy. Monthly evaluations of asthma will allow the opportunity to step up therapy if necessary and to step down therapy if possible.

- **Albuterol is the preferred SABA.** The most data related to safety during human pregnancy are available for abuterol.
- **ICSs are the preferred long-term control medication. Budesonide is the preferred ICS** because more data are available on using budesonide in pregnant women than are available on other ICSs, and the data are reassuring. However, no data indicate that the other ICS preparations are unsafe during pregnancy.

Surgery

Patients who have asthma are at risk for complications during and after surgery. These complications include acute bronchoconstriction triggered by intubation, hypoxemia and possible hypercapnia, impaired effectiveness of cough, atelectasis, and respiratory infection, and, if a history of sensitivity is present, reactions to latex exposure or some anesthetic agents.

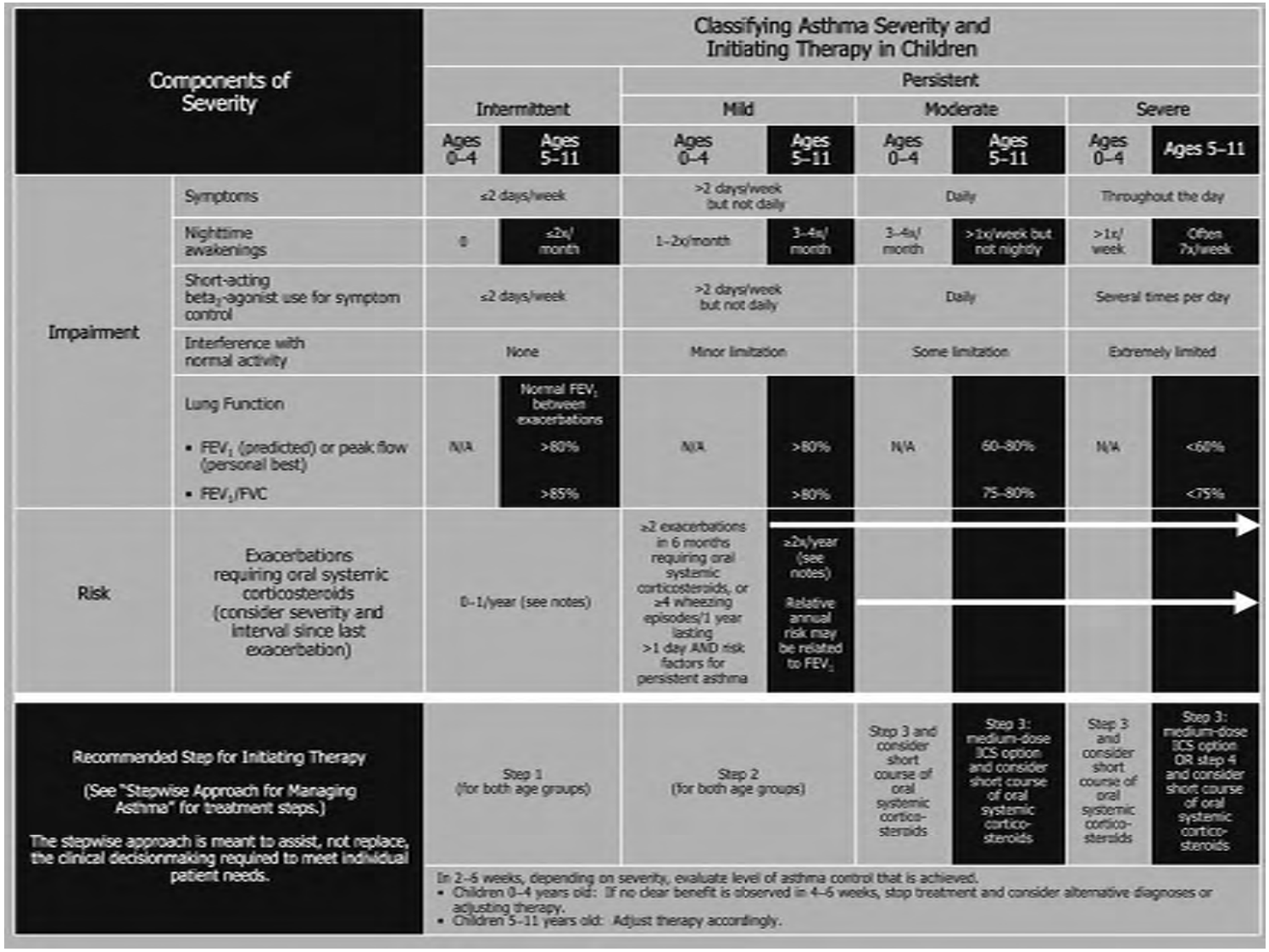
The following actions are recommended to reduce the risk of complications during surgery:

- Before surgery, review the level of asthma control, medication use (especially oral systemic corticosteroids within the past 6 months), and pulmonary function.
- Provide medications before surgery to improve lung function if lung function is not well controlled. A short course of oral systemic corti costeroids may be necessary.
- For patients receiving oral systemic corticosteroids during the 6 months prior to surgery and for selected patients on long-term high-dose ICS, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period, and reduce the dose rapidly within 24 hours after surgery.

Disparities

Multiple factors contribute to the higher rates of poorly controlled asthma and asthma deaths among Blacks and Latinos compared to Whites. These factors include socioeconomic disparities in access to quality medical care, underprescription and underutilization of long-term control medication, cultural beliefs and practices about asthma management, and perhaps biological and pathophysiological differences that affect the underlying severity of asthma and response to treatment. **Heightened awareness of disparities and cultural barriers, improving access to quality care, and improving communication strategies between clinicians and ethnic or racial minority patients regarding use of asthma medications may improve asthma outcomes.**

FIGURE 11. CLASSIFYING ASTHMA SEVERITY AND INITIATING THERAPY IN CHILDREN

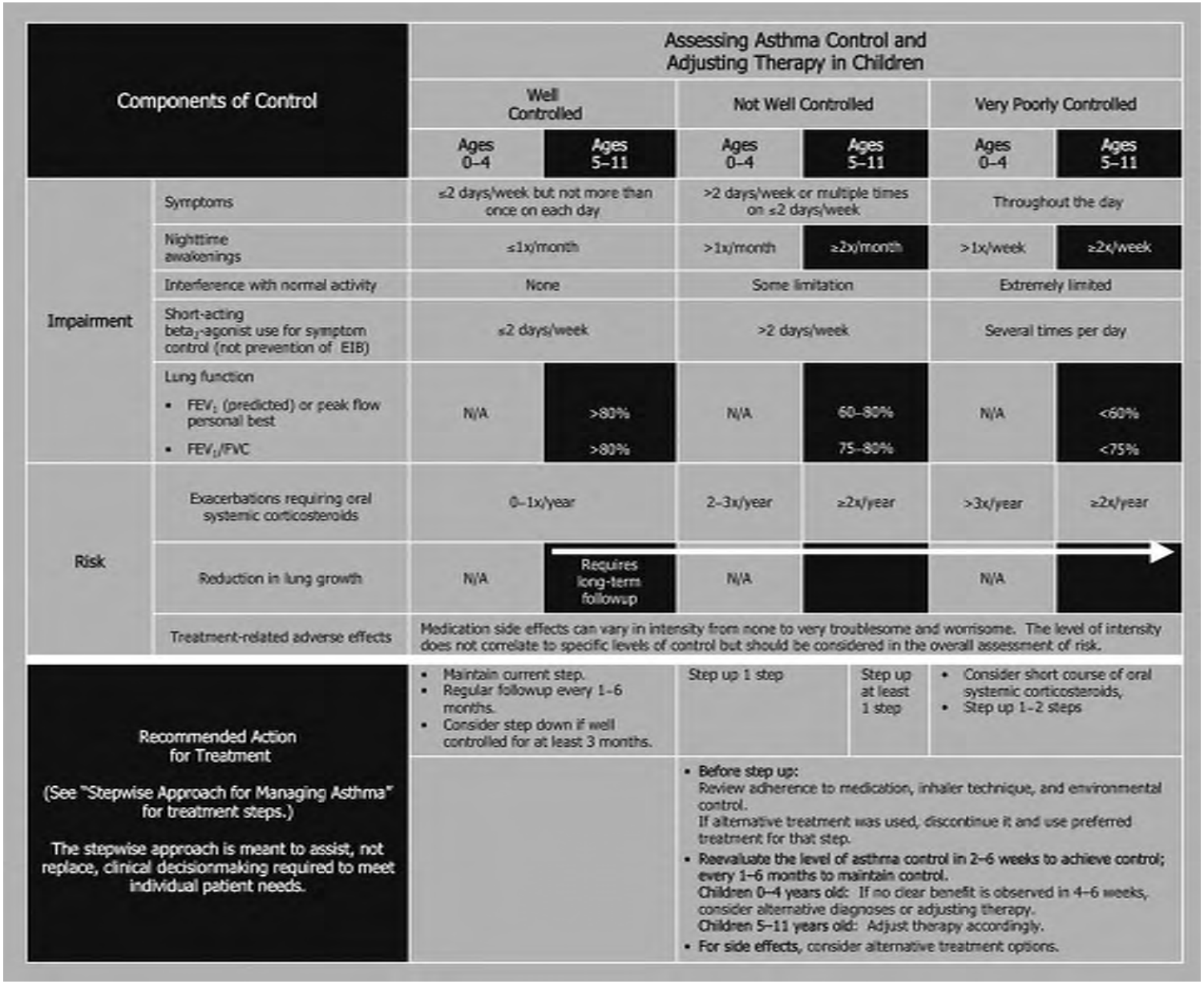


Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit; N/A, not applicable

Notes:

- Level of severity is determined by both impairment and risk. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Assign severity to the most severe category in which any feature occurs.
- Frequency and severity of exacerbations may fluctuate over time for patients in any severity category. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and severe exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients with ≥2 exacerbations described above may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 12. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN



Key: EIB, exercise-induced bronchospasm, FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; N/A, not applicable

Notes:

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's or caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment, such as whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control.

FIGURE 13. STEPWISE APPROACH FOR MANAGING ASTHMA LONG TERM IN CHILDREN, 0–4 YEARS OF AGE AND 5–11 YEARS OF AGE

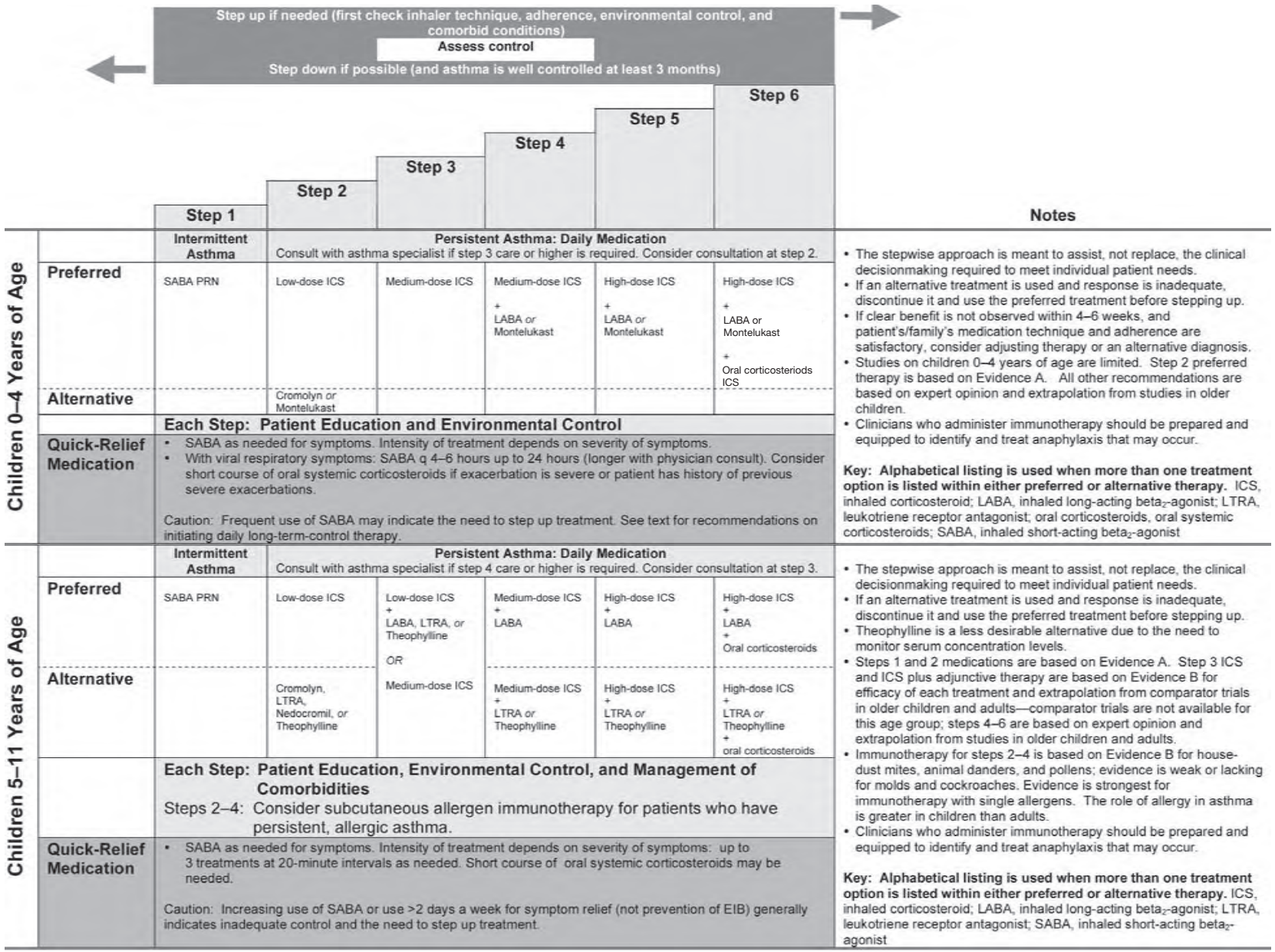


FIGURE 14. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS 12 YEARS OF AGE AND ADULTS

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		Step 1	Step 2	Step 3	Step 4 or 5
				and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm, FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 15. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		• Maintain current step. • Regular followup at every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step. • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids. • Step up 1–2 steps. • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.
Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

Notes:

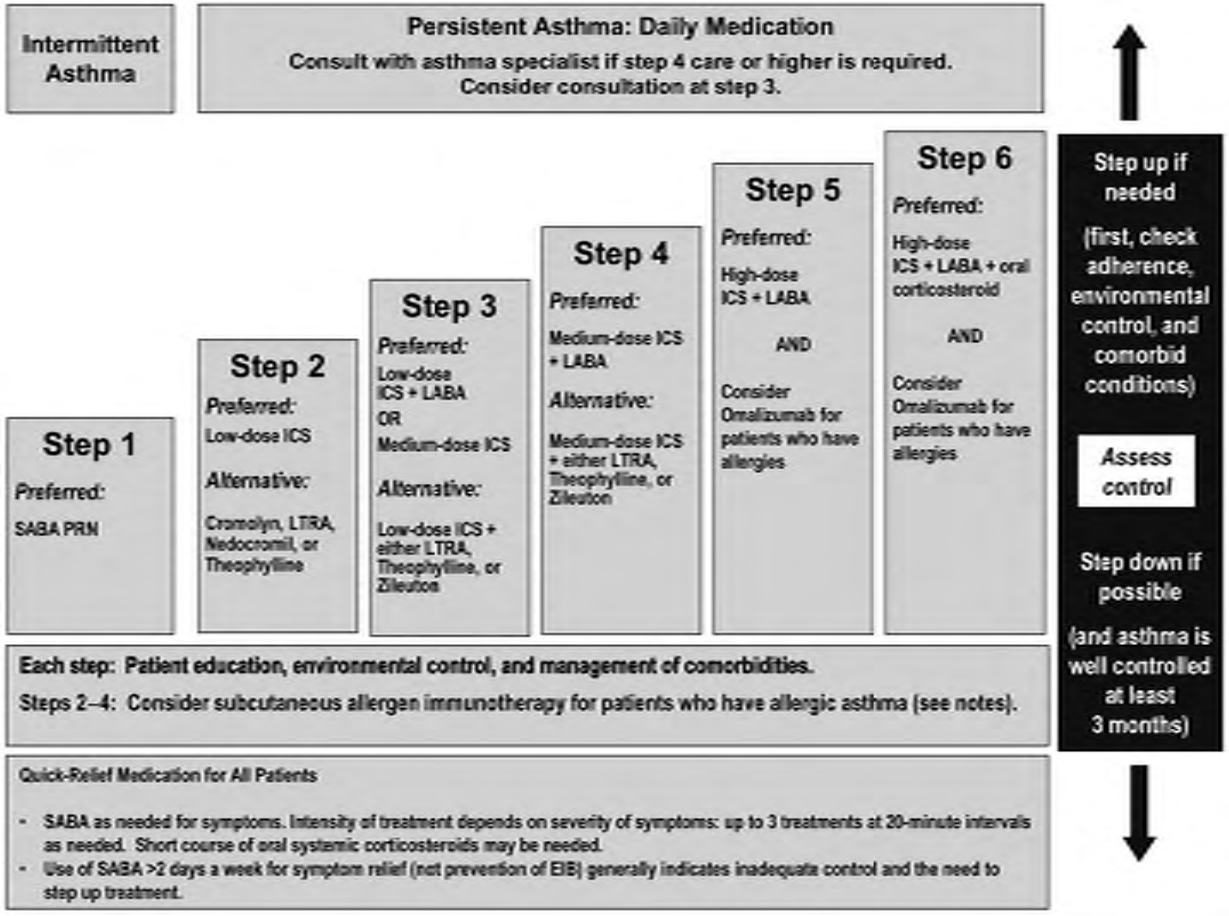
- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
  ATAQ = Asthma Therapy Assessment Questionnaire©
  ACQ = Asthma Control Questionnaire©
  ACT = Asthma Control Test™
  Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.

Before step up in therapy:

— Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.

— If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

FIGURE 16. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 17. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS*

Medication	0–4 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Inhaled Corticosteroids (See Figure 18, "Estimated Comparative Daily Dosages for ICSs.")					
Oral Systemic Corticosteroids					**(Apply to all three corticosteriods.)**
Methylprednisolone 2, 4, 8, 16, 32 mg tablets Prednisolone 5 mg tablets, 5 mg/5 cc, 15 mg/5 cc Prednisone 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	7.5–60 mg daily in a single dose in a.m. or qod as needed for control Short-course "burst": to achieve control, 40–60 mg per day as single or 2 divided doses for 3–10 days	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and Strongyloides	■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse. ■ Children receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects, and it appears to be equally efficacious. ■ For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression.
Inhaled Long-Acting Beta$_2$-Agonists (LABAs)					**(Apply to both LABAs.)**
Salmeterol DPI 50 mcg/blister Formoterol DPI 12 mcg/single-use capsule	NA NA	1 blister q 12 hours 1 capsule q 12 hours	1 blister q 12 hours 1 capsule q 12 hours	■ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose. ■ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ■ Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.	■ **Should not be used for acute symptom relief or exacerbations. Use only with ICSs.** ■ Decreased duration of protection against EIB may occur with redgular use. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated. ■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours. ■ Capsules should be used only with the inhaler and should not be taken orally.

Key: DPI, dry powder inhaler; EIB, exercise-induced broncospasm; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta$_2$-agonist

***Note:** Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

FIGURE 17. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS* (continued)

Medication	0–4 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Combined Medication					
Fluticasone/Salmeterol DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/ 50 mcg HFA 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	NA	1 inhalation bid, dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control	■ See notes for ICS and LABA.	■ There have been no clinical trials in children <4 years of age. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated. ■ 100/50 DPI or 45/21 HFA for patients who have asthma not controlled on low- to medium-dose ICS ■ 250/50 DPI or 115/21 HFA for patients who have asthma not controlled on medium to high dose ICS.
Budesonide/ Formoterol HFA MDI 80 mcg/4.5 mcg 160mcg/4.5 mcg	NA	2 puffs bid, dose depends on level of severity or control	2 puffs bid; dose depends on level of severity or control	■ See notes for ICS and LABA.	■ There have been no clinical trials in children <4 years of age. ■ Currently approved for use in youths ≥12 years of age. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics. ■ 80/4.5 for patients who have asthma not controlled on low- to medium-dose ICS. ■ 160/4.5 for patients who have asthma not controlled on medium- to high-dose ICS.
Cromolyn/Nedocromil					
Cromolyn MDI 0.8 mg/puff	NA	2 puffs qid	2 puffs qid	■ Cough and irritation. ■ 15–20 percent of patients complain of an unpleasant taste from nedocromil.	■ One dose of cromolyn before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled $beta_2$-agonists for EIB as SABA.
Nebulizer 20 mg/ampule	1 ampule qid NA <2 years of age	1 ampule qid	1 ampule qid	■ Safety is the primary advantage of these	■ 4- to 6-week trial of cromolyn or nedocromil may be needed to determine maximum benefit. ■ Dose by MDI may be inadequate to affect hyperresponsiveness. ■ Once control is achieved, the frequency of dosing may be reduced.
Nedocromil MDI 1.75 mg/puff	NA <6 years of age	2 puffs qid	2 puffs qid		

FIGURE 17. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS* (continued)

Medication	0–4 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Immunomodulators					
Omalizumab (Anti IgE) Subcutaneous injection, 150 mg/ 1.2 mL following reconstitution with 1.4 mL sterile water for injection	NA	NA	150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level	■ Pain and bruising of injection sites in 5–20 percent of patients. ■ Anaphylaxis has been reported in 0.2% of treated patients. ■ Malignant neoplasms were reported in 0.5 percent of patients compared to 0.2 percent receiving placebo; relationship to drug is unclear.	■ Do not administer more than 150 mg per injection site. ■ Monitor patients following injections; be prepared and equipped to identify and treat anaphylaxis that may occur. ■ Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.
Leukotriene Modifiers					
Leukotriene Receptor Antagonists (LTRAs)					
Montelukast 4 mg or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1–5 years of age)	5 mg qhs (6–14 years of age)	10 mg qhs	■ No specific adverse effects have been identified. ■ Rare cases of Churg-Strauss have occurred, but the association is unclear.	■ Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults. ■ No more efficacious than placebo in infants ages 6–24 months. ■ As long-term therapy may attenuate exercise-induced bronchospasm in some patients, but less effective than ICS therapy.
Zafirlukast 10 mg tablet 20 mg tablet	NA	10 mg bid (7–11 years of age)	40 mg daily (20 mg tablet bid)	■ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Zarfirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly. ■ Monitor hepatic enzymes (ALT). Warn patients to discontinue use if they experience signs and symptoms of liver dysfunction.
5-Lipoxygenase Inhibitor Zileuton 600 mg tablet	NA	NA	2,400 mg daily (give tablets qid)	■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	■ For zileuton, monitor hepatic enzymes (ALT). ■ Zileuton is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.
Methylxanthines					
Theophylline Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual maximum: ■ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥1 year of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum: 800 mg/day	■ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ■ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.	■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential. ■ Patients should be told to discontinue if they experience toxicity. ■ Various factors (diet, food, febrile illness, age, smoking, and other medications) can affect serum concentrations. See EPR—3 Full Report 2007 and package inserts for details.

FIGURE 18. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS

Drug	Low Daily Dose			Medium Daily Dose			High Daily Dose		
	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults
Beclomethasone HFA 40 or 80 mcg/puff	NA	80–160 mcg	80–240 mcg	NA	>160–320 mcg	>240–480 mcg	NA	>320 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	NA	180–400 mcg	180–600 mcg	NA	>400–800 mcg	>600–1,200 mcg	NA	>800 mcg	>1,200 mcg
Budesonide Inhaled Inhalation suspension for nebulization	0.25–0.5 mg	0.5 mg	NA	>0.5–1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide 250 mcg/puff	NA	500–750 mcg	500–1,000 mcg	NA	1,000–1,250 mcg	>1,000–2,000 mcg	NA	>1,250 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	NA	160 mcg	320 mcg	NA	320 mcg	>320–640 mcg	NA	≥640 mcg	>640 mcg
Fluticasone **HFA/MDI:** 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	88–264 mcg	>176–352 mcg	>176–352 mcg	>264–440 mcg	>352 mcg	>352 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	100–300 mcg	NA	>200–400 mcg	>300–500 mcg	NA	>400 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	NA	NA	200 mcg	NA	NA	400 mcg	NA	NA	>400 mcg
Triamcinolone acetonide 75 mcg/puff	NA	300–600 mcg	300–750 mcg	NA	>600–900 mcg	>750–1,500 mcg	NA	>900 mcg	>1,500 mcg

Key: DPI, dry power inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group)

Therapeutic Issues:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. Once control of asthma is achieved, the dose should be carefully titrated to the minimum dose required to maintain control.
- Preparations are not interchangeable on a mcg or per puff basis. This figure presents estimated comparable daily doses. See EPR—3 Full Report 2007 for full discussion.
- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only inhaled corticosteroid (ICS) with FDA-approved labeling for children <4 years of age.
- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions. For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years of age is higher than for children 5–11 years of age due to lower dose delivered with face mask and data on efficacy in young children.

Potential Adverse Effects of Inhaled Corticosteroids:

- Cough, dysphonia, oral thrush (candidiasis).
- Spacer or valved holding chamber with non-breath-actuated MDIs and mouthwashing and spitting after inhalation decrease local side effects.
- A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.
- In high doses, systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.

FIGURE 19. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS*

Medication	<5 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Inhaled Short-Acting Beta$_2$-Agonists					
	Dose applies to Albuterol.	***Dose applies to Albuterol/and Levalbuterol.***	***Dose applies to all four SABAs***		***Apply to all four (SABAs)***
MDI					
Albuterol CFC 90 mcg/puff, 200 puffs/canister	1–2 puffs 5 minutes before exercise	2 puffs 5 minutes before exercise	2 puffs 5 minutes before exercise	■ Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	■ Drugs of choice for acute bronchospasm. ■ Differences in potencies exist, but all products are essentially comparable on a puff per puff basis. ■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy. ■ May double usual dose for mild exacerbations. ■ For levalbuterol, prime the inhaler by releasing 4 actuations prior to use. ■ For HFA: periodically clean HFA actuator, as drug may plug orifice. ■ For autohaler: children <4 years of age may not generate sufficient inspiratory flow to activate an auto-inhaler. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
Albuterol HFA 90 mcg/puff, 200 puffs/canister	2 puffs every 4–6 hours, as needed for symptoms	2 puffs every 4–6 hours, as needed for symptoms	2 puffs every 4–6 hours, as needed for symptoms		
Levalbuterol HFA 45 mcg/puff, 200 puffs/canister	NA <4 years of age				
Pirbuterol CFC Autohaler 200 mcg/puff, 400 puffs/canister	NA	NA			
Nebulizer solution					■ May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations.
Albuterol 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed	1.25–5 mg in 3 cc of saline q 4–8 hours, as needed	1.25–5 mg in 3 cc of saline q 4–8 hours, as needed	(Same as with MDI)	■ Does not have FDA-approved labeling for children <6 years of age. ■ Compatible with budesonide inhalant suspension. The product is a sterile-filled preservative-free unit dose vial.
Levalbuterol (R-albuterol) 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.31–1.25 mg in 3 cc q 4–6 hours, as needed for symptoms	0.31–0.63 mg, q 8 hours, as needed for symptoms	0.63 mg–1.25 mg q 8 hours, as needed for symptoms	(Same as with MDI)	

Key: CFC, chlorofluorocarbon; ED, emergency department; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); PEF, peak expiratory flor; SABA, short-acting beta$_2$-agonist

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration (FDA) or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

FIGURE 19. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS* (continued)

Medication	<5 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Anticholinergics					
Ipratropium HFA					
MDI					
17 mcg/puff, 200 puffs/canister	NA	NA	2–3 puffs q 6 hours	■ Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the ED, produces less cardiac stimulation than SABAs.	■ Multiple doses in the emergency department (not hospital) setting provide additive benefit to SABA. ■ Treatment of choice for bronchospasm due to beta-blocker medication. ■ Does not block EIB. ■ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. ■ May be an alternative for patients who do not tolerate SABA. ■ Has not proven to be efficacious as long-term control therapy for asthma.
Nebulizer solution					
0.25 mg/mL (0.025%)	NA	NA	0.25 mg q 6 hours		
Ipratropium with albuterol					
MDI					
18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol 200 puffs/canister	NA	NA	2–3 puffs q 6 hours		
Nebulizer solution					
0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	NA	NA	3 mL q 4–6 hours		■ Contains EDTA to prevent discoloration of the solution. This additive does not induce bronchospasm.
Systemic Corticosteroids					
Methylprednisolone 2, 4, 6, 8, 16, 32 mg tablets Prednisolone 5 mg tablets, 5 mg/5 cc, 15 mg/5 cc Prednisone 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc	***Dosages apply to first three corticosteroids.*** Short course "burst:" 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	Short course "burst": 1-2 mg/kg/day maximum 60 mg/day for 3–10 days	Short course "burst": 40–60 mg/day as single or 2 divided doses for 3–10 days	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides*.	***(Applies to the first three corticosteroids.)*** ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. Action may begin within an hour. ■ The burst should be continued until patient achieves 80 percent PEF personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse in asthma exacerbations. ■ Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone.

FIGURE 19. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS* (continued)

Medication	<5 Years of Age	5–11 Years of Age	≥12 Years of Age and Adults	Potential Adverse Effects	Comments (not all inclusive)
Systemic Corticosteroids (continued)					
Repository injection (Methylprednisolone acetate) 40 mg/mL 80 mg/mL	7.5 mg/kg IM once	240 mg IM once	240 mg IM once		■ May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

Managing Exacerbations

Asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness, or some combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow; objective measures of lung function (spirometry or PEF) are more reliable indicators of severity than symptoms are. Individuals whose asthma is well controlled with ICSs have decreased risk of exacerbations. However, these patients can still be vulnerable to exacerbations, for example, when they have viral respiratory infections.

Effective management of exacerbations incorporates the same four components of asthma management used in managing asthma long term: assessment and monitoring, patient education, environmental control, and medications.

Classifying Severity

Do not underestimate the severity of an exacerbation. Severe exacerbations can be life threatening and can occur in patients at any level of asthma severity—i.e., intermittent, or mild, moderate, or severe persistent asthma. See figure 20, "Classifying Severity of Asthma Exacerbations in the Urgent or Emergency Care Setting."

Patients at high risk of asthma-related death require special attention—particularly intensive education, monitoring, and care. Such patients should be advised to seek medical care early during an exacerbation. Risk factors for asthma-related death include:

- Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
- Two or more hospitalizations or >3 ED visits in the past year
- Use of >2 canisters of SABA per month
- Difficulty perceiving airway obstruction or the severity of worsening asthma
- Low socioeconomic status or inner-city residence
- Illicit drug use
- Major psychosocial problems or psychiatric disease
- Comorbidities, such as cardiovascular disease or other chronic lung disease

Home Management

Early treatment by the patient at home is the best strategy for managing asthma exacerbations. Patients should be instructed how to:

- **Use a written asthma action plan** that notes when and how to treat signs of an exacerbation. A peak flow-based plan may be particularly useful for patients who have difficulty perceiving airflow obstruction or have a history of severe exacerbations.
- **Recognize early indicators of an exacerbation,** including worsening PEF.
- **Adjust their medications** by increasing SABA and, in some cases, adding a short course of oral systemic corticosteroids. Doubling the dose of ICSs is not effective.
- **Remove or withdraw from allergens or irritants** in the environment that may contribute to the exacerbation.
- **Monitor response to treatment and promptly communicate with the clinician about any serious deterioration** in symptoms or PEF or about decreased responsiveness to SABA treatment, including decreased duration of effect.

The following home management techniques are not recommended because no studies demonstrate their effectiveness and they may delay patients from obtaining necessary care: drinking large volumes of liquids; breathing warm, moist air; or using over-the-counter products, such as antihistamines or cold remedies. Pursed-lip and other forms of breathing may help to maintain calm, but these methods do not improve lung function.

FIGURE 20. CLASSIFYING SEVERITY OF ASTHMA EXACERBATIONS IN THE URGENT OR EMERGENCY CARE SETTING

Note: Patients are instructed to use quick-relief medications if symptoms occur or if PEF drops below 80 percent predicted or personal best. If PEF is 50–79 percent, the patient should monitor response to quick-relief medication carefully and consider contacting a clinician. If PEF is below 50 percent, immediate medical care is usually required. In the urgent or emergency care setting, the following parameters describe the severity and likely clinical course of an exacerbation.

	Symptoms and Signs	Initial PEF (or FEV1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF ≥ 70 percent predicted or personal best	■ Usually cared for at home ■ Prompt relief with inhaled SABA ■ Possible short course of oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40–69 percent predictedor personal best	■ Usually requires office or ED visit ■ Relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for 1–2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40 percent predicted or personal best	■ Usually requires ED visit and likely hospitalization ■ Partial relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun ■ Adjunctive therapies are helpful
Subset: Life threatening	Too dyspneic to speak; perspiring	PEF <25 percent predicted or personal best	■ Requires ED/hospitalization; possible ICU ■ Minimal or no relief from frequent inhaled SABA ■ Intravenous corticosteroids ■ Adjunctive therapies are helpful

Key: ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist

Management in the Urgent or Emergency Care and Hospital Settings

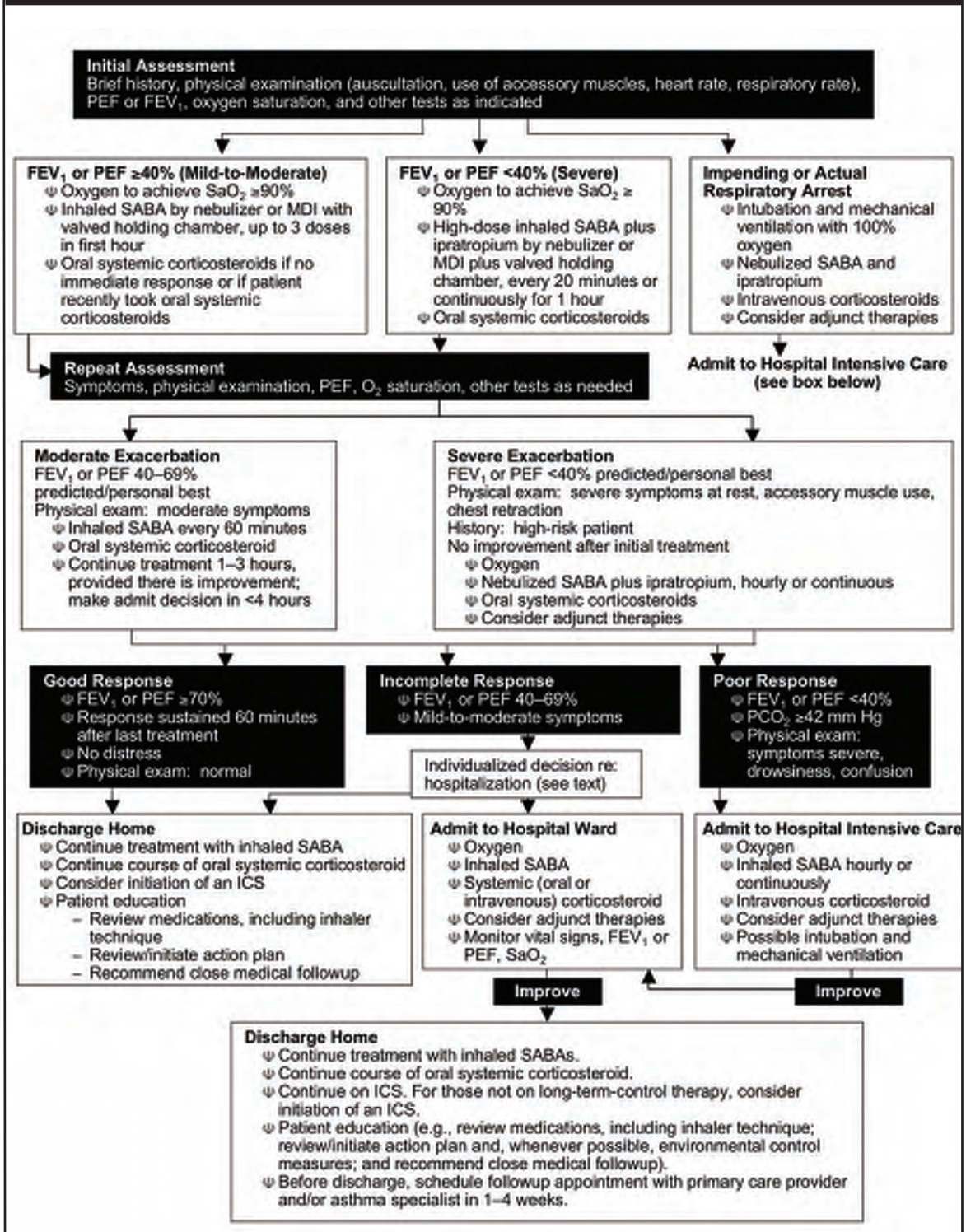
Emergency medical services providers should have prehospital protovols that allow administration of SABA, supplemental oxygen, and (with appropriate medical oversight) anticholinergics and oral systemic corticosteriods to patients who have signs or symptoms of an asthma exacerbation.

Treatment strategies for managing moderate or severe exacerbations in the urgent or emergency care setting are described below. Also see figure 21 for a detailed sequence of recommended actions for monitoring and treatment and figure 22 for dosages of drugs for asthma exacerbations.

- **Administer supplemental oxygen** to correct significant hypoxemia in moderate or severe exacerbations.
- **Administer repetitive or continuous administration of SABA** to reverse airflow obstruction rapidly.
- **Administer oral systemic corticosteroids** to decrease airway inflammation in moderate or severe exacerbations or for patients who fail to respond promptly and completely to SABA treatment.
- **Monitor response to therapy with serial assessments.**

  — For children:

FIGURE 21. MANAGEMENT OF ASTHMA EXACERBATIONS: EMERGENCY DEPARTMENT AND HOSPITAL-BASED CARE



Key: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PCO2, partial pressure carbon dioxide; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist; SaO2, oxygen saturation

FIGURE 22. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS

Medication	Dosage		
	Child Dose*	Adult Dose	Comments (not all inclusive)
Inhaled Short-Acting Beta$_2$-Agonists (SABA)			
Albuterol Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5.0 mg/mL)	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously.	Only selective beta$_2$ agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min. Use large volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI (90 mcg/puff)	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver as needed. Use VHC; add mask in children <4 years.	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed.	In mild-to-moderate exacerbations, MDI plus VHC is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.
Bitolterol Nebulizer solution (2 mg/mL)	See albuterol dose; thought to be half as potent as albuterol on mg basis.	See albuterol dose.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Levalbuterol (R-albuterol) Nebulizer solution (0.63 mg/3 mL, 1.25 mg/0.5 mL 1.25 mg/3 mL)	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed.	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed.	Levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety. Has not been evaluated by continuous nebulization.
MDI (45 mcg/puff)	See albuterol MDI dose	See albuterol MDI dose.	
Pirbuterol MDI (200 mcg/puff)	See albuterol MDI dose; thought to be half as potent as albuterol on a mg basis.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations
Systemic (Injected) Beta$_2$-Agonists			
Epinephrine 1:1,000 (1 mg/mL)	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq.	0.3–0.5 mg every 20 minutes for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq.	0.25 mg every 20 minutes for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Anticholinergics			
Ipratropium bromide Nebulizer solution (0.25 mg/mL)	0.25–0.5 mg every 20 minutes for 3 doses, then as needed	0.5 mg every 20 minutes for 3 doses, then as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI (18 mcg/puff)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years. Studies have examined ipratropium bromide MDI for up to 3 hours.

FIGURE 22. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS (continued)

Medication	Dosage		
	Child Dose*	Adult Dose	Comments (not all inclusive)
Anticholinergics (continued)			
Ipratropium with albuterol Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	1.5-3 mL every 20 minutes for 3 doses, then as needed	3 mL every 20 minutes for 3 doses, then as needed	May be used for up to 3 hours in the initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years.
Systemic Corticosteroids (Apply to all three corticosteriods.)			
Prednisone Methylprednisolone Prednisolone	1-2 mg/kg in 2 divided doses (maximum = 60 mg/day) until PEF is 70 percent of predicted or personal best	40–80 mg/day in 1 or 2 divided doses until PEF reaches 70 percent of predicted or personal best	For outpatient "burst," use 40–60 mg in single or 2 divided doses for total of 5–10 days in adults (children: 1–2 mg/ kg/day maximum 60 mg/day for 3–10 days).

* Children ≤ 12 years of age

Key: ED, emergency department; MDI, metered-dose inhaler; PEF, peak expiratory flow, VHC, valved holding chamber

Notes:

- There is no known advantage for higher doses of corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired.
- The total course of systemic corticosteroids for an asthma exacerbation requiring an ED visit of hospitalization may last from 3 to 10 days. For corticosteroid courses of less than 1 week, there is no need to taper the dose. For slightly longer courses (e.g., up to 10 days), there probably is no need to taper, especially if patients are concurrently taking ICSs.
- ICSs can be started at any point in the treatment of an asthma exacerbation.

- No single measure is best for assessing severity or predicting hospital admission.
- Lung function measures (FEV_1 or PEF) may be useful for children ≥5 years of age, but these measures may not be obtainable during an exacerbation.
- Pulse oximetry may be useful for assessing the initial severity; a repeated measure of pulse oximetry of <92–94 percent after 1 hour is predictive of the need for hospitalization.
- Signs and symptoms scores may be helpful. Children who have signs and symptoms after 1–2 hours of initial treatment and who continue to meet the criteria for a moderate or severe exacerbation have a >84 percent chance of requiring hospitalization.

— For adults:

- Repeated lung function measures (FEV_1 or PEF) at 1 hour and beyond are the strongest single predictor of hospitalization. Such measures may not be helpful, or easily obtained, during severe exacerbations.
- Pulse oximetry is indicated for patients who are in severe distress, have FEV_1 or PEF <40 percent predicted, or are unable to perform lung function measures. Only repeat assessments after initial treatment, not a single assessment upon admission, are useful for predicting the need for hospitalization.
- Signs and symptoms scores at 1 hour after initial treatments improve the ability to predict need for hospitalization. The presence of drowsiness is a useful predictor of impending respiratory failure and is reason to consider immediate transfer to a facility equipped to offer ventilatory support.

- **Consider adjunctive treatments, such as intravenous magnesium sulfate or heliox,** in severe exacerbations, if patients are unresponsive to the initial treatments listed above (e.g., FEV_1 or PEF <40 percent predicted or personal best after initial treatments).
- **Provide the following to prevent relapse of the exacerbation** and recurrence of another exacerbation:
  - — Referral to followup asthma care within 1–4 weeks. In addition, encourage the patient to contact (e.g., by telephone) his/her asthma care provider during the first 3–5 days after discharge. A followup visit is essential to review the patient's written asthma action plan, adherence, and environmental control and to consider a step up in therapy. If appropriate, consider referral to an asthma self-management education program.
  - — An ED asthma discharge plan. See figure 23a, b "Emergency Department—Asthma Discharge Plan."
  - — Review of inhaler technique whenever possible.
  - — Consideration of initiating ICS.
- **Treatments that are not recommended in the emergency care or hospital setting include:** methylxanthines, antobiotics (except as needed for comorbid conditions), aggressive hydration, chest physical therapy, mucolytics, or sedation. Inhaled ipratropium bromide is a helpful adjunctive therapy in the emergency care setting, but does not provide additional benefit after a patient is hospitalized for a severe exacerbation.

FIGURE 23a. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN

EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN

Name: _____ was seen by **Dr.**_____ on ___/___/___

- Take your prescribed medications as directed—do not delay!
- -term treatment plan.
- Even when you feel well, you may need daily medicine to keep your asthma in good control and prevent attacks.
- Visit your doctor or other health care provider as soon as you can to discuss how to control your asthma and to develop *your own* action plan.

Your followup appointment with _____ is on: ___/___/___. **Tel:** _____

YOUR MEDICINE FOR THIS ASTHMA ATTACK IS:

Medication	Amount	Doses per day, for # days
Prednisone/prednisolone (oral corticosteroid)		_____ a day for _____ days Take the entire prescription, even when you start to feel better.
Inhaled albuterol		_____ puffs every 4 to 6 hours if you have symptoms, for _____days

YOUR DAILY MEDICINE FOR LONG-TERM CONTROL AND PREVENTING ATTACKS IS:

Medication	Amount	Doses per day
Inhaled corticosteroids		

YOUR QUICK-RELIEF MEDICINE WHEN YOU HAVE SYMPTOMS IS:

Medication	Amount	Number of doses/day
Inhaled albuterol		

ASK YOURSELF 2 TO 3 TIMES PER DAY, EVERY DAY, FOR AT LEAST 1 WEEK:

"How good is my asthma compared to when I left the hospital?"

If you feel much better:	**If you feel better, but still need your quick-relief inhaler often:**	**If you feel about the same:**	**If you feel worse:**
• Take your daily long-term control medicine.	• Take your daily long-term control medicine. • See your doctor as soon as possible.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • See your doctor as soon as possible—don't delay.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • Immediately go to the emergency department or call 9–1–1.

YOUR ASTHMA IS UNDER CONTROL WHEN YOU:

① Can be active daily and sleep through the night.	② Need fewer than 4 doses of quick-relief medicine in a week.	③ Are free of shortness of breath, wheeze, and cough.	④ Achieve an acceptable "peak flow" (discuss with your health care provider).

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Source: Camargo CA Jr, Emond SD, Boulet L, Gibson PG, Kolbe J, Wagner CW, Brenner BE. Emergency Department Asthma Discharge Plan. Developed at "Asthma Education in the Adult Emergency Department: A Multidisciplinary Consensus Conference," New York Academy of Medicine, New York, NY; 2001 April 1–5. Boston, MA: Massachusetts General Hospital, 2001. 2 pp.

FIGURE 23b. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN: HOW TO USE YOUR METERED-DOSE INHALER

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor, nurse, other health care provider, or pharmacist to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below (A or B are best, but C can be used if you have trouble with A and B). (Your doctor may give you other types of inhalers.)

Steps for Using Your Inhaler

Getting ready

1. Take off the cap and shake the inhaler.
2. Breathe out all the way.
3. Hold your inhaler the way your doctor said (A, B, or C below).

Breathe in slowly

4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. Within5 seconds, begin to breathe in slowly.)
5. Keep breathing in slowly, as deeply as you can.

Hold your breath

6. Hold your breath as you count to 10 slowly, if you can.
7. For inhaled quick-relief medicine (short-acting $beta_2$ agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other medicines.

A. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).

B. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.

C. Put the inhaler in your mouth. Do not use for steroids.

Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to your doctor, other health care provider, or pharmacist.

For More Information

The National Heart, Lung, and Blood Institute (NHLBI) Health Information Center (HIC) is a service of the NHLBI of the National Institutes of Health. The NHLBI HIC provides information to health professionals, patients, and the public about the HIC treatment, diagnosis, and prevention of heart, lung, and blood diseases and sleep disorders. For more information, contact:

NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
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U.S. Department of Health and Human Services
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National Heart
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SHORT COMMUNICATION

The scope for biased recall of risk-factor exposure in case-control studies: Evidence from a cohort study of Scottish men

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Abstract

Aims: Case-control studies are prone to recall bias, a participant's case-control status influencing their recall of exposure to risk factors. We aimed to demonstrate empirically the scope for this bias. *Methods:* Two thousand five hundred and fifty men without coronary heart disease at enrolment to a prospective cohort study underwent two health assessments, about 5 years apart. The association between the development of coronary heart disease in the intervening period and changes in reported stress and cigarette smoking were investigated. *Results:* Men admitted to hospital with coronary heart disease reported a greater increase in psychological stress ($p=0.032$) and greater cessation of smoking (22% vs. 10%; $p=0.007$) than men not admitted. Consequently, when exposure data are collected at the end rather than at the start of the follow-up period, coronary heart disease is observed to be more strongly associated with psychological stress, and more weakly associated with smoking. ***Conclusions:*** **At the time when a case-control study is conducted, levels of exposure to risk factors will have been influenced by disease development. When participants are asked about their level of exposure for a previous time period, recall is likely to be influenced by present outcome and exposure status, especially when psychological states are being investigated.**

Key Words: *Bias (epidemiology), case-control studies, coronary disease, psychological stress, risk factors, smoking*

Background

Case-control studies are prone to recall bias, such that a participant's case-control status influences their recall of exposure to risk factors. We have previously suggested [1] that a recent case-control study has overestimated the effect of psychological stress on the occurrence of myocardial infarction, due to people being asked to recall their previous exposure to stress several days after the infarction [2]. In that situation, reports of higher stress exposure among patients may have more to do with the effect of a first heart attack on a person's mental state (myocardial infarction influencing the recall of stress) than with any pathophysiological process triggered by stress (stress causing myocardial infarction).

This report uses data from a prospective cohort study to determine empirically the scope for recall bias. Focusing on men who completed a health questionnaire and physical examination on two occasions, we investigate how the development of coronary heart disease in the intervening 5-year period influences the reporting of psychological stress and cigarette smoking. Cigarette smoking is included as being a more established risk factor for coronary heart disease, and as being measured more objectively than psychological stress. Subsequently, we discuss how the observed associations between risk factors and coronary heart disease are affected by the time of measurement.

Material and methods

Participants

The data for this analysis come from the West of Scotland Collaborative Study [3,4]. In brief, 6022

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men and 1006 women were recruited from a variety of workplaces in the west of Scotland between 1970 and 1973. At enrolment, all members of the cohort were invited to complete a questionnaire and undergo a physical examination. The present analysis is based upon 2550 men aged between 35 and 64 years, without evidence of ischaemia on a six-lead electrocardiogram [3] at enrolment, who underwent a second health screening in 1977, and who provided full data on the variables used in the present analysis. Women were excluded from this analysis because they formed a minority of the cohort and few developed coronary heart disease in the study period.

Exposure measurement

Psychological stress was measured using the Reeder Stress Inventory [5] (Table I), a measure of daily stress that we have described in detail elsewhere [6]. Current cigarette smokers included men who reported having given up less than 1 year previously [3].

Outcome measurement

Completion of the Rose Angina Questionnaire [7] (Table I) at the second health screening allowed men who reported symptoms consistent with ''definite angina'' to be identified. For analyses using this outcome, 122 men reporting definite angina at the first health screening were excluded. A record linkage with the Scottish Morbidity Records identified those men admitted to hospital between screening assessments, and receiving a hospital discharge diagnosis of coronary heart disease (ICD-9: 410–414).

Statistical analysis

Logistic regression analyses were used to investigate associations between exposures and outcomes. Adjustment for age at first screening assessment was achieved by including two dummy covariates distinguishing three age groups: <50, 50–54 and 55+ years. Adjustment for additional confounders was not undertaken, as the varying associations between a confounder and, for example, stress at the first assessment, stress at the second assessment and change in stress may have obscured comparisons between the different models required for this investigation. Stata statistical software, version 9, was used for all analyses (StataCorp, College Station, TX, USA).

Table I. Descriptions of the two questionnaire measures used in this study.

Reeder Stress Inventory

Please indicate by a tick in the appropriate box in each of the following sections which description fits you best.

1. In general, I am usually tense or nervous.
   THIS DESCRIBES ME:
2. There is a great amount of nervous strain connected with my daily activities.
   THIS DESCRIBES MY SITUATION:
3. At the end of the day I am completely exhausted mentally and physically.
   THIS DESCRIBES ME:
4. My daily activities are extremely trying and stressful.
   THIS DESCRIBES MY ACTIVITIES:

Response options for each item are ''Exactly'', ''To some extent'', ''Not very accurately'', or ''Not at all''. Possible total scores range from 1 to 8, with higher scores indicating greater daily stress.

Rose Angina Questionnaire

1. Have you ever had any pain or discomfort in your chest?
   [] Yes [] No (if no, respondent is directed to skip the following questions)
2. Do you get this pain or discomfort when you walk uphill or hurry?
   [] Yes [] No
3. Do you get it when you walk at an ordinary pace on the level?
   [] Yes [] No
4. When you get any pain or discomfort in your chest what do you do?
   [] Stop [] Slow down [] Continue at the same pace
5. Does it go away when you stand still?
   [] Yes [] No
6. How soon?
   [] 10 minutes or less [] More than 10 minutes
7. Where do you get this pain or discomfort? Mark the place(s) with X on the diagram (diagram of the abdomen)

Definite angina is recorded when responses are YES to question 1, YES to question 2, STOP or SLOW DOWN to question 4, YES to question 5, 10 MINUTES OR LESS to question 6, and the sternum or both left chest and left arm indicated on the diagram. Question 3 distinguishes grade II (YES) and grade I (NO) angina.

Results

The mean age of the 2550 men was 48 years (standard deviation 6 years). The mean interval between the two health screens was 5 years (90% range: 4–6 years). At the second health screening, 141 of 2428 men (5.8%) reported symptoms of angina, and 51 of 2550 men (2.0%) had been admitted with coronary heart disease.

An association between the development of angina symptoms and higher psychological stress was apparent whether stress was reported at the onset or conclusion of follow-up (Table II). There was, however, no association between these newly reported symptoms and a greater increase in stress reported at the end of follow-up ($p=0.64$). The expected greater increase in reported stress was observed in those admitted with coronary heart disease, relative to men not so admitted ($p=0.032$). Consequently, very weak evidence of a protective effect of psychological stress measured at the start of follow-up becomes very weak evidence of a harmful effect of psychological stress when measured at the end of follow-up (Table II).

There was evidence of an association between the development of coronary heart disease, whether ascertained from symptoms of angina or hospital admission, and smoking status as reported at the start of the follow-up period (Table II). These associations were weaker with smoking status reported at the end of follow-up, as there was a higher rate of smoking cessation among men reporting symptoms of angina, or admitted with coronary heart disease, than among other men. However, only the latter association was supported by strong statistical evidence ($p=0.007$).

Discussion

This analysis demonstrates the potential for recall bias in case-control studies, hospital admission with coronary heart disease being followed by reports of higher psychological stress and greater smoking cessation. Consequently, there were discernable differences in the associations between coronary heart disease and these risk factors, depending upon whether risk-factor exposure was measured before or after admission. There was no evidence of angina symptoms impacting upon the reported exposure to stress or smoking, consistent with previous research suggesting that the likelihood of smoking cessation is proportional to the severity of smoking-related disease [8,9].

The experience of heart disease is known to be a source of substantial distress in itself [10], and admission for coronary heart disease is likely to be followed by reports of increased psychological stress. This [11] and the long-held popular assumption of a causal association between psychological stress and heart disease [12] are likely to influence attempts to recall preadmission levels of psychological stress. There may be a greater effect for the recall of cigarette smoking, given that a causal relationship between smoking and heart disease risk has been well known for many years and that this has let to growing social disapproval of smoking [13–15], especially for smokers requiring treatment for smoking-related illness [13,16–18].

This study adds to the sparse empirical data on the scope for recall bias in case-control studies. The development of cardiovascular disease is associated with increases in reported psychological stress and with a high rate of smoking cessation. Current

Table II. Mean (standard deviation) psychological stress and percentage of smokers at the two screening assessments by outcome (symptoms or admission), plus the change in reported exposure between assessments. For each outcome in turn, age-adjusted odds ratios (ORs) indicate the effect of higher exposure at the stated screening assessment[a], or of a greater increase in stress or a greater smoking cessation rate between assessments.

	Angina symptoms at screen 2 (n=141/2428[b])					CHD admission between screen 1 and 2 (n=51/2550[c])				
	Yes	No	OR	95% CI	p	Yes	No	OR	95% CI	p
Stress										
Screen 1	4.04 (1.76)	3.76 (1.66)	1.12	(1.00–1.24)	0.041	3.51 (1.64)	3.82 (1.67)	0.90	(0.76–1.06)	0.20
Screen 2	4.16 (1.62)	3.85 (1.72)	1.13	(1.02–1.26)	0.016	4.04 (1.57)	3.90 (1.71)	1.06	(0.90–1.25)	0.51
Screen 2–Screen 1	0.12 (1.54)	0.12 (1.54)	1.03	(0.92–1.15)	0.64	0.53 (1.47)	0.08 (1.55)	1.21	(1.02–1.44)	0.032
Smoking										
Screen 1	61.7%	52.1%	1.54	(1.08–2.19)	0.016	74.5%	53.1%	2.63	(1.39–4.97)	0.003
Screen 2	49.7%	43.1%	1.33	(0.94–1.87)	0.10	52.9%	44.0%	1.44	(0.83–2.51)	0.20
Ex-smokers	12.8%	9.9%	1.39	(0.83–2.32)	0.22	21.6%	10.0%	2.55	(1.29–5.05)	0.007

CHD, coronary heart disease; CI, confidence interval. [a]ORs are for one unit greater stress and smoking vs. not smoking. [b]Excludes men with electrocardiogram ischaemia or Rose "definite angina" at screen 1. [c]Excludes men with electrocardiogram ischaemia at screen 1.

psychological state is likely to influence attempts to recall psychological state for previous periods. Consequently, recent case-control studies that rely upon recall of pre-disease psychological stress are likely to have overestimated the association between psychological stress and coronary heart disease [2,19,20].

The present study is limited in that it indicated the scope for recall bias with different risk factors, but did not assess men's ability to recall their exposure level for a previous time period. A cohort of women with breast cancer was found to be more likely to underestimate past alcohol consumption than a control group, although the bias was small in magnitude [21]. Furthermore, our second measure of psychological stress was taken some time after admission, and we may have observed a greater effect had we measured stress pre-discharge, as in two recent case-control studies [2,19,20].

Conclusion

We conclude that case-control studies that have relied upon retrospective recall of risk-factor exposure may give biased estimates when that exposure is modified following the development of disease, with an overestimate of associations between disease and psychological risk factors being particularly likely. In consequence, the need for and nature of policies to address psychological risk factors for disease cannot be fully informed by data from case-control studies alone.

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Original article

Scand J Work Environ Health – online first

Pesticide exposure and risk of Parkinson's disease – a population-based case–control study evaluating the potential for recall bias

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Rugbjerg K, Harris MA, Shen H, Marion SA, Tsui JKC, Teschke K. Pesticide exposure and risk of Parkinson's disease – a population-based case–control study evaluating the potential for recall bias. *Scand J Work Environ Health* – online first

Objective The aim of this study was to investigate whether pesticide exposure was associated with Parkinson's disease in a population-based case–control study in British Columbia, Canada.

Methods Patients reimbursed for anti-parkinsonian agents were identified and screened for eligibility as cases. Controls were selected from the universal health insurance database, frequency-matched to the case sample on birth year, gender, and geographic region. A total of 403 cases and 405 controls were interviewed about their job, medical and personal habits histories, and beliefs about disease risk factors. Among those reporting pesticide exposure, an occupational hygiene review selected participants exposed "beyond background" (ie, above the level expected in the general population). Unconditional logistic regression was used to estimate associations for different pesticide categories.

Results Of the cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background. Self-reported exposure was associated with increased risk [odds ratio (OR) 1.76, 95% confidence interval (95% CI) 1.15 2.70], however the risk estimate was reduced following the hygiene review when restricted to those considered exposed (OR, 1.51, 95% CI, 0.85 2.69). When agricultural work was added to the model, the risk for hygiene-reviewed pesticide exposure was not elevated (OR 0.83, 95% CI 0.43 1.61), but agricultural work was (OR 2.47, 95% CI 1.18 5.15). More than twice as many cases as controls thought chemicals cause Parkinson's disease.

Discussion This study provides little support for pesticide exposure as a cause of Parkinson's disease. The observed pattern of step-wise decreases in risk estimates might indicate differential recall by case status. The relationship to agricultural jobs suggests that farming exposures - other than pesticides - should be considered as risk factors for Parkinson's disease.

Key terms agricultural job; British Columbia; Canada; job history; self-report.

The etiology of Parkinson's disease is partly unknown, though 5–10% of the cases are attributed to genetic mutations (1). Parkinson's disease is thought to result from an interplay between genetic susceptibility and environmental risk factors (2). An association between pesticides and Parkinson's disease was first suspected in 1983, when the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which has a chemical structure similar to the herbicide paraquat, was observed to cause acute Parkinsonism (3). Since then, exposure to pesticides and subsequent development of Parkinson's disease has been studied intensively (eg, 4–17) and many studies (4–8, 12–17) have confirmed associations, though some were weak and not significant, and other studies have not found an effect (9, 10).

Methods of pesticide exposure ascertainment have varied from study to study, but it would be extraordinarily difficult to include direct exposure measurement due to the rarity and late-life incidence of Parkinson's disease. Retrospective self-reporting of exposures is the most commonly used method for estimation of pesticide exposure (4–10); however, this method has the

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potential for recall bias (11). Some studies have gathered self-report of exposure prospectively (12, 13) or used more objective methods, such as job exposure matrices (14–16) or combinations of geographic information and historical data on pesticide use (17).

Here we report the results of a population-based case–control study of the relationship between pesticide exposure and Parkinson's disease. Self reports in combination with an occupational hygiene review were used to estimate exposures. We also investigated whether study participants believed that chemicals, including pesticides, cause Parkinson's disease and whether such a belief may have confounded exposure–response relationships.

Methods

Study population

Cases and controls were sampled from two areas of the province of British Columbia, Canada: Metro Vancouver representing an urban area (2.1 million people, population density ~735 per km^2); and all of Vancouver Island, except Greater Victoria, representing a rural area (400 000 people, population density ~10 per km^2). The rural area was included to increase the diversity of occupations. Persons between the ages of 40–69 years inclusive (as of 31 December 2002) who were alive and residing in the study area at the time of interview and who were able to communicate with the interviewer in English were eligible. Subjects in the age group 40 69 years were chosen because they were less likely to suffer from dementia or other illnesses that could complicate an interview and because they were in, or close to, their working years and therefore more likely to recall exposures correctly.

Potential cases were identified using the PharmaCare database of the provincial prescription payment plan, which included all those who had more than CAN$800 in prescription costs in a given year. For inclusion, individuals had to have had at least one prescription for anti-parkinsonian drugs for at least one calendar year from 1995–2002 inclusive. The following were defined as anti-parkinsonian drugs: levodopa, bromocriptine mesylate, pergolide mesylate, levodopa/benserazide hydrochloride, levodopa/carbidopa, or seligiline hydrochloride. The populations meeting the potential case definition were identified on two occasions: in 2001 (data from 1995–1998) and 2005 (data from 1999–2002). To blind the data extractors, the extract was supplemented with a 20% "camouflage" sample of other individuals in the database.

All potential cases were verified by an initial screening phone interview about chronic diseases, anti-parkinsonian drugs taken, and the reason for their use. This screened out those taking the drugs for much different purposes (eg, bromocriptine for lactation cessation or levodopa for restless legs syndrome). Those taking the drugs for known or suspected Parkinson's disease had an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist with a specialty in movement disorders. The following clinical criteria for Parkinson's disease were used: (i) two of the following symptoms present on examination: Parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance; (ii) absence of specific signs of other diseases that would account for these findings. Dates of Parkinson's disease diagnosis, first symptoms, and first treatment were also recorded.

The control sample was frequency-matched to the case sample on birth year (six 5-year periods), gender, and geographic region. Controls were selected using stratified random sampling from the British Columbia (BC) Ministry of Health Services client registry, which includes all individuals covered by provincial medical insurance and represents 97.5% of the population. All potential controls were screened by phone for eligibility, including a question about whether they had any chronic diseases. Anyone who indicated Parkinson's disease were excluded.

Subject contact procedure

This study was required to use a two-stage consent process. The BC Ministry of Health Services sent out invitation letters asking potential subjects to contact the University of BC team. If no response was received within two weeks of the mailing date, a clerk at the Ministry of Health Services phoned to ask the potential subject if their name could be released to the study team. Those who agreed were then contacted by the study coordinator who conducted the screening interview and requested study participation.

Questionnaire information on pesticide exposure

The questionnaire was pre-tested in several steps on a sample of 40 people selected to represent the age range of the subjects. The interviewers underwent formal training about all aspects of the interview, questionnaire, and clinical examination, and were observed during mock and initial interviews to ensure consistency.

In an in-person interview, participants were asked about their job, medical, and personal habits histories. The following questions were asked for all jobs: "During this job, did you use or were you exposed to any chemicals, for example, solvents, oils, plastics, paints, metals or pesticides?" As an aid to recall, an interview guide was sent to the participants prior to the interview and

was referred to during the interview. It listed chemicals with an a priori hypothesis and included common and brand names (see the Appendix for the list of pesticides). If a participant answered "yes", the following questions were asked: "Was this substance (i) breathed in, (ii) on skin, (iii) both, (iv) no direct contact, (v) don't know"; and "What operations were you performing when you were exposed to this substance?" for which a list of about 90 operations was provided in the interview guide. Participants were asked about weeks exposed per year, hours exposed per week, and start and end date of the exposure in that job. At the end of the interview, participants were asked: "What do you think causes Parkinson's disease?"

Each participant's job history was reviewed by an occupational hygienist (blind to case status) for sensitivity (ie, to check whether potential exposures of interest commonly associated with an occupation were reported). Where exposures were missed, the participant was phoned and asked about the exposures noted by the hygienist.

Assigning exposure to pesticides

After all interviews were completed, the self-reported exposures were again reviewed, blind to case status, this time for specificity. Using defined criteria and the information on job title, job duties, mode of exposure, operations conducted during exposure, and duration of exposure, assessments were made about whether self-reported pesticide exposures were likely to be "beyond background" or above the level expected in the general population. Of 121 persons who self-reported pesticide exposures, 53 were excluded because the reported exposure was judged to be limited. For example, sales personnel handling closed containers, construction workers occasionally handling wood treated with preservatives, and restaurant workers, security guards, administrative personnel, and care aides in locations where pesticides were occasionally applied by others were all judged to have limited exposure. In comparison, those judged to have exposures above background were mainly farmers, farm workers, forestry personnel, sawmill workers applying antisapstain fungicides, florists, and kennel and stable hands. Among those judged unlikely to be exposed beyond background, only 34% named a specific pesticide, whereas among those judged exposed, 73% did. A further 8 persons were excluded due to missing information on hours per week exposed (N=7) and whether the exposure was every week (N=1); on checking the job duties, it was likely that the information was missing because the exposure was rare in the job (eg, public health nurse applying lindane for lice)." Among those reporting exposure to pesticides, 60 were judged to be exposed beyond background.

Categorizing pesticides

Since most previous studies have categorized pesticides according to function (insecticides, herbicides, fungicides, and wood preservatives), for comparison purposes we did the same.

We also created categories by chemical class: organochlorines and organophosphates. Finally, we grouped specific pesticides reported by the participants into two categories based on neurotoxicity (18–20): (i) pesticides with evidence of human neurotoxicity: allethrin, azinphosmethyl, diazinon, dichlorodiphenyltrichloroethane (DDT), 2,4-dichlorophenoxyacetic acid (2,4-D), dieldrin, glyphosate, lindane, malathion, 2-methyl-4-chlorophenoxyacetic acid (MCPA), nicotine, paraquat, pentachlorophenol, rotenone, tetrachlorophenol, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and (ii) pesticides with limited or no evidence of neurotoxicity: borax, brodifacoum, calcium polysulfide, captan, copper oxychloride, creosote, chromate copper arsenate, didecyl dimethyl ammonium chloride, lime sulphur, mineral oil, simazine, and sulphur. These categories were based on available evidence for neurotoxicity in case studies, animal studies, and in vitro studies (18–20).

Statistical analysis

Unconditional logistic regression was used to estimate associations with Parkinson's disease for different categories of pesticides: functional groups (insecticide, herbicide, fungicide, wood preservative); chemical groups (organophosphates, organochlorines); neurotoxic pesticides; and any specific pesticide reported by at least ten participants. In all analyses, persons reporting exposure to pesticides other than those relevant in the specific analysis were excluded.

Analyses were conducted for self-reported exposure and for hygiene-reviewed exposures beyond background. Analyses were performed for exposure via any job operation and for the subgroup reporting pesticide spraying operations. We also estimated risks with exposure duration and with censoring of exposures five and ten years prior to the date of diagnosis or the corresponding date for controls.

Finally, we estimated Parkinson's disease risk among those with agricultural jobs. Two adjustment models were used: model 1 adjusted for gender, birth year (5-year age groups), and smoking (cumulative pack-years); and model 2 adjusted for the same variables as model 1 in addition to a variable indicating whether the subject believed Parkinson's disease has a chemical cause.

Analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 3783 potential subjects were initially sent letters from the Ministry of Health Services. Figure 1 is a participation flowchart showing the classification of potential subjects. A large proportion of potential cases did not have Parkinson's disease (most used antiparkinsonian drugs for other indications). The multistage consent process resulted in uncertainty about the proportion of potential subjects who were eligible to participate. However, if we assume that the proportion of contacted subjects who were eligible (554/1580=0.35 for cases and 603/726=0.83 for controls) was the same in the initially extracted samples, we can calculate the "potentially eligible" numbers (0.35×2261=791 for cases; 0.83×1522=1264 for controls) and use these as denominators for the calculation of the participation rate. Using this method, the estimated participation rate was 403/791 (51%) for cases and 405/1264 (32%) for controls. The characteristics of the final study sample of 403 cases and 405 controls are summarized in table 1.

Pesticide exposure

Among cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background following the hygiene review. In the control group, 47 (12%) self-reported pesticide exposure and 23 (6%) were judged to be exposed beyond background. In both the case and control groups, insecticides and herbicides were the most frequently reported types of pesticides (table 1).

Table 2, model 1 (adjusted for birth year, gender and smoking) shows the results for both self-reported and hygiene-reviewed pesticide exposure via any job operation and spraying operations. For self-reported pesticide exposure, we found a significantly increased risk of Parkinson's disease. Among those judged exposed beyond background after the hygiene review, the odds ratio (OR) was lower than among those self-reporting exposure. In the hygiene-reviewed group, exposure via spraying pesticides had a higher risk estimate than via any job operation, though neither of these risk estimates were statistically significant. The

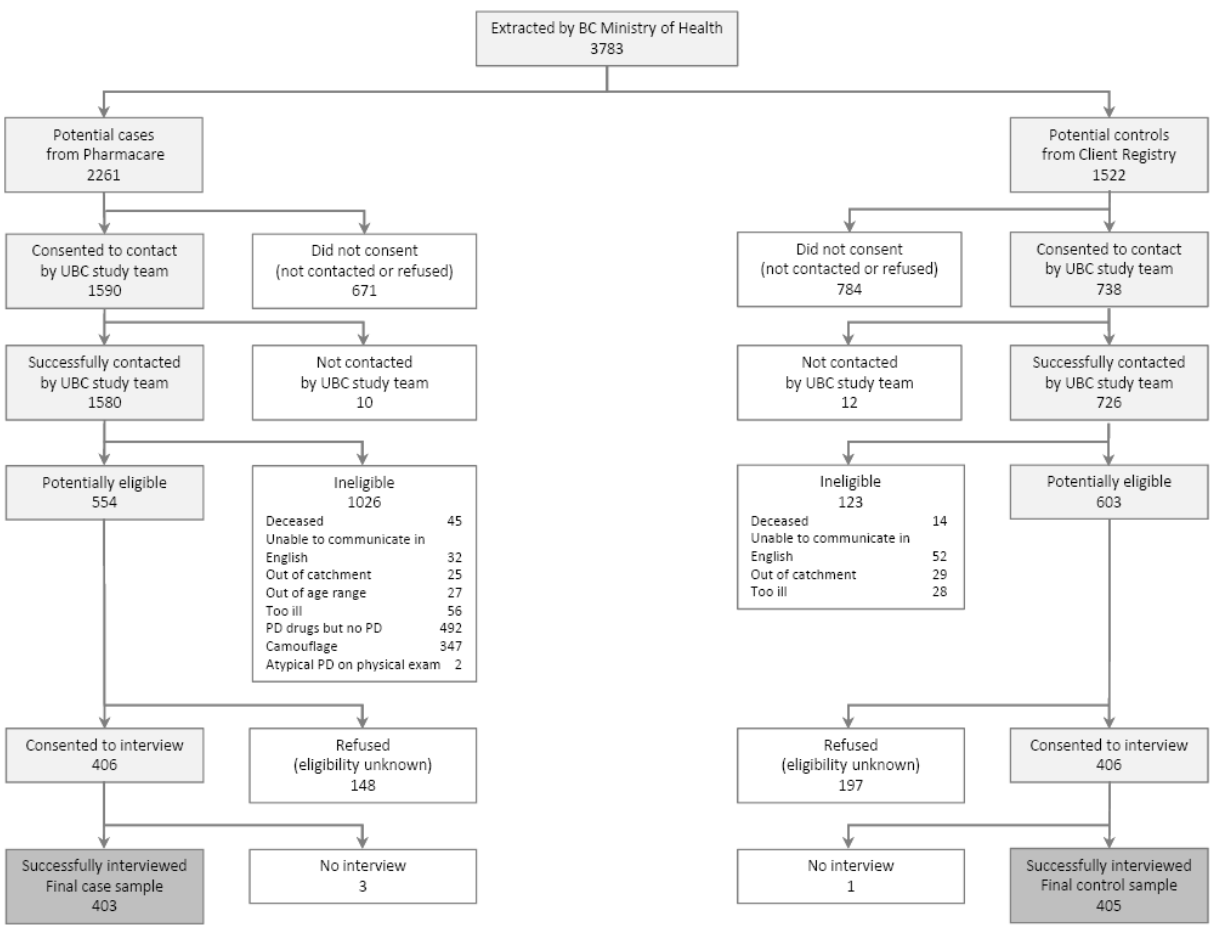

Figure 1. Flow chart showing the classification of potential participants in a case control study of Parkinson's disease in British Columbia, Canada. Potential cases were those with a prescription for antiparkinsonian drugs during the study period.

Table 1. Characteristics of the study population: 403 patients with Parkinson's disease and 405 controls. [SD=standard deviation.]

Characteristic	Cases				Controls			
	N	%	Mean	SD	N	%	Mean	SD
Men	266	66.0	·	·	204	50.4	·	·
Women	137	34.0	·	·	201	49.6	·	·
Birth year								
1929–1938	245	60.8	·	·	175	43.2	·	·
1939–1948	131	32.5	·	·	129	31.9	·	·
1949–1958	27	6.7	·	·	101	25.0	·	·
Geographic region: Metro Vancouver	263	62.3	·	·	242	59.8	·	·
Self-reported pesticide exposure	74	18.3	·	·	47	11.6	·	·
Hygiene-reviewed pesticide exposure	37	9.2	·	·	23	5.7	·	·
Insecticides	18	4.5	·	·	13	3.2	·	·
Herbicides	17	4.2	·	·	13	3.2	·	·
Fungicides	7	1.7	·	·	6	1.5	·	·
Wood preservatives	10	2.5	·	·	5	1.2	·	·
No pesticide exposure	329	81.6	·	·	358	88.4	·	·
Ever smoker[a]	184	45.7	·	·	226	55.8	·	·
Named chemicals as cause of Parkinson's disease	111	27.5	·	·	43	10.6	·	·
Smoking, cumulative pack-years			11.4	20.4	·	·	15.4	22.4
Mean age at diagnosis of Parkinson's disease (years)			56.0	7.1	·	·	·	·
Mean age at the time of interview (years)			65.0	6.6	·	·	62.2	9.0

[a] At least 100 cigarettes in the period prior to Parkinson's disease diagnosis and a corresponding period for controls.

risk estimates for subcategories of pesticides tended to follow similar patterns: the highest risk estimates were for self-reports; the hygiene review resulted in reductions in risk estimates; and there were slightly higher risk estimates for spraying exposures. None of the OR for pesticide subcategories were statistically significant, except self-reported insecticide exposure. Risk estimates for hygiene-reviewed pesticide exposures were slightly above 1.0 in all categories of pesticides, except for organophosphates, organochlorines and DDT, however, most risk estimates had wide 95% confidence intervals (95% CI) (table 2). Censoring exposures five and ten years prior to diagnosis did not change the risk estimates markedly (data not shown) and analyses including duration of pesticide exposure showed no significant associations with Parkinson's disease (data not shown).

We also examined the relationship between agricultural work and Parkinson's disease: 36 cases and 17 controls reported an agricultural job. Of these, 20 cases and 7 controls were exposed to pesticides. Participants who reported agricultural jobs had a significantly increased risk of Parkinson's disease (OR 2.36, 95% CI 1.23 4.55, adjusted for gender, birth year and smoking). When the hygiene-reviewed pesticide exposures were added to this model, the elevated and statistically significant OR for agricultural work remained (OR 2.47, 95% CI 1.18 5.15), but the risk for pesticide exposure was no longer elevated (OR 0.83, 95% CI 0.43 1.61). A similar pattern held for each pesticide category: when added to a model with agricultural job, the elevated risk for the job remained, but the risk estimate for the pesticide was always <1.0. There were no significant interactions between agricultural job and any of the pesticide categories.

The analyses reported above suggest that differences in exposure recall between cases and controls may have contributed to the higher risk estimates for self-reported pesticide exposures, so we examined the responses to the question about what causes Parkinson's disease. A total of 154 participants reported "chemicals" as a suspected cause of Parkinson's disease (111 cases and 43 controls). Most did not name a specific class of chemical, however 21 participants specifically mentioned "pesticides" and all of these were cases. To see whether beliefs about causes of the disease might alter the association with pesticides, we conducted an additional set of analyses with adjustment for the participants' beliefs that chemicals are a cause of Parkinson's disease (table 2, model 2). The OR for pesticides in the model 2 analyses were consistently lower than those of model 1, and none were statistically significant. In contrast, in analyses of agricultural job with adjustment for participants' beliefs that chemicals are a cause of the disease, the increased risk persisted (OR 2.28, 95% CI 1.16 4.47).

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for Parkinson's disease among persons who self-reported pesticide exposure and among those judged - by a hygiene review - to have pesticide exposure beyond background. Statistically significant OR **in bold**. [DDT= dichlorodiphenyltrichloroethane.]

Pesticide category	Model 1 [a]									Model 2 [b]								
	Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations			Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations		
	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI
Pesticides		**1.76**	**1.15–2.70**		1.51	0.85–2.69		1.91	0.82–4.49		1.49	0.96–2.32		1.18	0.65–2.14		1.38	0.56–3.40
Cases	74			37			20			74			37			20		
Controls	47			23			9			47			23			9		
Insecticides		**1.80**	**1.03–3.15**		1.26	0.58–2.74		1.86	0.66–5.24		1.44	0.81–2.58		0.86	0.38–1.93		1.24	0.42–3.65
Cases	40			18			13			40			18			13		
Controls	26			13			6			26			13			6		
Herbicides		1.82	0.97–3.40		1.33	0.60–2.97		1.60	0.53–4.87		1.59	0.84–3.00		1.16	0.51–2.60		1.49	0.47–4.71
Cases	33			17			10			33			17			10		
Controls	19			13			6			19			14			6		
Fungicides		0.94	0.38–2.32		1.18	0.35–4.00		·	··		0.80	0.31–2.03		0.95	0.27–3.31		·	··
Cases	11			7			3 [c]			11			7			3 [c]		
Controls	11			6			2 [c]			11			6			2 [c]		
Wood preservatives		2.20	0.90–5.34		1.56	0.51–4.77		·	··		1.80	0.70–4.62		1.34	0.42–4.28		·	··
Cases	17			10			4 [c]			17			10			4 [c]		
Controls	9			5			0 [c]			9			5			0 [c]		
Organo-phosphates		1.57	0.53–4.64		0.74	0.20–2.78		·	··		1.47	0.49–4.45		0.72	0.19–2.68		·	··
Cases	10			5			4 [c]			10			5			4 [c]		
Controls	6			5			3 [c]			6			5			3 [c]		
Organo-chorines		1.23	0.53–2.85		0.62	0.19–2.00		·	··		1.05	0.44–2.52		0.38	0.11–1.31		·	··
Cases	16			6			5 [c]			16			6			5 [c]		
Controls	10			6			4 [c]			10			6			4 [c]		
Pesticides with neuro-toxic effects		1.76	0.95–3.25		1.08	0.49–2.36		1.34	0.53–3.40		1.48	0.78–0.80		0.86	0.38–1.93		1.06	0.40–2.82
Cases	35			17			14			35			17			14		
Controls	19			13			8			19			13			8		
DDT		1.32	0.55–3.18		0.76	0.22–2.62		·	··		1.09	0.44–2.75		0.45	0.12–1.65		·	··
Cases	15			6			5 [c]			15			6			5 [c]		
Controls	9			5			3 [c]			9			5			3 [c]		

[a] Model 1: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years).
[b] Model 2: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years), and naming chemicals as a cause of Parkinson's disease.
[c] Fewer than ten subjects exposed, odds ratios and confidence intervals not reported.

Discussion

In this study, we observed significantly increased risks of Parkinson's disease with self-reported pesticide or insecticide exposures, but reductions in risk for those considered exposed based on the hygiene review, and when more specific categories of pesticides are mentioned. There were no increases in risk with censoring of exposures five and ten years prior to diagnosis, nor increasing risks with increasing duration of exposure. Only one pattern was suggestive of an association: the increases in risk for hygiene-reviewed exposures from "any job operation" to "spraying operations," though none of these OR were statistically significant. In analyses with agricultural job, pesticide exposures no longer had elevated OR. This pattern of results does not add convincing support to the proposed association between pesticides and Parkinson's disease, and for the most part, was counter to what would be expected to support pesticides as a cause.

Two patterns suggested the potential for recall bias to explain at least a portion of the observed associations between pesticide exposure and Parkinson's disease: decreases in risk between self-reported and hygiene-reviewed exposures and decreases in risk after adjustment for participants' belief that chemicals were a cause. In our study, 27.5% of cases with Parkinson's disease reported chemicals (including pesticides) as a cause of Parkinson's disease; the corresponding percentage for controls was 10.6%. This difference indicates a greater suspicion of a chemical cause among cases than controls; the risk esti-

mates for pesticide exposures decreased when controlling for this factor, meaning that suspecting a chemical cause was also associated with reporting pesticide exposure.

Evidence of recall bias in case–control studies has generally been sparse, except with open-ended questioning of exposure or where participants suspect a disease cause (22, 23). Difficulties in recall of pesticides have been shown to differ between cases and controls in a general population sample (24). Adjusting for suspicions of hypothesized causation may be inadvisable as a routine practice, particularly if knowledge is causally related to exposure or if exposed cases become knowledgeable about the hypotheses post-diagnosis (25). The former seems unlikely in our study, although the latter is possible, so we cannot know with certainty that the effect we observed was indeed due to recall bias.

Our results raise the question of whether the prior studies may have been subject to recall bias. Previous studies that, like ours, obtained information on exposure to pesticides from interviews have this potential (4–11, 21). Nevertheless, two cohort studies using prospective self-reports of exposure, which should not be prone to recall bias, found associations between exposure to pesticides as a group and risk of Parkinson's disease (12, 13).

Non-differential misclassification of exposure to pesticides is also an important issue, which could exist in our study and thus bias our results towards the null (26). Reducing non-differential misclassification of exposure was one of the purposes of the industrial hygiene review of exposures. We expected risk estimates to be higher for hygiene-reviewed than self-reported exposures, but the opposite was the case, initiating our suspicion of recall bias.

Agricultural employment versus pesticide exposure: what is measured?

We observed a significantly increased risk of Parkinson's disease among those reporting an agricultural job, with a risk estimate higher than those for pesticides. The finding for agricultural jobs was little influenced by adjustment for pesticide exposure or participants' beliefs that chemicals are a cause.

This raises the question of whether there is something else about agricultural work that might be related to Parkinson's disease. A number of studies (27–29), though not all (30), have reported associations between agricultural jobs and Parkinson's disease. Most investigators have related these associations to the use of pesticides in these jobs. However, a recent Australian study investigated the extent to which farm-related jobs indicated pesticide exposure (31) and found that only 22% likely had exposure. In our study, 51% of those in agricultural jobs were classified as "pesticide exposed". Farming jobs may share many other potential exposures, including solvents, fuels, fuel exhaust, dusts, micro-organisms, and traumatic injuries, many of which would be useful to examine in the context of Parkinson's disease. An exposure of particular interest could be endotoxin, a lipopolysaccharide component of gram-negative bacterial cell walls. Lange and coworkers (32) are among the researchers who have posited that part of the elevated risk of Parkinson's disease associated with agriculture could be explained by exposure to endotoxin, because exposure is common in the agricultural sector and there is mechanistic support from animal experiments (33).

It would be worthwhile to consider the potential for other etiological exposures to explain at least some portion of the increased risks of Parkinson's disease observed among farmers or those assessed as being exposed to pesticide due to farming jobs (12, 14–16).

Recent case–control studies

In other recent case–control studies, the diversity of results related to pesticide exposures and agricultural work has continued. Elbaz and colleagues (4) found increased risks with professional pesticide use, especially insecticides, though they mentioned the possibility of increased awareness among cases of the possible link between Parkinson's disease and pesticides (4). Tanner et al (8) found increased risks for self-reported use of pesticides, increasing when restricted to eight specific pesticides with high neurotoxic plausibility (very similar to our classification), but agricultural work was not found to be a risk factor. Firestone and colleagues (10) found no significant association between self-reported exposure to pesticides or agricultural work and Parkinson's disease. Regional differences in exposure patterns between study populations and methodological differences (eg, different methods of ascertaining exposure) might partly explain these inconsistent results.

Despite the large number of studies investigating the possible association between pesticide exposure and Parkinson's disease, few epidemiological studies have found associations between exposure to a specific pesticide and Parkinson's disease. In a study using geographic information systems and historic information on pesticide use, exposure to the pesticides maneb and paraquat was found to be associated with risk of Parkinson's disease (17). To pinpoint specific pesticides in an interview based case–control study, the participants' memories need to be exceptional and the number of study participants needs to be very large. To illustrate the number of subjects needed to detect a significantly increased risk of Parkinson's disease for a specific

pesticide, we calculated the sample size needed, using the pesticide with the highest proportion of controls exposed in this study [DDT (5 of 405)]. With a significance level of 5%, power of 80% and equal numbers of cases and controls, 1500 cases and controls would be needed to detect an OR of 2.0.

Strengths and limitations

Like most case–control studies, we had in-person physical assessment of potential cases and included assessments of participants' lifestyle habits to allow control for smoking's negative association with Parkinson's disease (34). The assessment of pesticide exposure collected detailed information on the type of contact and operations performed enabling two hygiene reviews on sensitivity and specificity, respectively, both blind to case status. A list of pesticides with common names and brand names were provided to participants in advance to improve recall (see appendix) (22). Our study appears to be the only one to date that has attempted to evaluate recall bias based on participants' beliefs about the causes of Parkinson's disease.

A limitation of our study was the potential for participation bias, since those agreeing to take part in the study might differ from those refusing. Our study population was restricted to those in the age group 40 69 years, potentially limiting the generalizability of our results to older Parkinson's patients.

Further, our study was underpowered to detect 2-fold-difference associations between subcategories of pesticide exposure with a prevalence of <4% in controls. Most of our pesticide groups had sufficient power, but the number of participants who reported exposure to individual pesticides was very small, preventing analyses of most individual pesticides. The diversity of pesticide active ingredients used by this study sample reflects the diversity of farming in the province, including fruit (apple, peaches, cherries, grapes, plums, blueberries, raspberries, cranberries), market vegetable (lettuce, tomatoes, sweet peppers, cucumbers, mushrooms), grain, and flower crop farming, as well as cattle ranching and dairy farming. The resulting variety of pesticides used is another factor that lessens the likelihood that pesticides are an important cause of Parkinson's disease in this population; there is little specificity of the chemicals. In addition, few of the study subjects had exposures to the pesticides used in animal models of Parkinson's disease (35): one case and four controls reported exposure to rotenone; three cases and three controls reported exposure to paraquat; and no one reported exposure to maneb.

In summary, the results of this study do not lend support to an association between pesticide exposure and Parkinson's disease. Our results emphasize the importance of considering recall bias, via a hygiene review to ensure specificity of exposure ascertainment, and by considering the participants' beliefs about the disease cause. The results related to agricultural work suggest that it would be valuable for future studies to explore other exposures of this occupational group that may be related to Parkinson's disease, such as bacterial endotoxin (32, 36).

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Appendix. List of pesticides sent out to the participants prior to the interview.

Chemical name	Brand and common names
Fungicides	
Captan	Agrox D-L Plus, Orthocide
Chlorothalonil	Bravo, daconil 2787, Exotherm Termil, Termil
Copper oxychloride	Basicop, Coprantol, Fixed copper, mar-cop, neutron-Cop, Tri-Cop
Dodine	Cyprex, Equal
Formaldehyde	Formalin, Methanol
Lime sulphur or calcium polysulphide	Orthorix
Mancozeb	Dithane M-45, manzate 200
Maneb	Co-op DP, Ditane M-22, Mantox, Manzae, Mergamma, Pool NM Dual, Tersan LSRF
Metam	Pole-Fume, SMDC, Unifume Soil, Vapam, VPM, Woodfume
Metiram	Polyram
Quintozene	Brassicol, PCNB, terrachlor
Sulphur	Flortex, Giant Destroyer, Gopher Gasser, Kolodust, Kolospray, Magnetic 6, Ortho Flotox, Woodchuck Bombs
Ziram	Zerate
Herbicides and plant growth regulators	
2,4,5-T	Dacamine-4T, Esteron 2,4,5-T, Poison Ivy and Brush Killer, Reddox, Trinoxol, Veon, Verton 2T, Weedone 2,4,5-T
2,4-D	2,4-D, Amkil, Aqua-Kleen, Calmix, Chlorxone, Dacamine, Desormone 7, Diachlorprop, Driamine, Estakil, Estasol, Estemine 500, Esteron, Esteron 64, Foestamine, For-ester, Formula 40-F, Herbate, Hoe-Grass, Kilmor, Rustler, Salvo, Silvaprop, Sure-Shot Forest amine, Target, Ten-Ten, Verton, Weedar, Weedar-64, Weedaway, Weed-B-Gone, Weedex, Weedone, Weed-Rhap
Atrazine	Aatrex, Atra-Mix, Eramox 80W, gesaprim, Laddox, Marzone, Primatol A, Primextra, Vectal Atrazine
Bifenox	Modown
Chlormequat	Cycocel
Difenzoquat	Avenge
Diquat	Reglone, Reglone-A, Weedrite
Ethalfluralin	Edge
Glyfosate	Roundup, Rustler, Side-Kick, Vision
MCPA amine	Agritox, Agroxone, Bromox, Buctril, Estemine MCPA, Estakil MCPA, MCP, Mephanac, Methoxone Amine 500, No Weed, Sabre, Weedar MCPA, Weedgone MCPA
Metolachlor	Dual, Primextra
Morfamquat	Morfoxone
Norflurazon	Evitol, Zorial
Paraquat	Gramoxone, Gramoxone S, Paraquat CL, Sweep, Terraklene, Weed Rite
Simazine	Gestatop, Primatol S, Princep, Simmaprim, Simadex
Sodium chlorate	Atlacide, Atratol, Chlorax, Monobor-Chlorate, Ureabor
Sodium metaborate tetrahydrate	Borate, Ureabor
Triallate	Avadex-BW
Insecticides	
Allethrin	Allethrin, Synthetic Pyrethrin
Azinphos-methyl	APM, Gurhion
Cypermethrin	Ripcord
Dichlorodiphenyltrichloroethane	DDT
Diazinon	Basudin
Dieldrin	Dieldrin
Heptachlor	Heptachlor
Lindane	Agrox D-L Plus, Benolin, Co-op DP, Gamma BHC, Gammasan, Mergamma, Pool NM Dual, Thiralin, Vitaflo DP, Vitavax
Malathion	Cythion
Mineral oil	Agricultural Weedkiller #1, Dormant Oils, Petroleum Oils, Petroleum Solvents, Stoddart Solvents, Summer Oil, Superior Oil, Supreme Oil, Volck Oil, Weed Oils
Nicotine	Black Leaf 40, Nicotine, Nicotine Sulfate
Rotenone	Atox, Deritox, Derris, Noxfish Fish Toxicant, Rotenone Fish Poison
Wood preservatives	
3-iodo-2-propyl butyl carbamate	IPBC, NP-1, Troysan Polyphase P 100, Troysan Polyphase
Borax	Borascu, Boron, Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, Ecobrite III, F-2, Pole-Peg
Chromated copper arsenate	CCA
Creosote	Coal Tar Creosote, Pole-Peg
Didecyl dimethyl ammonium chloride	DDAC, Ecobrite III, F-2, NP-1, Timbercote II, Timbercote 2000
Pentachlorophenol	Alchem, Dowwicide, Diatox, PCP, Penta, Pole-Peg, Santobrite, Woodbrite, Woodsheath
Sodium carbonate	Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, SCB
Rodenticides	
Brodifacoum Bromadiolone	Ratak, Talon
Fumigants	
Methyl bromide	Brom-O-Gas, Dowfume, Dowfume MC-2, Meth-O-Gas, Sanex MB-C-2, Terr-O-Gas 67
Carbon disulfide	Dowfume, FIA 80-2, Kenfume bin fumigant, Sanifume
Hydrogen cyanide	Cyanogas, calcium cyanide, HCN

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Self-reported chemicals exposure, beliefs about disease causation, and risk of breast cancer in the Cape Cod Breast Cancer and Environment Study: a case-control study

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Abstract

Background: Household cleaning and pesticide products may contribute to breast cancer because many contain endocrine disrupting chemicals or mammary gland carcinogens. This population-based case-control study investigated whether use of household cleaners and pesticides increases breast cancer risk.

Methods: Participants were 787 Cape Cod, Massachusetts, women diagnosed with breast cancer between 1988 and 1995 and 721 controls. Telephone interviews asked about product use, beliefs about breast cancer etiology, and established and suspected breast cancer risk factors. To evaluate potential recall bias, we stratified product-use odds ratios by beliefs about whether chemicals and pollutants contribute to breast cancer; we compared these results with odds ratios for family history (which are less subject to recall bias) stratified by beliefs about heredity.

Results: Breast cancer risk increased two-fold in the highest compared with lowest quartile of self-reported combined cleaning product use (Adjusted OR = 2.1, 95% CI: 1.4, 3.3) and combined air freshener use (Adjusted OR = 1.9, 95% CI: 1.2, 3.0). Little association was observed with pesticide use. In stratified analyses, cleaning products odds ratios were more elevated among participants who believed pollutants contribute "a lot" to breast cancer and moved towards the null among the other participants. In comparison, the odds ratio for breast cancer and family history was markedly higher among women who believed that heredity contributes "a lot" (OR = 2.6, 95% CI: 1.9, 3.6) and not elevated among others (OR = 0.7, 95% CI: 0.5, 1.1).

Conclusions: Results of this study suggest that cleaning product use contributes to increased breast cancer risk. However, results also highlight the difficulty of distinguishing in retrospective self-report studies between valid associations and the influence of recall bias. Recall bias may influence higher odds ratios for product use among participants who believed that chemicals and pollutants contribute to breast cancer. Alternatively, the influence of experience on beliefs is another explanation, illustrated by the protective odds ratio for family history among women who do not believe heredity contributes "a lot." Because exposure to chemicals from household cleaning products is a biologically plausible cause of breast cancer and avoidable, associations reported here should be further examined prospectively.

Background

Pesticides, household cleaners, and air fresheners are of interest in breast cancer research because many contain ingredients that are mammary gland carcinogens in animals [1] or endocrine disrupting compounds (EDCs), including compounds that affect growth of estrogen-sensitive human breast cancer cells [2] or affect mammary gland development [3]. Mammary gland tumors have been observed in animal studies of pesticides such as dichlorvos, captafol, and sulfallate; methylene chloride (in some fabric cleaners); nitrobenzene (soaps, polishes); and perfluorinated compounds (stain-resistant, waterproof coatings) [1,4,5]. Phthalates, alkylphenols, parabens, triclosan, and polycyclic musks used as

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surfactants, solvents, preservatives, antimicrobials, and fragrances have shown weak estrogenic or anti-androgenic effects in both *in vitro* and *in vivo* tests [4-16]. Pesticides identified as EDCs include dichlorodiphenyl trichloroethane (DDT), chlordane, methoxychlor, atrazine, lindane (lice control), vinclozolin and benomyl (fungicides), and several current use insecticides such as cypermethin [6-13]. When given early in life, atrazine, nonylphenol, perfluorinated compounds, and the plastics monomer bisphenol A influence rat mammary gland development in a way that may affect tumor susceptibility [14-18]. These chemicals are widely used and many have been detected in blood and urine from a representative sample of the US population; concentrations vary over several orders of magnitude [19-26]. In household air and dust and women's urine tested in the Cape Cod Breast Cancer and Environment Study, we detected an average of 26 EDCs per home, including 27 pesticides and a variety of estrogenic phenols from household cleaners [27]. Taken together, the laboratory studies of biological activity and evidence of widespread human exposure suggest that use of products containing mammary gland carcinogens or EDCs may contribute to breast cancer in humans.

No epidemiological studies we know of have reported on the relationship between cleaning product use and breast cancer, and previous breast cancer studies of pesticides have been largely limited to organochlorine compounds [28]. Organochlorine studies have been mostly null, but interpretation is limited because proxies of exposure were measured in blood taken years after the compounds were banned in the US, often in older women and after diagnosis [29]. In a study that avoids these limitations by using archived blood collected from young women in 1959 to 1967, Cohn et al. [30] reported five-fold higher breast cancer risk among women who had the highest residues of DDT and were exposed before they were 14 years old. In addition, the Long Island Breast Cancer Study found 30% higher breast cancer risk among women who reported the highest home pesticide use [31]. Self-reported product use, such as the Long Island measures, has the potential to represent exposure over many years to a wide range of compounds; although retrospective reports may be biased by differential reporting accuracy between cases and controls [32].

To investigate the relationship between use of cleaning and pesticide products and risk of breast cancer, while considering possible recall bias, we conducted a case-control study of breast cancer and self-reported product use on Cape Cod, Massachusetts, in which we also measured beliefs about breast cancer causation, a possible source of recall bias. Cape Cod is a coastal peninsula where breast cancer incidence has been elevated. Annual female breast cancer incidence in 2002 - 2006 was 151.0 per 100,000 (95% CI 142.6 - 159.8) [33]. The pattern of higher incidence in Cape Cod towns than elsewhere in Massachusetts dates to the initiation of the state cancer registry in 1982 [34]. In the Collaborative Breast Cancer Study, risk was elevated among Cape Cod women compared with other Massachusetts participants after controlling for breast cancer risk factors [35]. In the Cape Cod Breast Cancer and Environment Study case-control study, longer years of residence on Cape Cod was associated with higher risk after controlling for established breast cancer risk factors [36].

Methods

Study population

Details of the Cape Cod Study have been described previously [37]. Briefly, we conducted a case-control study of invasive breast cancer occurring on Cape Cod in 1988-1995. Cases were female permanent residents of Cape Cod for at least six months before a breast cancer diagnosis reported to the Massachusetts Cancer Registry (MCR). Controls were female permanent Cape Cod residents during the same years, had resided there at least six months, and were frequency matched to cases on decade of birth and vital status. Controls under 65 years of age were selected using random digit dialing; controls over 65 years of age were randomly selected from the Centers for Medicare and Medicaid Services (CMS).

The Cape Cod Study expands on a study of breast cancer and tetrachloroethylene (PCE) in drinking water [38]. Cases diagnosed in 1988-1993 in eight towns and their controls were interviewed in 1997-1998 in the PCE study. Cases diagnosed in 1994-1995 in those eight towns and in 1988-1995 in the remaining seven towns and their controls were interviewed in 1999-2000. Among 1,578 eligible living and deceased cases identified by MCR, 1,165 women (74%) or their proxies participated, 228 (14%) could not be located or contacted, and 185 (12%) refused to participate. Among 1,503 eligible controls, 1,016 (68%) participated.

For the present analysis, we excluded 368 cases and 287 controls who were interviewed by proxy, and 10 cases and eight controls who were missing data for one or more key analytic variables. Given that most women for whom we obtained proxy interviews were deceased, excluded women were older, and, consistent with being older, they were less educated. Within the included or excluded groups, cases and controls did not differ demographically, suggesting no selection bias. Exclusions left 787 cases and 721 controls for pesticide analyses. Cleaning product questions were asked only in 1999-2000 interviews, resulting in 413 cases and 403 controls for whom these data were available.

We obtained permission to use confidential data from MCR, CMS, and hospitals where cases were diagnosed. The Boston University Institutional Review Board and Massachusetts Department of Public Health Human Research Review Committee approved the study protocol. Participants were asked for informed consent at the outset of interviews.

Interviews

Trained telephone interviewers administered a structured questionnaire on established and hypothesized breast cancer risk factors including family history of breast cancer, menstrual and reproductive history, height, weight, alcohol and tobacco use, physical activity, pharmaceutical hormone use, and education. Information on residential cleaning product and pesticide use was obtained. Participants in 1999-2000 interviews were asked about five categories of cleaning products, including solid and spray air fresheners, surface cleaners, oven cleaners, and mold/mildew products. All participants were asked about use of 10 categories of pesticides in and around their homes, including insecticides, lawn care, herbicides, lice control, insect repellents, and pest control on pets. The 1999-2000 interviews asked about mothballs and treatments for termites and carpenter ants. Participants were first asked if the product was ever used in their home. Participants were then asked to estimate frequency of use using predefined categories. To exclude exposures after diagnosis or index year, participants were asked to report the first and last years of use for pesticides, and use before their diagnosis or index year for cleaning products. At the end of the interview, participants were asked about their beliefs about four factors that may contribute to breast cancer: heredity, diet, chemicals and pollutants in the air or water, and a woman's reproductive or breastfeeding history. Participants were asked whether each contributes to breast cancer "a lot, a little, or not at all." "Don't know" responses were coded. Interview questions can be viewed at http://silentspring.org/cape-cod-breast-cancer-and-environment-study-survey-instruments.

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The following "core" matching variables and potential confounders were included in adjusted odds ratio analyses based on *a priori* consideration of the research design and well-established breast cancer risk factors: age at diagnosis or index year, education, family history of breast cancer in a first degree female relative, breast cancer diagnosis prior to the current diagnosis or index year, and age at first live or still birth (≥ 30 years of age or nulliparous vs. < 30 years of age). Pesticide analyses were adjusted for study (PCE or Cape study). Missing values for family history for 45 (3%) participants were imputed as "no." The percent missing information on family history did not differ between cases and controls. The following potential confounders were evaluated: mammography use, medical radiation, lactation, hormone replacement therapy, oral contraceptive use, diethylstilbestrol exposure, body mass index, smoking, alcohol consumption, teen and adult physical activity, race, marital status, and religion. None of these variables changed the "core"-adjusted odds ratio estimates by ≥ 10%, so they were not included in final models.

We evaluated ever vs. never use and categorical variables reflecting frequency of use. "Never users" of each product type formed the reference group. If a participant reported ever using a product but the frequency was missing, frequency was imputed as the median for that product. To aggregate "like" exposures, three variables were constructed by summing frequency of use for two types of air fresheners, five types of cleaning products, and eight types of pesticides. Aggregated scores were divided into quartiles based on the distribution of controls. The lowest quartile constituted the reference group. Tests for trends were conducted by modeling ordinal terms for categories of product use or quartiles in the multivariate model.

Because participants' awareness of a hypothesis may bias exposure reporting [39], we evaluated differences in beliefs about disease causation between cases and controls using the chi square test. We evaluated differences in product-use odds ratios by beliefs about whether chemicals/pollutants contribute to breast cancer by 1) including an interaction term for beliefs and product use in the final model and 2) stratifying by beliefs. Beliefs were dichotomized as those who said chemicals/pollutants contribute to breast cancer "a lot" versus "a little," "not at all," or "don't know."

Weiss [40] notes that recall bias is not the only explanation for differences in odds ratios by knowledge or attitudes about a hypothesis; so to aid interpretation of product use results, we conducted a comparison analysis of differences in family history odds ratios by beliefs about whether heredity contributes "a lot" to breast cancer. This comparison is useful, because the accuracy of self-reported family history can be compared with medical records, and the relationship between family history and breast cancer is well-established independent of self-reports. As a sensitivity analysis, we also examined un-stratified and stratified family history odds ratios excluding those subjects who were missing information on family history.

All analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC). Figures were constructed in R software 2.6.1, (R Foundation for Statistical Computing,

Vienna, Austria). Statistical significance was defined by a (two-sided) P -value of 0.05 or lower.

Results

Study participants were predominantly white (98%), 60-80 years of age (60%) with high school or higher education (94%); more cases (25%) than controls (19%) reported a family history of breast cancer. Characteristics of participants are shown in Table 1. Participants in this analysis of product use were demographically similar to characteristics previously reported for all cases and controls, except for being younger and more educated, due to exclusion of proxy interviews [37].

Table 1 Characteristics of Cape Cod Breast Cancer and Environment Study participants with completed pesticide use self-reports

	Cases (N = 787)		Controls (N = 721)	
Characteristic	**N**	**%**	**N**	**%**
Age at diagnosis or index year				
< 50	128	16	149	21
50-59	115	15	129	18
60-69	277	35	226	31
70-79	221	28	184	26
≥ 80	46	6	33	5
Education				
< High school graduate	36	5	48	7
High school graduate	241	31	226	31
1-3 years college/vocational school	253	32	230	32
College graduate	144	18	122	17
Graduate work/degree	113	14	95	13
Family history of breast cancer				
Yes	196	25	135	19
No	591	75	586	81
Prior history of breast cancer				
Yes	48	6	46	6
No	739	94	675	94
Age at first live or stillbirth				
< 20	171	22	122	17
20-29	104	13	80	11
> = 30	458	58	456	63
Nulliparous	54	7	63	9
Menopause status at diagnosis or index year				
Pre-menopause	144	19	194	28
Post-menopause	615	81	505	72

Data for 27 cases and 18 controls were missing for the "Family history of breast cancer" characteristic. Data for 28 cases and 22 controls were missing for the "Menopause status at diagnosis or index year" characteristic.

Products use

Breast cancer risk increased approximately two-fold in the highest compared with lowest quartile of combined cleaning product use (OR = 2.1, 95% CI: 1.4, 3.3) and combined air freshener use (OR = 1.9, 95% CI: 1.2, 3.0) (Table 2). Ever use of air freshener spray (OR = 1.2, 95% CI: 0.9, 1.8), solid air freshener (OR = 1.7, 95% CI: 1.2, 2.3) or mold/mildew control (OR = 1.7, 95% CI: 1.2, 2.3) was associated with higher risk, with evidence of positive dose response and significant P_{trend} for solid air freshener and mold/mildew control with bleach. Surface and oven cleaners were not associated with breast cancer risk.

Combined use of pesticide products was not associated with risk of breast cancer (Table 3). Odds ratios for individual pesticide types were null or slightly and nonsignificantly elevated, with the exception of insect repellent use (OR = 1.5, 95% CI: 1.0, 2.3 for most frequent insecticide use compared with never use; P_{trend} = 0.05).

Differences by beliefs about disease causation

Cases and controls differed significantly in beliefs about the role of heredity and of chemicals and pollutants in breast cancer (Table 4). Among controls, 66% said heredity contributes "a lot" compared with 42% of cases (P < 0.01); 57% of controls and 60% of cases said "chemicals and pollutants in the air or water" contribute "a lot" (P < 0.05).

In stratified analyses, odds ratios for cleaning products were consistently elevated within the group who said chemicals/pollutants contribute "a lot" to breast cancer, but associations moved towards the null in the other participants (Table 5). For example, the odds ratio for the highest quartile of combined cleaning product use was 3.2 (95% CI: 1.8, 5.9) among women who believed chemicals/pollutants contribute "a lot" compared to 1.2 (95% CI: 0.6, 2.6) among others. The interaction was not statistically significant (P = 0.25). (However, the interaction term does not detect departures from additivity.)

Similarly, odds ratios for pesticides were higher among participants who believed that chemicals/pollutants contribute "a lot" to breast cancer. For example, the odds ratio for most frequent insect repellent use was 2.0 (95% CI: 1.1, 3.4) in this belief group compared with 0.8 (95% CI: 0.4, 1.6) among others. Pesticide odds ratios stratified by beliefs are shown in Table 6.

In addition, a similar pattern was observed in the odds ratios for family history of breast cancer stratified by

Table 2 Adjusted odds ratios for breast cancer and reported cleaning product use, Cape Cod, Massachusetts, 1988-1995

Product category	Cases (No.)	Controls (No.)	Adjusted OR	95% CI	P_{trend}
Combined cleaning product use					
Quartile 1	91	99	1.0	Reference	
Quartile 2	100	107	1.1	0.8, 1.7	
Quartile 3	112	125	1.1	0.7, 1.7	
Quartile 4	104	70	2.1	1.4, 3.3	0.003
Combined air freshener use (sprays and solids)					
Quartile 1	74	77	1.0	Reference	
Quartile 2	113	117	1.1	0.7, 1.7	
Quartile 3	123	138	1.0	0.7, 1.6	
Quartile 4	101	71	1.9	1.2, 3.0	0.02
Air freshener spray					
Never use	90	95	1.0	Reference	
Any use	322	308	1.2	0.9, 1.8	
< Once a month	83	88	1.1	0.7, 1.7	
Monthly	47	41	1.3	0.8, 2.3	
Weekly	114	110	1.3	0.8, 1.9	
Daily	78	69	1.3	0.8, 2.1	0.15
Solid air freshener					
Never use	259	288	1.0	Reference	
Any use	153	115	1.7	1.2, 2.3	
< 2 times/year	50	41	1.4	0.9, 2.2	
2-6 times/year	77	58	1.7	1.2, 2.6	
≥ 7 times/year	26	16	2.0	1.0, 4.0	0.001
Oven cleaner					
Never use	33	33	1.0	Reference	
Any use	379	370	1.0	0.6, 1.7	
< 2 times/year	145	143	1.0	0.6, 1.8	
2-6 times/year	199	196	1.0	0.6, 1.7	
≥ 7 times/year	35	31	1.2	0.6, 2.3	0.80
Surface cleaner					
Never use	53	54	1.0	Reference	
Any use	359	348	1.1	0.7, 1.7	
< Once a month	61	60	1.0	0.6, 1.6	
Monthly	57	57	1.0	0.6, 1.8	
Weekly	186	171	1.2	0.8, 1.9	
Daily	55	60	1.2	0.7, 2.2	0.22

Table 2 Adjusted odds ratios for breast cancer and reported cleaning product use, Cape Cod, Massachusetts, 1988-1995 *(Continued)*

Mold/mildew control					
Never use	296	322	1.0	Reference	
Any use	114	81	1.7	1.2, 2.3	
Mold/mildew control with bleach					
Never use	320	334	1.0	Reference	
Any use	90	68	1.5	1.0, 2.1	
< Once a month	47	38	1.2	0.8, 2.0	
Monthly	14	11	1.5	0.7, 3.5	
≥ Weekly	29	19	2.0	1.1, 3.8	0.02

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories). "Combined cleaning product use" combines frequency of use across five product categories: air freshener spray, solid air freshener, oven cleaner, surface cleaner, and mold/mildew control with bleach.

beliefs about heredity as a cause. The odds ratio for breast cancer and family history was markedly higher among women who believed that heredity contributes "a lot" (OR = 2.6, 95% CI: 1.9, 3.6) and not elevated among others (OR = 0.7, 95% CI: 0.5, 1.1, interaction term $P < 0.01$). The parallel pattern of results for both cleaning products and family history when stratified by relevant beliefs is shown in Figure 1. (For all participants, the odds ratio for family history was 1.4 (95% CI: 1.1, 1.9)). The un-stratified and stratified effect estimates for family history of breast cancer in adjusted models remain virtually unchanged after removing subjects with imputed values for family history.

Discussion

Women with the highest combined cleaning product use had two-fold increased breast cancer risk compared to those with the lowest reported use. Use of air fresheners and products for mold and mildew control were associated with increased risk. To our knowledge, this is the first published report on cleaning product use and risk of breast cancer.

Some common ingredients of air fresheners and products for mold and mildew have been identified as EDCs or carcinogens, supporting the biological plausibility of the elevated odds ratios we observed [1,15,41-51]. EDCs such as synthetic musks and phthalates are commonly used in air fresheners [19,25-27,43,48,52-54] and antimicrobials, phthalates, and alkylphenolic surfactants are often in mold and mildew products [19,22-24,26,27,41,42,44,47,49,55]. In addition, air fresheners may contain: terpenes, which can react with background ozone to form formaldehyde, a human carcinogen [50]; benzene and styrene [51], which are animal mammary gland carcinogens [1]; and other chemicals whose mechanisms of action are not understood [56]. Although exposure levels may be low and EDCs are typically less potent than endogenous hormones, limited knowledge of product formulations, exposure levels, and the biological activity and toxicity of chemical constituents alone and in combination make it difficult to assess risks associated with product use. Additionally, the products we assessed may be proxies for other products that we did not include, and mold/mildew products may be proxies for exposure to mycotoxins, some of which are EDCs [2,57-59].

Our results do not corroborate the findings of a Long Island, NY, case-control study [31]. The Long Island study found increased breast cancer risk associated with self-reported overall pesticide use and use of lawn and garden pesticides, but we did not. Neither study found associations for nuisance pest control (roaches, ants, etc.). While we observed increased risk with frequent use of insect repellent, the Long Island study did not. Differences between the studies may be due to differences in pesticide practices in the two regions, greater statistical power in the Long Island study, or differences in the survey instruments. Phthalates and permethrins, which are in some insect repellents, have been identified as EDCs [10,13,46,60].

Using interviews to assess product-related exposures, as we did in this study, has several advantages. It is inexpensive, noninvasive, and integrates exposures over many years and to frequently-occurring chemical mixtures. Currently available biological measures cannot achieve these important characteristics.

However, self-reported exposures are subject to multiple sources of error resulting in misclassification. Our questions were cognitively demanding in that they asked participants to report behaviors occurring months to years before. Responses failed to capture use by others, including residues from before the participant moved into the

Table 3 Adjusted odds ratios for breast cancer and residential pesticide use, Cape Cod, Massachusetts, 1988-1995

Product category	Cases (no.)	Controls (no.)	Adjusted OR	(95% CI)	P_{trend}
Combined pesticide use					
Quartile 1	173	152	1.0	Reference	
Quartile 2	110	99	1.0	0.7, 1.5	
Quartile 3	169	143	1.1	0.8, 1.5	
Quartile 4	153	126	1.1	0.8, 1.6	0.52
Insect or bug control					
Never use	161	151	1.0	Reference	
Any use	569	514	1.1	0.9, 1.4	
Once or twice	161	155	1.0	0.7, 1.4	
3-10 times	203	188	1.1	0.8, 1.5	
> 10 times	205	171	1.2	0.8, 1.6	0.21
Termite or carpenter ant control					
Never use	293	265	1.0	Reference	
Any use	165	161	0.9	0.6,1.2	
Once or twice	105	85	1.0	0.7,1.5	
3-10 times	35	49	0.6	0.4,1.0	
> 10 times	25	27	0.8	0.4,1.4	0.11
Mosquito control					
Never use	314	312	1.0	Reference	
Any use	91	87	1.0	0.7, 1.5	
Once or twice	15	18	0.9	0.5. 1.9	
3-10 times	35	31	1.1	0.7, 1.9	
> 10 times	41	38	1.0	0.6, 1.7	0.79
Mothball control					
Never use	73	91	1.0	Reference	
Any use	340	312	1.2	0.8, 1.7	
< 5 times	92	90	1.2	0.8, 1.9	
5-10 times	62	73	0.9	0.6, 1.5	
> 10 times	186	149	1.3	0.9, 1.9	0.29
Lawn care					
Never use	316	286	1.0	Reference	
Any use	408	343	1.1	0.9, 1.3	
Once or twice	43	35	1.2	0.7, 1.9	
3-20 times	174	136	1.2	0.9, 1.6	

Table 3 Adjusted odds ratios for breast cancer and residential pesticide use, Cape Cod, Massachusetts, 1988-1995 *(Continued)*

> 20 times	191	172	1.0	0.7, 1.3	0.88
Outdoor and indoor plant care					
Never use	407	359	1.0	Reference	
Any use	334	300	1.0	0.8, 1.2	
Once or twice	33	26	1.1	0.6, 1.8	
3-20 times	158	146	1.0	0.7, 1.3	
> 20 times	143	128	1.0	0.7, 1.3	0.71
Insect repellent					
Never use	286	271	1.0	Reference	
Any use	482	428	1.2	0.9, 1.5	
Rarely	283	263	1.1	0.9, 1.5	
Sometimes	133	115	1.2	0.9, 1.7	
Often/Very often	66	50	1.5	1.0, 2.3	0.05
Lice control					
Never use	692	626	1.0	Reference	
Any use	89	83	1.2	0.8, 1.6	
Flea collar for pets					
No	257	238	1.0	Reference	
Yes	529	482	1.2	0.9, 1.5	
Flea control for pets					
Never use	465	395	1.0	Reference	
Any use	294	286	1.0	0.8, 1.2	
Once or twice	43	41	0.9	0.6, 1.5	
3-10 times	101	109	0.9	0.6, 1.2	
> 10 times	150	136	1.1	0.8, 1.4	0.95

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories), study (Cape, PCE). "Combined pesticide use" product category includes frequency data for: insect or bug control, lawn care, outdoor and indoor plant care, insect repellent, flea control on pets. Product use for termite or carpenter ant control, mosquito control, and mothball control not included because they were only assessed in study participants from the 1999-2000 interviews.

residence; exposures specific to critical periods such as adolescence; exposures outside the home; or all products that contain the chemicals of interest. Although we asked about the first and most recent years of pesticide use, we considered the quality of these data inadequate to evaluate effects of duration of use. Much of the error resulting from limitations in exposure measurement is likely nondifferential, biasing odds ratios toward the null.

Self-reports are also vulnerable to bias from differential recall between cases and controls. Women diagnosed with breast cancer may have searched their history for explanations, priming greater recall of product use than for controls. Werler [39], among others, hypothesizes that this type of bias occurs when cases are aware of the study hypothesis, resulting in higher exposure reporting and, consequently, an elevated odds ratio. We empirically investigated this possibility by stratifying odds ratios by beliefs about breast cancer causes, and, consistent with Werler's hypothesis, we observed higher odds ratios for product use among women who believe chemicals and pollution contribute "a lot" to breast cancer than among others.

Table 4 Beliefs about the causes of breast cancer by case status, Cape Cod, Massachusetts, 1988-1995

		Cases		Controls		
How much does ... contribute to breast cancer?		**No.**	**%**	**No.**	**%**	
Heredity	A lot	331	42	474	66	**
	A little	295	37	163	23	
	Not at all	99	13	36	5	
	Don't know	62	8	48	7	
Diet	A lot	217	28	205	28	
	A little	327	42	294	41	
	Not at all	160	20	125	17	
	Don't know	83	11	97	13	
Chemicals and pollutants in the air or water	A lot	476	60	412	57	*
	A little	188	24	203	28	
	Not at all	53	7	31	4	
	Don't know	70	9	75	10	
Women's reproductive or breast feeding history	A lot	67	9	70	10	
	A little	262	33	261	36	
	Not at all	245	31	225	31	
	Don't know	213	27	165	23	

Percentages may not add to 100% because of rounding. Two-sided P value calculated using chi square test; * indicates $P < 0.05$ and ** indicates $P < 0.001$.

However, the family history odds ratios stratified by beliefs suggest another interpretation. The much higher family history odds ratios for women who said heredity contributes "a lot" is unlikely to be primarily due to recall bias, given that self-reporting of first degree family members with breast cancer is generally accurate [61-66]. Previous research indicates that over-reporting of first degree breast cancer family history is negligible [63,65,66] and that some under-reporting by controls in comparison with cases is likely to occur (and could bias odds ratios), but this effect is unlikely to be substantial [64-66]. More likely, our results are primarily driven by cases who formed their belief that heredity does not contribute "a lot" after their own diagnosis, based on their own lack of relatives with breast cancer. Our data support this idea: 36% of cases with no family history said heredity contributes "a lot" to breast cancer compared with 61% of cases who did have a family history (Table 7). In this situation, an odds ratio for women who do not think heredity contributes "a lot" over-represents cases with no family history, lowering the effect estimate. Thus, our results support Weiss's argument [40] that limiting estimates to a subgroup based on beliefs about disease causation may introduce error. Among the group who do not believe heredity contributes "a lot" to breast cancer, the odds ratio of 0.7 (95% CI: 0.5, 1.1) contrasts sharply with the pooled odds ratio of 2.1 (95% CI: 2.0, 2.2) for first degree family history of breast cancer from previous studies [67]. Generally, Weiss argues, effect estimates based on one belief or knowledge subgroup lack precision and may underestimate the true effect, since they are limited to smaller numbers and not representative of the study population [40].

The divergent odds ratios in the stratified analysis for family history, which is not likely affected much by recall bias, warns us that the elevated odds ratios for cleaning products should not be too quickly dismissed as resulting from recall bias, since an alternative interpretation is that women's beliefs about disease causation result from their experience. Women who have been intensive product users and are then diagnosed with breast cancer may form the belief that chemicals influenced their risk, or they may be sensitized to news media stories about associations between chemicals and disease and form beliefs from this experience. Social scientists have studied the phenomenon of health beliefs formed from experience in a variety of settings, including the emergence of beliefs about environmental causation among breast cancer activists [68].

Furthermore, the substantial underestimate of risk for family history among women who said heredity does

Table 5 Adjusted odds ratios for breast cancer and cleaning product use stratified by disease causation beliefs

	Beliefs about environmental chemicals/pollutants and breast cancer									
	Contributes "a lot"					Does not contribute "a lot"				
Product category	**Cases (no.)**	**Controls (no.)**	**Adj. OR**	**95% CI**	**P_{trend}**	**Cases (no.)**	**Controls (no.)**	**Adj. OR**	**95% CI**	**P_{trend}**
Combined cleaning product use										
Quartile 1	39	55	1.0	Ref.		52	44	1.0	Ref.	
Quartile 2	58	69	1.4	0.8, 2.4		42	38	0.9	0.5, 1.8	
Quartile 3	71	74	1.6	0.9, 2.8		41	51	0.8	0.4, 1.4	
Quartile 4	77	47	3.2	1.8, 5.9	0.0001	27	23	1.2	0.6, 2.6	0.96
Combined air freshener use (sprays and solids)										
Quartile 1	34	43	1.0	Ref.		40	34	1.0	Ref.	
Quartile 2	67	71	1.3	0.7, 2.4		46	46	0.9	0.5, 1.7	
Quartile 3	76	86	1.3	0.7, 2.2		47	52	0.8	0.4, 1.6	
Quartile 4	69	46	2.4	1.3, 4.5	0.01	32	25	1.4	0.7, 3.0	0.53
Air freshener spray										
Never use	44	50	1.0	Ref.		46	45	1.0	Ref.	
Any use	203	196	1.3	0.8, 2.1		119	112	1.2	0.7, 2.0	
< Once a month	50	57	1.1	0.6, 2.0		33	31	1.1	0.6, 2.2	
Monthly	32	32	1.2	0.6, 2.3		15	9	1.9	0.7, 5.0	
Weekly	71	62	1.5	0.8, 2.6		43	48	1.0	0.6, 2.0	
Daily	50	45	1.4	0.8, 2.7	0.12	28	24	1.2	0.6, 2.6	0.66
Solid air freshener										
Never use	144	174	1.0	Ref.		115	114	1.0	Ref.	
Any use	102	72	1.9	1.3, 2.9		51	43	1.4	0.8, 2.3	
< 2/year	27	28	1.3	0.7, 2.3		23	13	1.9	0.9, 4.1	
2-6/year	58	32	2.6	1.6, 4.4		19	26	0.9	0.4, 1.8	
≥ 7/year	17	12	1.7	0.8, 3.9	0.0007	9	4	2.8	0.8, 10.2	0.31
Oven cleaner										
Never use	11	19	1.0	Ref.		22	14	1.0	Ref.	
Any use	236	227	1.8	0.8, 4.0		143	143	0.6	0.3, 1.2	
< 2/year	96	86	2.0	0.9, 4.6		49	57	0.4	0.1, 1.3	
2-6/year	112	121	1.5	0.6, 34		87	75	0.7	0.3, 1.5	
≥ 7/year	28	20	2.4	0.9, 6.5	0.58	7	11	0.4	0.1, 1.3	0.73
Surface cleaner										
Never use	29	36	1.0	Ref.		24	18	1.0	Ref.	
Any use	218	209	1.5	0.9,2.7		141	139	0.7	0.4,1.5	
< Once a month	23	30	0.9	0.4, 1.9		38	30	0.9	0.4, 2.0	
Monthly	39	36	1.5	0.7, 3.1		18	21	0.6	0.2, 1.4	
Weekly	120	103	1.7	1.0, 3.0		66	68	0.7	0.3, 1.5	

Table 5 Adjusted odds ratios for breast cancer and cleaning product use stratified by disease causation beliefs *(Continued)*

Daily	36	40	1.7	0.8, 3.6	0.02	19	20	0.8	0.3, 2.1	0.45
Mold/mildew control										
Never use	166	197	1.0	Ref.		130	125	1.0	Ref.	
Any use	80	49	2.1	1.4, 3.3		34	32	1.1	0.6, 2.0	
Mold/mildew control with bleach										
Never use	179	202	1.0	Ref.		141	132	1.0	Ref.	
Any use	67	44	1.8	1.2, 2.9		23	24	1.0	0.5, 2.0	
< Once a month	33	25	1.4	0.8, 2.5		14	13	1.1	0.5, 2.4	
Monthly	10	7	1.8	0.6, 5.1		4	4	1.1	0.3, 4.7	
≥ Weekly	24	12	3.2	1.4, 7.1	0.002	5	7	0.8	0.2, 2.7	0.83

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories). "Combined cleaning product use" product category combines frequency of use across five product categories: air freshener spray, solid air freshener, oven cleaner, surface cleaner, and mold/mildew control with bleach.

not contribute "a lot" cautions us against limiting product use analyses to a non-belief subgroup as a strategy for dealing with possible recall bias. In addition, the findings of elevated risk for some cleaning products and not others lends evidence that recall bias may not account for elevated risks, even if it contributes in part, since bias would be expected to similarly influence reporting for all the products.

Studies that rely on questionnaire data can sometimes assess the validity of self-reported data against another metric, such as chemical concentrations in relevant exposure media. For example, Colt et al. [69] found significant associations between self-reports of type of pest treated and concentrations of specific pesticides in house dust. We collected air, dust, and urine measurements for 120 homes and their residents, but comparison of these data with self-reports was not conducted for several reasons. The number of homes is small, the one-time environmental measurements may not correspond well with product use over years, measurements capture sources other than home product use, and our self-reports cover past residences as well as the sampled homes. Our ambiguous self-report findings point to the value of thoughtfully incorporating environmental chemical measurements into prospective cohort studies such as the National Children's Study and the Sister Study.

Overall strengths of our study are the population-based design with case identification from the MCR, extensive interviews allowing evaluation of possible confounding by established and hypothesized breast cancer risk factors, and assessment of exposures that extend years before diagnosis and encompass chemicals in use during the past 30 years as well as the more-studied banned organochlorines. Limitations include loss of information due to deaths of women with less treatable cancers. Also, we lack a truly unexposed reference group, limiting contrast in levels of exposure. The self-reported product use exposures have potential for differential and nondifferential error. We did not have adequate numbers to separately evaluate effects in younger women, though some other studies suggest that environmental pollutants may have greater influence on premenopausal disease [28].

To our knowledge, this is the first epidemiological study to suggest an association between cleaning product use, in particular air fresheners and products for mold and mildew control, and elevated breast cancer risk. This association is biologically plausible based on ingredients of these products, such as musks, antimicrobials, and phthalates [1-27,41-49,70-73], and these reported exposures may be proxies for other un-assessed causative exposures. The modest association and possibility of recall bias make interpretation tentative. Given widespread exposure to cleaning products and scented products, follow-up study is important. Prospective designs, which avoid differential recall, can be helpful. The difficulty of obtaining human evidence on environmental chemicals and breast cancer in the short-term means we must rely more on laboratory evidence as a basis for public health policies to control exposure.

Conclusions

Laboratory studies have found that many chemicals in home-use pesticides and household cleaning products are mammary gland carcinogens in rodents, influence

Table 6 Adjusted odds ratios for breast cancer and residential pesticide use stratified by disease causation beliefs

	Beliefs about environmental chemicals/pollutants and breast cancer									
	Contributes "a lot"					Does not contribute "a lot"				
Product category	**Cases (no.)**	**Controls (no.)**	**Adj. OR**	**95% CI**	**P_{trend}**	**Cases (no.)**	**Controls (no.)**	**Adj. OR**	**95% CI**	**P_{trend}**
Combined pesticide use										
Quartile 1	91	87	1.0	Ref.		82	65	1.0	Ref.	
Quartile 2	66	47	1.5	0.9, 2.5		44	52	0.7	0.4, 1.1	
Quartile 3	104	89	1.2	0.8, 1.9		65	54	1.0	0.6, 1.7	
Quartile 4	106	75	1.5	1.0, 2.4	0.16	47	51	0.7	0.4, 1.3	0.53
Insect or bug control										
Never use	81	78	1.0	Ref.		80	73	1.0	Ref.	
Any use	367	305	1.2	0.9, 1.8		202	209	0.9	0.6, 1.3	
Once or twice	105	90	1.1	0.7, 1.8		56	65	0.8	0.5, 1.3	
3-10 times	130	117	1.1	0.8, 1.7		73	71	1.0	0.6, 1.6	
> 10 times	132	98	1.4	0.9, 2.1	0.12	73	73	0.9	0.6, 1.4	0.86
Termites/carpenter ants										
Never use	161	146	1.0	Ref		132	119	1.0	Ref	
Any use	112	102	1.0	0.7, 1.4		53	59	0.7	0.4, 1.1	
Once or twice	68	54	1.1	0.7, 1.7		37	31	1.0	0.5, 1.7	
3-10 times	28	30	0.9	0.5, 1.6		7	19	0.2	0.1, 0.6	
> 10 times	16	18	0.8	0.4, 1.7	0.55	9	9	0.7	0.3, 2.1	0.06
Mosquito control										
Never use	176	186	1.0	Ref.		138	126	1.0	Ref.	
Any use	65	58	1.1	0.7, 1.7		26	29	0.8	0.4, 1.4	
Once or twice	10	11	1.2	0.7, 2.2		5	7	0.7	0.2, 2.3	
3-10 times	23	22	1.1	0.6, 2.1		12	9	1.2	0.5, 3.2	
> 10 times	32	25	1.2	0.7, 2.2	0.47	9	13	0.5	0.2, 1.4	0.33
Mothball control										
Never use	40	56	1.0	Ref.		33	35	1.0	Ref.	
Any use	207	190	1.3	0.8, 2.1		133	122	1.0	0.6,1.8	
< 5 times	50	55	1.2	0.7, 2.1		42	35	1.3	0.7, 2.7	
5-10 times	40	53	1.0	0.5, 1.8		22	20	0.9	0.4, 2.0	
> 10 times	117	82	1.6	1.0, 2.8	0.06	69	67	0.9	0.5, 1.7	0.41
Lawn care										
Never use	190	169	1.0	Ref.		126	117	1.0	Ref.	
Any use	250	196	1.1	0.8,1.5		158	147	1.1	0.8,1.5	
Once or twice	24	21	1.0	0.5, 2.0		19	14	1.4	0.7, 3.0	
3-20 times	115	83	1.2	0.8, 1.7		59	53	1.1	0.7, 1.8	

Table 6 Adjusted odds ratios for breast cancer and residential pesticide use stratified by disease causation beliefs *(Continued)*

> 20 times	111	92	1.0	0.7, 1.5	0.58	80	80	1.0	0.6, 1.5	0.98
Outdoor and indoor plant care										
Never use	235	198	1.0	Ref.		172	161	1.0	Ref.	
Any use	214	173	1.0	0.8, 1.4		120	127	0.8	0.6, 1.2	
Once or twice	18	12	1.2	0.5, 2.6		15	14	0.9	0.4, 2.0	
3-20 times	104	86	1.0	0.7, 1.5		54	60	0.8	0.5, 1.2	
> 20 times	92	75	1.0	0.7, 1.4	0.99	51	53	0.9	0.5, 1.4	0.39
Insect repellent										
Never use	153	134	1.0	Ref.		133	137	1.0	Ref.	
Any use	312	261	1.2	0.9, 1.6		170	167	1.2	0.8, 1.7	
Rarely	179	149	1.2	0.8, 1.6		104	114	1.1	0.7, 1.6	
Sometimes	85	85	1.0	0.6, 1.5		48	30	1.9	1.1, 3.4	
Often/Very often	48	27	2.0	1.1, 3.4	0.12	18	23	0.8	0.4, 1.6	0.45
Lice control										
Never use	414	344	1.0	Ref.		278	282	1.0	Ref.	
Any use	59	58	1.1	0.7, 1.7		30	25	1.4	0.8, 2.5	
Flea collar for pets										
No	132	122	1.0	Ref.		125	116	1.0	Ref.	
Yes	344	290	1.3	0.9, 1.8		185	192	1.0	0.7, 1.4	
Flea control for pets										
Never use	256	214	1.0	Ref.		209	181	1.0	Ref.	
Any use	196	177	1.1	0.8, 1.4		98	109	0.8	0.5,1.1	
Once or twice	23	23	0.9	0.5, 1.6		20	18	1.0	0.5, 2.1	
3-10 times	63	74	0.8	0.5, 1.2		38	35	0.9	0.6, 1.6	
> 10 times	110	80	1.4	0.9, 2.0	0.27	40	56	0.6	0.4, 1.0	0.07

Odds ratios are adjusted for age at diagnosis/reference year, birth decade (six categories), previous breast cancer diagnosis, family history of breast cancer, age at first live or still birth (< 30, ≥ 30/nulliparous), education (five categories), study (Cape, PCE). "Combined pesticide use" product category includes frequency data for: insect or bug control, lawn care, outdoor and indoor plant care, insect repellent, flea control on pets. Product use for termite or carpenter ant control, mosquito control, and mothball control not included because they were only assessed in study participants from the 1999-2000 interviews.

the proliferation of estrogen-sensitive cells, or affect mammary gland development following prenatal exposure. These findings suggest effects of pesticide and cleaning product use on breast cancer risk, so we undertook a case-control study of breast cancer and self-reported product use. We found increased breast cancer risk among women reporting the highest use of cleaning products and air fresheners. We found little association with home pesticide use. The self-reported product use measures we used have the advantage of integrating exposure over many years to chemical mixtures. However, these measures remain incomplete, likely resulting in nondifferential misclassification, and they are open to recall bias. Investigators sometimes try to avoid the influence of recall bias by limiting analyses to participants who do not subscribe to the study hypothesis, but our results show this may not be a good strategy, given that in our study it would obscure the well-established association between family history and breast cancer risk. In order to avoid possible recall bias, we

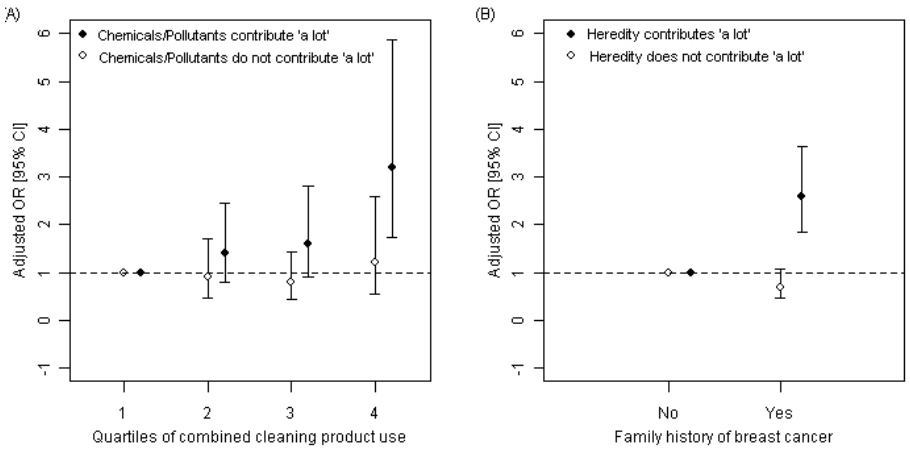

Figure 1 Cleaning product use, family history, and risk of breast cancer, stratified by beliefs about causation. Adjusted odds ratios are shown for breast cancer and A) combined cleaning product use stratified by beliefs about environmental chemicals and breast cancer and B) family history of breast cancer stratified by beliefs about heredity and breast cancer, among participants living in Cape Cod, Massachusetts, 1988-1995. Odds ratios are adjusted for age, previous breast cancer diagnosis, age at first birth, and education; additionally, Figure 1A is adjusted for family history of breast cancer and Figure 1B is adjusted for study.

Table 7 Beliefs about heredity as a cause of breast cancer by family history and case status

		Cases				Controls			
		Family history of breast cancer				Family history of breast cancer			
		Yes		No		Yes		No	
Belief		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Heredity contributes "a lot" to breast cancer	Yes	120	61	211	36	83	61	391	67
	No	76	39	380	64	52	39	195	33

recommend further study of cleaning products and breast cancer using prospective self-reports and measurements in environmental and biological media.

Abbreviations

CI: confidence interval; CMS: Centers for Medicare and Medicaid Services; EDCs: endocrine-disrupting compounds; OR: odds ratio; MCR: Massachusetts Cancer Registry; PCE: tetrachloroethylene; Ref: reference; Adj OR: adjusted odds ratio; NY: New York; US: United States.

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Authors' contributions

ARZ conducted the statistical analyses and led drafting of the manuscript. AA designed and oversaw the PCE Study; contributed to the design, data collection, and epidemiological analysis of the Cape Cod Study; and collaborated on editorial issues. RAR contributed to the design, data collection, and analysis of the Cape Cod Study, particularly with respect to the toxicologic characteristics of exposures, and collaborated in drafting the manuscript. JGB led the design, implementation, and analysis of the Cape Cod Study and collaborated in drafting the manuscript; she conceptualized the comparative analysis of product use and family history odds ratios stratified by beliefs as a strategy for understanding possible response bias. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Review

The Placebo and Nocebo Phenomena: Their Clinical Management and Impact on Treatment Outcomes

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ABSTRACT

Purpose: This overview focuses on placebo and nocebo effects in clinical trials and routine care. Our goal was to propose strategies to improve outcomes in clinical practice, maximizing placebo effects and reducing nocebo effects, as well as managing these phenomena in clinical trials.

Methods: A narrative literature search of PubMed was conducted (January 1980–September 2016). Systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on placebo or nocebo effects in clinical practice were included in the qualitative synthesis. Search terms included: *placebo, nocebo, clinical, clinical trial, clinical setting, placebo effect, nocebo effect, adverse effects*, and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature.

Findings: Placebo and nocebo effects are psychobiological events imputable to the therapeutic context. Placebo is defined as an inert substance that provokes perceived benefits, whereas the term nocebo is used when an inert substance causes perceived harm. Their major mechanisms are expectancy and classical conditioning. Placebo is used in several fields of medicine, as a diagnostic tool or to reduce drug dosage. Placebo/nocebo effects are difficult to disentangle from the natural course of illness or the actual effects of a new drug in a clinical trial. There are known strategies to enhance clinical results by manipulating expectations and conditioning.

Implications: Placebo and nocebo effects occur frequently and are clinically significant but are underrecognized in clinical practice. Physicians should be able to recognize these phenomena and master tactics on how to manage these effects to enhance the quality of clinical

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Key words: adverse effects, clinical trial, nocebo, pharmacology, placebo, treatment.

INTRODUCTION

The placebo effect has been studied extensively throughout history.[1,2] The nocebo effect, also called "the evil brother of the placebo effect," has been less studied, but in recent years has become a subject of growing interest.[3–5] Both phenomena are composed of several intertwined biological and environmental mechanisms, displaying a complex interaction. Their operative mechanisms not only are affected by the characteristics of the individuals but also on the context in which they operate; thus, the search for a simple equation to predict the effect of placebo and nocebo has been met with limited success.

A precise definition of the placebo and nocebo phenomena is difficult to pinpoint, as different researchers have used different definitions, often depending on the context. A starting definition would be psychobiological events attributable to the overall therapeutic context[6]; herein, placebo effect would be the benefits provoked by an inert substance, and the nocebo effect is the induction of true or perceived harm after treatment with an inactive substance. Thus, a response to treatment, not attributable to the known mechanism of action of the treatment, is the core feature of both phenomena. This means that the definition can also be applied to an active substance treatment, then referring to the (extra) effects it elicits and that are not explained by its pharmacologic action. Many disorders have a natural course of illness in which symptoms fluctuate, making it difficult to differentiate between a placebo or nocebo response and the natural course of illness at an individual patient level. Similarly, many "side effects" occur commonly with or without pharmacotherapies (eg, headache), making it often difficult to disentangle, at an individual patient level, between a treatment-emergent adverse event that is a nocebo response or one that has occurred independently of treatment.

Paradigmatically, the placebo and nocebo phenomena have been most extensively studied in analgesia[7–10] and irritable bowel syndrome (IBS).[11] These phenomena have been studied more recently in the field of dermatology[12–14] and in psychiatry, particularly in depression.[15]

The underpinnings of placebo and nocebo are psychological and neurobiological. Psychological mechanisms include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning, and "placebo-by-proxy" induced by clinicians and family members.[16] Two principal mechanisms are well supported. The first aspect involves expectancy: the administration of placebo creates expectations in future responses by using simple verbal cues as modulators of expectations. Researchers can nudge a subject's expectations and boost the placebo effect. The second aspect involves classical conditioning: repeated associations between a neutral stimulus and an unconditioned stimulus (active drug) can result in the ability of the neutral stimulus by itself to provoke a response characteristic of the unconditioned stimulus.[4,17,18] In a study of placebo/nocebo in thermal pain, neither conditioning nor expectation alone seemed to be able to elicit placebo or nocebo effects; however, the combination of experience (conditioning) and expectation resulted in significant placebo (analgesia) or nocebo (hyperalgesia) effects.[19]

Misattribution is the inappropriate attribution of improvement or worsening to a treatment when it was actually caused by the disorder's natural fluctuation of symptoms or other causes.[20] Misattribution may have a more significant role in nocebo effects than in placebo effects, although this theory remains a focus of active debate.[21,22]

The neurobiology of the response to placebo and nocebo has been studied mostly in the paradigmatic field of analgesia and has been shown to be mainly related to the opioid and dopaminergic pathways.[6,23,24] A companion paper published in this issue of *Clinical Therapeutics* reviews the theoretical and biological underpinnings of the nocebo and placebo phenomena.[25]

It is important to note that placebo and nocebo responses are highly variable across individuals. Some individual differences have been associated with genetic polymorphisms or underlying neurologic impairments. For example, patients with frontal lobe impairment, especially prefrontal lobe, have decreased expectancy and learning, and thus they partially or totally lose their placebo response. In a study of Alzheimer's disease and pain, patients with reduced Frontal Assessment Battery scores exhibited a reduced placebo component of the analgesic treatment.[26] In intellectually disabled patients, a higher intelligence quotient was positively related with placebo response.[27]

Catechol-O-methyl transferase is involved in dopamine degradation, affecting the prefrontal lobe. The catechol-O-methyl transferase Val^{158}Met polymorphism

is a G to A mutation leading to amino acid substitution at codon 158 in the transmembrane form of the enzyme.[28] It was suggested as a biomarker of placebo response in IBS and a potential biomarker of placebo response in other conditions.[11] Thus, people who carry this polymorphism are more likely to experience the placebo effect.

The tryptophan hydroxylase-2 polymorphism (serotonin-related gene) seems a significant predictor of clinical placebo response in social anxiety disorder. Homozygosity for the G allele was associated with serotonergic modulation of amygdala activity and greater improvement in symptoms of anxiety.[29] People who experience anxiety disorder and carry this polymorphism are more likely to experience the placebo effect. Thus, psychological and neurobiological factors can predict individual differences in placebo and nocebo response.

The present review first focuses on the impact of placebo and nocebo effects in routine clinical settings as well as in clinical trials, and then offers strategies on how to use that knowledge to improve the quality of care and results in research.

MATERIALS AND METHODS

A literature search of PubMed was conducted for articles published between January 1980 and September 2016. Search terms included: *placebo, nocebo, clinical, clinical trial, clinical setting, placebo effect, nocebo effect, adverse effects,* and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature. Systematic reviews, randomized controlled trials (RCTs), observational studies, and case series were identified. Articles that had an emphasis on placebo or nocebo effects in clinical practice were selected for the qualitative synthesis.

CLINICAL APPLICATION

The clinical understanding of the placebo effect is a relevant issue. Placebo responses may be a major driver of clinical change after diverse therapies. Placebos are used in several fields of medicine (eg, neurology, psychiatry, rheumatology, pain management, ophthalmology), although ethical considerations limit their use in some areas. When surveyed, 45% of American physicians admitted to having used a placebo.[30] An English study found that only 12% of general practitioners use pure placebos (totally inert interventions) but the number was 97% for impure ones (interventions with clear efficacy for certain conditions but are prescribed for conditions in which their efficacy is unknown).[31] The most common reason to use a placebo was to tranquilize the patient (18%) and as a supplemental treatment (18%). Other reasons included "after 'unjustified' demand for medication" (15%), "for nonspecific complaints" (13%), "after all clinically indicated treatment possibilities were exhausted" (11%), "to control pain" (6%), "to get the patient to stop complaining" (6%), and "as a diagnostic tool" (4%).[30] It has been argued that the clinical benefits from many poorly evidence based complementary and alternative disciplines derive largely or even solely from cultivation of the factors that drive placebo effects.[32] Local regulations, however, preclude clinical use of placebos in some jurisdictions.

Patients need a greater dose of analgesic to achieve an equivalent outcome if their placebo response is impaired. When patients with postoperative pain were given intravenous saline (placebo), and buprenorphine was made available on request, the group told that the intravenous saline was a powerful painkiller took 33% less analgesia for the same pain compared with a control group (who were told they were receiving a rehydrating solution).[33]

CHALLENGES IN CLINICAL TRIALS

The placebo or nocebo response is related to common biochemical pathways that are activated both by social stimuli and therapeutic rituals on one hand and by drugs on the other. It has been shown that when an opioid agent is administered, it binds to μ-opioid receptors, but the very same μ-opioid receptors are activated by the patient's expectations about the drug.[34] This outcome is concordant with the finding that drugs without therapeutic rituals are less effective.[35] A suitable therapeutic setting can thus enhance the placebo response.[36]

The placebo effect has been well established in RCTs. In depression, its magnitude has been shown to vary depending on the investigators. Some propose that up to 75% of the drug effect is mediated by the placebo effect.[37,38] Others question these results, arguing that an unrepresentative subset of clinical trials (including many cases of mild to moderate depression) were analyzed, and therefore the data are not accurate.[39,40] This theory suggests that patients with less severe depression have a lower biological substrate and are more vulnerable to the

placebo effect. In 2002,[41] a meta-analysis was conducted with US Food and Drug Administration data containing RCTs that had not been published. This study revealed a small significant difference between antidepressant drug and placebo but not a clinical difference; the mean difference between drug and placebo was ~2 points on the Hamilton Depression Rating Scale. An alternative hypothesis to explain this difference in antidepressant trials is "breached blind." Because of the side effects of the drugs, the RCT patients may know if they are in the placebo or the active group.[42] Furthermore, when another active antidepressant is used as the comparator, instead of placebo, there is a significant increase in the effectiveness of the drug.[43]

It remains controversial whether the placebo effect is increasing across time in RCTs of depression. It has been proposed that the placebo effect has progressively increased over time[44] within the general population as a result of inflation of baseline severity to meet threshold inclusion criteria; that is, trials with less ill people, in which regression to the mean is more likely, and more comprehensive and frequent assessment procedures. Others have argued that pharmaceutical companies try to select only severely depressed patients because pharmacotherapy RCTs for mild and moderate depression often do not show statistically significant separation between the treatment and placebo trial arms,[45] thus downplaying the role of decreased baseline depression severity as an explanation. In contrast, a recent meta-analysis using published and unpublished data found stable placebo responses in the last 25 years,[46] implying the increase across time effect may be an artifact.

PLACEBO/NOCEBO AND SEPARATION FROM THE NATURAL COURSE OF ILLNESS

Understanding the natural course of illness is essential before commencing a clinical trial design or trying to separate drug from placebo effects. Given the fact that symptom severity does not stay frozen in time when no intervention is applied, the spontaneous progress or improvement of a pathological process can obviously confound or pose as a placebo or nocebo effect. These types of studies present numerous challenges, especially as modern medicine shifts its attention from infectious disorders to chronic or mental disorders (which wax and wane, where the natural history of illness extends greatly in time or has poor or no biomarkers available).[47]

Prospective nonintervention studies are increasingly ethically challenging as fewer diseases are lacking effective treatment. Therefore, in many cases, it is impossible to include a nontreatment arm in a clinical trial to guide our interpretation of results and discount the influence of natural progression. A loophole to this problem was found in studies of psychotherapy efficacy on major depressive disorder that use a wait-list as a control group. A meta-analysis[48] found that "wait-listers" experience ~33% of the symptomatic improvement of treated patients and 40% of the ones receiving placebo. An important caveat is that a wait-list is thus a very poor control group for clinical trials, despite being used often. Some studies even found that wait-list results in nocebo effects.[49]

STRATEGIES (USING PLACEBO TO IMPROVE RESULTS)

Maximizing Placebo

Patient expectations contribute toward the outcome of several disorders. This has been demonstrated for analgesia, treatment of myocardial infarction and Parkinson's disease, deep brain stimulation, orthopedic surgery, and antidepressant treatment.[22] Positively influencing patients' beliefs about therapeutic success is one way to maximize the placebo effect.[50] However, being too optimistic is also ethically problematic and can be construed as disingenuous if one is not cautious. Manipulating a patient's expectations may not necessarily require lying or deceiving. In a study of IBS, patients were informed they were being treated with placebo and still developed a positive clinical response.[51]

A partial reinforcement paradigm, placebo-controlled drug reduction (PCDR) (use of a full dose of medication for a set period of time [acquisition period] followed by a maintenance or evocation period with interposed placebo) has been shown to lower the dose needed to elicit a therapeutic response. This finding opens the door for a panoply of chronic disorders treated with medications with substantial side effects (Table I). PCDR allowed children with attention-deficit/hyperactivity disorder to be effectively treated with 50% of their optimal stimulant dose[52] and reduced the corticosteroid dose needed in psoriasis.[53]

Table I. Strategies to maximize the placebo effect.

Managing Expectations	Conditioning
Screen for patients with negative beliefs	Placebo-controlled drug reduction (PCDR)
Hidden applications when discontinuing a drug expected to cause withdrawal symptoms	Use salient stimuli and constant context when administering treatment including sensorial cues, same room and time of day when giving treatment
Promote social contact with other successful patients	Use effective pretreatments
Reduce anxiety	Avoid extinction in long-term treatments Motivation strategies, changes in situational cues Enhance physician–patient relationship Empathic style, more time of contact Describe the procedure before executing to improve attention

Adapted from Enck et al.[22]

It is usually assumed that more complex, time-consuming, and invasive interventions are more likely to be associated with placebo effects than other interventions. For instance, different colors and sizes of a pill seem to influence the clinical outcome.[54] However, to our knowledge, only 1 systematic review[55] has found mixed evidence of more invasive placebos having larger effects (7 of 12 studies with >1 placebo found no difference, 4 found single-outcome differences, and 1 found a large effect; 2 of 4 studies designed to differentiate placebo intensity were positive). The extant data may not be sufficient to discount its influence. To design studies directly comparing very different placebo interventions (ie, pill vs injection) while ensuring blinding for both patients and researchers ranges from very difficult to impossible. Also, to try to design studies controlling for context or for patient or clinician bias in expectancies might be a Sisyphean-like task, as the differences in context and expectancies themselves may be the cause of the placebo effect.

Although the placebo could be more powerful, deliberately administering a more invasive or intense placebo may be both ethically challenging (especially one with potential to cause harm) and lacking in evidence. Conversely, a meta-analysis of 41 RCTs assessing the effects of antidepressant agents on major depressive disorder showed that the more follow-up observations that occur, the more intense are the placebo effects elicited.[56] The number of medical visits in clinical trials contrasts with the shorter contact in community settings. This strategy is well established and can be useful because it is nonharmful. Profiling or choosing the right person to try a placebo might be more problematic. There was limited evidence for the role of age or sex, at least in psychiatric disorders.[57] A stronger correlation was found for low symptom severity and short duration of illness. There were 2 studies in children reporting a higher placebo effect in those of non-white ethnic origin.[58,59]

Managing Placebo in Clinical Trials

When comparing a drug versus a placebo, the first thing to bear in mind is that the effect of an active drug includes in itself a placebo component. Furthermore, issues are further complicated because the relation of the effects between the placebo and drug groups may not always be additive; that is, the measured effect in the active drug arm may be more (or less) than expected just by adding the placebo

Table II. Strategies to optimize drug–placebo differences in clinical trials.

Avoid enrichment/multidosing studies
Aim for a 50/50 probability of receiving placebo
Use treatment-naive patients
Randomized run-in and withdrawal periods
Use active placebos
Incorporate "no-treatment" groups
Avoid comparative effectiveness trials
Prioritize outcome evaluation in the following order:
1. Death
2. Biomarkers
3. Physician assessment
4. Patient-reported outcomes

effect to the actual active drug effect.[22,60] Therefore, perhaps "optimizing the drug–placebo difference" (vs minimizing placebo) is a preferable denomination.

Designing clinical trials is a specialized field in its own right. Separating a drug effect from a placebo effect always at the core of a clinical trial design, so that general quality guidelines for a clinical trial usually will work to optimize the drug–placebo difference: standardizing for symptom severity; avoiding physician's selection bias; controlling for center effects and patient adherence; and ensuring effective blinding.

However, sometimes these strategies are accompanied by other undesirable effects. For example, if we identify drug responders during a run-in phase or preselect patients who were previously exposed to a similar drug, we may increase the drug–placebo difference, but we also risk limiting a drug indication and overestimating benefits. If the population of previous responders comprised a specific group (eg, women), the trial will never generate approval for men. Some strategies involve deceit and thus have ethical concerns. Cost and feasibility are concerns as well (eg, when considering augmenting sample size). Therefore, it is up to the researcher to weigh the risks and benefits of each strategy.

Because the chance of being in a treatment group increases the magnitude of placebo responses,[61] a study design of equal likelihood of receiving placebo or treatment (ie, avoid enrichment or multidosing studies) should be preferred. Contrary to common belief, trying to exclude placebo responders using run-in phases early in the study was not able to prevent later placebo response.[62] Randomized run-in (ie, in a double-blind manner, patients first start receiving placebo and are then switched to the active drug after a few days) and withdrawal periods seem to hold more promise.[63] Crossover designs may promote conditioning[64] and may lead to unblinding of the study due to perceived side effects. Using active placebos (drugs that mimic the active treatment side effects) is a possible perfect placebo that rarely exists, mimicking all the side effects without any of the active mechanisms of the drug being tested. Controlling for the natural progression of the disease should also be a concern, even if in many situations it is ethically challenging and may motivate subjects to drop out. A way around this is using Zelen's design,[65] in which patients are randomly divided into an observational group and an interventional group comprising the active drug and placebo branches, allowing to control for the natural course of illness.

Comparative effectiveness trials are usually used when an efficacious treatment already exists for ethical standards. The new drug must then prove superiority, equivalence, or noninferiority. However, it has been shown that a drug tested against an active comparator performs better.[61,66] The placebo effect is also reportedly stronger when patients report the outcome than when the physician performs the assessment,[67] which is itself stronger than a biomarker-based evaluation.[68] The most objective outcome possible is death or survival rate, but this approach obviously cannot be used for many disorder endpoints (Table II).

Minimizing Nocebo

In the case of nocebo, no overt ethical dilemma is present. The intention of the physician is always to minimize its risk and effects. Also, we can expect the factors and strategies used to minimize the nocebo effect to be a mirror of the ones in placebo.

Of major importance would be to identify individuals more prone to develop nocebo effects. Several studies have been conducted to identify "risk factors" of the nocebo effect. A systematic review[4] found "learning/social observation," "perceived dose," "verbal suggestions of arousal and symptoms," and "baseline symptom expectations" to be the strongest predictors of nocebo effects. Interestingly, the type of administration again did not appear to be relevant, nor did self-awareness during exposure. Symptom severity at

Table III. Strategies to minimize nocebo.

Managing Expectations	Conditioning
Avoid informed consent overly focused on side effects	Low-dose initial regimen (when possible)
Framing of information	Hidden tapering in when feasible
Focus on the positive effects of treatment	
Conjoint plan	
Sense of control and ownership of the decision-making process (by the patient)	
Empathic attitude	

Adapted from Data-Franco and Berk.[73]

baseline (one of the strongest associations with placebo) also produced mixed results. Demographic factors such as sex, age, and literacy did not change the risk of a nocebo response. One study found that female investigator subjects report nocebo effects twice as frequently as male subjects after a social suggestion paradigm, but these data could have been confounded by the study design (the social cue was presented by a female).[69] In modern health systems in which access is good, participants who volunteer for trials may have presented with poor response or have not tolerated standard therapy. This earlier adverse experience increases the likelihood of these subjects being primed for nocebo responses.[70]

Managing patients' beliefs and experiences are at the core of possible strategies. Framing of information is an effective way to put the benefits and risks of treatment in perspective, focusing on the positive possibilities.[71] A caring and empathic relationship is beneficial.[72] When the medical problem allows for a small delay in the start of therapy, a lower initial dose might be helpful. Similarly, in RCTs, if a patient does not know when exactly he or she is getting exposed, nocebo effects are reduced (**Table III**). Nevertheless, this approach may be rarely feasible in outpatient settings or even time- and resource-consuming in a hospital setting.

CONCLUSIONS

Clinically, placebo and nocebo effects are of major importance, being present in daily medical practice. The overall effect of a drug stems from its pharmacodynamic actions plus the psychological effect derived from the act of its administration. Although both placebo and nocebo have been widely studied, the full complexity of their mechanisms needs further definition. Thus, when correctly applied, there are a number of strategies that can improve responses and patients' quality of life, maximizing placebo and reducing nocebo in clinical practice, and enhancing results in clinical trials. It underlines the impact of creating a good physician–patient relationship, increasing empathic attitudes, exposing information suitably, decreasing expectations of adverse effects, and promoting social contact between successfully treated patients.

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CONFLICTS OF INTEREST

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NEUROSCIENCE

Nocebo effects can make you feel pain

Negative expectancies derived from features of commercial drugs elicit nocebo effects

By **Luana Colloca**

The mysterious phenomenon known as the nocebo effect describes negative expectancies. This is in contrast to positive expectancies that trigger placebo effects (*1*). In evolutionary terms, nocebo and placebo effects coexist to favor perceptual mechanisms that anticipate threat and dangerous events (nocebo effects) and promote appetitive and safety behaviors (placebo effects). In randomized placebo-controlled clinical trials, patients that receive placebos often report side effects (nocebos) that are similar to those experienced by patients that receive the investigational treatment (*2*). Information provided during the informed consent process and divulgence of adverse effects contribute to nocebo effects in clinical trials (*1*). Nocebo (and placebo) effects engage a complex set of neural circuits in the central nervous system that modulate the perception of touch, pressure, pain, and temperature (*1, 3, 4*). Commercial features of drugs such as price and labeling influence placebos (*5, 6*). On page 105 of this issue, Tinnermann *et al.* (*7*) show that price also influences nocebo effects.

Tinnermann *et al.* evaluated the responses of healthy participants who received two placebo creams labeled with two distinct prices and presented in two boxes that had marketing characteristics of expensive or cheap medication. The creams were described as products that relieve itch but induce local pain sensitization (hyperalgesia). All creams, including controls, were identical and contained no active ingredients. Nocebo hyperalgesic effects were larger for the "more expensive" cream than for the "cheaper" cream. Combined corticospinal imaging revealed that the expensive price value increased activity in the prefrontal cortex. Furthermore, brain regions such as the rostral anterior cingulate cortex (rACC) and the periaqueductal gray (PAG) encoded the differential nocebo effects between the expensive and cheaper treatments. Expectancies of higher pain-related side effects associated with the expensive cream may have triggered a facilitation of nociception processes at early subcortical areas and the spinal cord [which are also involved in placebo-induced reduction of pain (*8*)]. The rACC showed a deactivation and favored a subsequent activation of the PAG and spinal cord, resulting in an increase of the nociceptive inputs. This suggests that the rACC–PAG–spinal cord axis may orchestrate the effects of pricing on nocebo hyperalgesia.

The anticipation of painful stimulation makes healthy study participants perceive nonpainful and low-painful stimulations as painful and high-painful, respectively (*9*). Verbally induced nocebo effects are as strong as those induced through actual exposure to high pain (*9*). Moreover, receiving a placebo after simulating an effective analgesic treatment, compared to receiving the same placebo intervention after a treatment perceived as ineffective, produces a 49.3% versus 9.7% placebo-induced pain reduction, respectively (*10*). The relationship between prior unsuccessful or successful pain relief interventions and placebo analgesic effects is linked to a higher activation of the bilateral posterior insula and reduced activation of the right dorsolateral prefrontal cortex (*11*).

Informing patients that a treatment has been stopped, compared to a covert treatment interruption, alters the response to morphine, diazepam, or deep-brain stimulation in postoperative acute pain, anxiety, or idiopathic Parkinson's disease, respectively (*12*). Patients openly informed about the interruption of each intervention experience a sudden increase of pain, anxiety, or bradykinesia (a manifestation of Parkinson's disease), whereas patients undergoing a hidden interruption do not (*12*). Neuroimaging approaches support the clinical observation. For example, the action of the analgesic remifentanil is overridden by activation of the hippocampus that occurs when healthy participants that receive heat pain stimulations are misleadingly told that the remifentanil administration was interrupted (*13*). These findings provide evidence that communication of treatment discontinuation might, at least in part, lead to nocebo effects with aggravation of symptoms.

In placebo-controlled clinical trials, nocebo effects can influence patients' clinical outcomes and treatment adherence. It was shown in a clinical trial that atorvastatin induced in the same individuals an excess rate of muscle-related adverse events in the nonblinded (i.e., patients knew they were taking atorvastatin), nonrandomized 3-year follow-up phase but not in the initial blinded 5-year phase when patients and physicians were unaware of the treatment allocation (atorvastatin or placebo) (*14*). Furthermore, misleading information about side effects for statins via public claims has led to treatment discontinuation and an increase in fatal strokes and heart attacks (*14*).

Given that nocebo effects contribute to perceived side effects and may influence clinical outcomes and patients' adherence to medication, we should consider how to avoid them in clinical trials and practices (*15*)—for example, by tailoring patient-clinician communication to balance truthful information about adverse events with expectancies of outcome improvement, exploring patients' treatment beliefs and negative therapeutic history, and paying attention to framing (i.e., treatment description) and contextual effects (i.e., price). Through an understanding of the physiological mechanisms, strategies could be developed to reduce nocebo effects. ■

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Nocebo effects can make you feel pain

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Review

A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena

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ABSTRACT

Purpose: Placebos are commonly used in experimental and patient populations and are known to influence treatment outcomes. The mechanism of action of placebos has been investigated by several researchers. This review investigates the current knowledge regarding the theoretical and biological underpinning of the nocebo and placebo phenomena.

Method: Literature was searched using PubMed using the following keywords: *nocebo*, *placebo*, *μ-opioid*, *dopamine*, *conditioning*, and *expectancy*. Relevant papers were selected for review by the authors.

Findings: The roles of conditioning and expectancy, and characteristics associated with nocebo and placebo responses, are discussed. These factors affect nocebo and placebo responses, although their effect sizes vary greatly, depending on inter-individual differences and different experimental paradigms. The neurobiology of the nocebo and placebo phenomena is also reviewed, emphasizing the involvement of reward pathways, such as the μ-opioid and dopamine pathways. Neurobiological pathways have been investigated in a limited range of experimental paradigms, with the greatest efforts on experimental models of placebo analgesia. The interconnectedness of psychological and physiological drivers of nocebo and placebo responses is a core feature of these phenomena.

Implications: Further research is needed to fully understand the underpinnings of the nocebo and placebo phenomena. Neurobiology pathways need to be investigated in experimental paradigms that model the placebo response to a broader range of pathologies. Similarly, although many psychological factors and inter-individual characteristics have been identified as significant mediators and moderators of nocebo and placebo responses, the factors identified to date are unlikely to be exhaustive. (*Clin Ther*. 2017;39:469–476) © 2017 Published by Elsevier HS Journals, Inc.

Key words: conditioning, dopamine, expectancy, μ-opioid, nocebo, pharmacology, placebo, treatment.

For the purpose of this review, a placebo response is an improvement in clinical symptoms when a person is administered an inert substance, whereas a nocebo response is a worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects. Typically, a placebo tablet is administered in control arms of

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0149-2918/$ - see front matter

clinical trials and is manufactured to look identical to the tablet in the active arm of a trial. Nocebo and placebo responses are also sometimes used to describe unexpected responses to active treatments that are not explained by the known mechanism of action of the treatment. It may not be possible to discern at an individual participant level between true placebo or nocebo responses and fluctuations in symptom severity due to the natural progression of the illness; however, insightful placebo and nocebo response data can often be obtained at a cohort level. While the importance of the placebo effect is widely understood, this is much less so for the nocebo effect. The biological bases of the nocebo and placebo effects are only now beginning to be unraveled. Attempts to understand the causes of the placebo effect have increased in the last 50 years, as placebo-controlled clinical trials have become the only accepted method for efficacy testing of new pharmaceuticals and the problems associated with placebos have become more apparent. Insights have been gained from exploring theoretical causes and influencing factors of the effect, which have probed the mechanisms underlying the phenomenon. This article reviews the theoretical and biological underpinning of the nocebo and placebo phenomena. A separate article also published in this issue reviews the clinical importance of the nocebo and placebo phenomena.

PSYCHOLOGICAL UNDERPINNINGS

There are a multitude of psychological elements that have been identified as the leading factors underpinning the placebo and nocebo effects.

The most well-known theories pertaining to the placebo and nocebo phenomena are the conditioning and expectancy hypotheses. Conditioning can occur when a person was pre-exposed to an active substance and had a reaction that imprints in memory. When they are then given an inert substance, they might respond to the inert substance in the same or similar way as they would to the active substance. A conditioned response is a triggering of a memory loop and, therefore, is driven by learning and adaptation.[1] The effect is mediated by many variables. The conditioning hypothesis alone is insufficient to explain the placebo and nocebo phenomena, for example, the extinction phenomenon in classic conditioning does not necessarily occur with placebos.[1]

Expectancy occurs where a pre-existing belief, or information received before being given an inert substance (or before reporting a response[2]), elicits a response to the inert substance predicated on what the person thinks will happen. It is not necessary to have ever been exposed to an active substance to have an expectation of response. This may be responding to a treatment that is not pharmacologically active because of a pre-existing belief that the treatment either works or might cause a specific reaction, and can be an important factor in alternative therapies in which pharmacologically active compounds are not included in the treatment.[3] Similarly, expectation can be a driver of inappropriate or over-prescription of some medications, including antibiotics, in a phenomenon that shares much in common with the placebo effect.[4] As with conditioning, expectancy also requires learning, which may come through direct receipt of information, suggestion, social cues, or the interaction of all these learning modalities.[5] Suggestion has also been used experimentally to extinguish a conditioned placebo response.[6] Extinction of a conditioned response requires learning, which in the case of a placebo response can be facilitated by suggestion, but may not necessarily occur solely through repeated administration of a placebo.

Hope for improvement has also been suggested as a driver of the placebo effect[1] and this has face validity; however, data have not been presented to support this theory. A corollary, where despair is suggested to drive the nocebo effect, has not been proposed in peer-reviewed literature. However, personality traits have been associated with placebo response,[7] leaving the possibility open to an association between personality traits, such as optimism and pessimism, being factors in the placebo and nocebo phenomena. However, considerable work needs to be done to unravel the relationship between personality and placebo response, including expanding the theoretic underpinnings of the association through hypothesis-driven research in addition to the current works that have focused on association between personality measures and placebo response.[8] State and trait variance are a limitation with personality measures[9] and may be relevant for the placebo response, for example, where there is variance in dependence.

The nature of the therapeutic alliance may also be a driver of the nocebo effect, with a hostile–dependent relationship being an exemplar. This relationship pattern occurs when one party is dependent on another, and the former is hostile or mistrusting of other people. This is a not uncommon but poorly recognized pattern in clinical practice, where people with insecure attachment styles are forced into trusting a clinician, and their interactional style makes this difficult Figure.

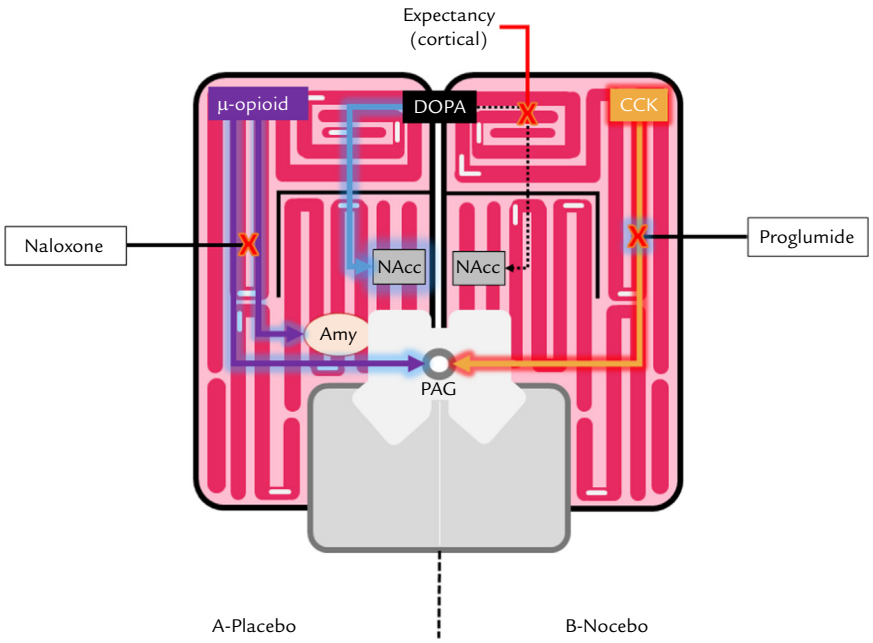

Figure. Summary of regions, circuits, and neurotransmitters implicated in placebo and nocebo. A-Placebo: Expectation activates cortical area signaling of dopamine to the nucleus accumbens and μ-opioid to the periaqueductal gray and elsewhere in the brain (the amygdala and other regions: not shown). The placebo effect is blocked by naloxone. B-Nocebo: Negative expectation has the opposite effect in the dopamine signaling and also activates cholecystokinin from the prefrontal cortex to the periaqueductal gray. The nocebo effect is blocked by proglumide. Amy = amygdala; CCK = cholecystokinin; DOPA = dopamine; NAcc = nucleus accumbens; PAG = periaqueductal gray.

In an open-labeled study, 80 women with irritable bowel syndrome were randomly assigned to placebo with a persuasive rationale but without deception, or to a control group with no treatment. Both groups received the same patient–provider relationship and contact time. Participants in the placebo-treated group had significantly higher global improvement scores.[10] In this study, the placebo effect occurred even though the participants were told they would be receiving an inert substance "like sugar pills." This may suggest that the placebo effect has multiple drivers, including expectancy, as participants were told that placebo "has been shown to produce significant improvement to [irritable bowel syndrome] symptoms," as well as the importance of the treatment rituals and therapeutic environment.

There is evidence that anxiety about the tolerability or efficacy of a treatment can be a driver of the nocebo effect. In a meta-analysis of placebo-treated participants in clinical trials of duloxetine versus placebo, treatment-emergent adverse events were reported more commonly in Phase II trials, then Phase III, and least in Phase IV.[11] This suggests that a nocebo response is more likely for a treatment that is more experimental and uncertain compared with one that is more established.

Choice of treatment and sense of control was found to influence both placebo and nocebo responses in an experiment where healthy participants (n = 61) were randomly assigned to choose between 2 equivalent β-blocker medications or be assigned to the medications. All study medications were actually placebos. There was an increased placebo response in the choice group and an increased nocebo response in the no-choice group.[12]

Neurobiological Findings

Numerous experiments have revealed insights into which regions of the brain are involved in the placebo response and which biochemical processes are occurring in association with placebo and nocebo events. Imaging studies have often used a placebo analgesia paradigm, as it is a reliable and convenient model.

Many variation of the analgesia paradigm exist. Placebos to replace psychotropic drugs are also a reliable and convenient paradigm, and a placebo antidepressant has been used for at least one imaging study. The placebo and nocebo phenomenon has been found in numerous medical conditions, across drug classes, and in non-pharmacologic contexts. It may be difficult to disentangle if a neurobiological response is applicable to the placebo and nocebo phenomena in general or only to a specific context or as treatment for a specific stimulus. The Figure summarizes brain regions, circuits, and neurotransmitters implicated in placebo and nocebo phenomena.

Neuroanatomic Regions

Studies using functional nuclear magnetic imaging (fMRI) and positron emission tomography (PET) have identified multiple brain regions involved in the placebo response. Several studies and a meta-analysis have identified the thalamus, primary and secondary somatosensory cortex, anterior cingulate cortex (ACC), amygdala, basal ganglia, and right lateral prefrontal cortex as brain regions; these were less activated when measured by fMRI, when placebo analgesia was used to modulate a response to a pain stimulus.[5] PET studies of placebo analgesia have identified the rostral ACC, prefrontal cortex, insula, thalamus, amygdala, nucleus accumbens and periaqueductal gray using a μ-opioid receptor radiotracers, and the basal ganglia using D2 and D3 receptor radiotracers as brain regions with neurotransmitter response to placebo analgesia.[13]

In a deceptive placebo analgesia paradigm fMRI study for visceral pain where participants are randomized to receive placebo and being told the substance is inert or placebo and being told that the substance is an analgesic, greater modulation by placebo analgesia of the posterior insula and dorsolateral prefrontal cortex was observed in women compared with men, although the efficacy of placebo analgesia in controlling expected or perceived pain did not differ between sexes.[14] A deceptive placebo analgesia paradigm fMRI study for noxious heat pain, where placebos were labeled as a popular branded original or a generic analgesic, original branded and generic labeled placebos were both associated with activation of the anterior insulae at baseline and activation of the dorsomedial prefrontal cortex after the interventions. Greater activation of the bilateral dorsolateral (as well as dorsomedial) prefrontal cortex (PFC) was observed for the placebo labeled as the original brand. The placebo labeled as the original brand was also associated with decreased pain intensity compared with the generic-labeled placebo.[15] A recent PET study using a μ-opioid receptor radiotracer, patients with major depressive disorder were treated with placebo in a crossover study in which one placebo was labeled "active" and the other "inactive," and told that the active treatment was a fast-acting antidepressant and the inactive treatment was a control. Active treatment was superior to inactive treatment for placebo-induced opioid release in brain regions subgenual ACC, nucleus accumbens, amygdala, thalamus, and hypothalamus.[16] Placebo activation of endogenous opioid neurotransmitters that bind to receptors in the pregenual and subgenual rostral ACC, the dorsolateral PFC, the insular cortex, and the nucleus accumbens, has also been observed in an analgesia paradigm using PET.[17] Substantial inter-individual variation has been reported for brain regions involved in placebo response to expectations of analgesia.[18]

An fMRI study of 24 healthy adults investigated neural activation in response to stimuli associated with different expectations. In 3 separate sessions (ie, training, conditioning, and scanning sessions) on different days, participants were subject to 12-second heat pain stimulus to their right forearm. At the conditioning and training sessions, participants skin was treated with an inert cream before the heat pain stimulus. One cream was labeled "lidocaine" (positive expectancy), one was labeled "neutral," and the third cream was labeled "capsaicin" (negative expectancy). Difference between positive and negative expectancy conditions were observed, either pre or post stimulus, in the dorsal ACC, right orbito-PFC, anterior insula, right dorsolateral PFC, left ventral striatum, orbitofrontal cortex, periaqueductal gray, and left operculum and putamen.[19] This experiment found that placebo and nocebo expectancies have effects on different brain networks in response to a pain stimulus.

There are limitations to using fMRI and PET to study models of the nocebo and placebo effects. Firstly, most experiments are conducted on health volunteers, so important drivers of the placebo response, such as hope and therapeutic alliance, are not included in the experimental construct. Secondly, study participants are inside a large piece of medical equipment, which is a specific experimental environment. Thirdly, the experimental environment limits the study design and duration.

Neurochemical Processes

The placebo response has been associated with the release of endorphins and dopamine, providing a neurochemical explanation of the efficacy of placebo analgesia.[13] Early evidence of the elevation of endogenous opioids in placebo analgesia was reported in 1978, when Levine et al[20] used placebo as an analgesic for dental postoperative pain and reversed the analgesic effects by administering the opiate antagonist naloxone. Endorphin and dopamine release and opioid and dopamine receptors are widely distributed, but are also clustered in specific brain regions that correspond with many of the regions identified by fMRI studies. There are 3 major types of opioid receptor, μ-opioid receptor, δ-opioid receptor, and κ-opioid receptor, which can be further divided into subtypes, and a fourth nociception or orphanin receptor.[21] These receptors are widely distributed through the brain and other organs, but with differences in expression and distribution.[21] Opioid receptors have a range of functions, including pain modulation and their association with analgesia, however, they are also associated with various functions, including mood regulation, homeostasis, cell proliferation, and neuroprotection.[21]

Much placebo neurobiological research has focused on analgesia, often investigating the μ-opioid receptor. Where major depressive disorder has been investigated[16] increased μ-opioid neurotransmission has been observed, similar to observations in analgesia research, which may suggest similarities to, or be a consequence of, using a similar research method. Inter-individual variation in μ-opioid neurotransmission has also been observed in a study of 50 healthy controls with and without placebo administration, where psychological trait scores measured with scales for altruism, straightforwardness, and angry hostility accounted for 25% of the variance in placebo analgesic response and also found that participants scoring above the median in a composite score of all 3 traits had increased μ-opioid neurotransmission in response to placebo administration.[22]

An experiment where hypertonic saline was injected into the masseter muscle of 20 healthy individuals to induce pain, with or without placebo analgesia, was investigated using PET to examine changes in dopamine and opioid neurotransmission. The study used [C^{11}]-labeled raclopride (selective for D_2 receptors) and carfentanil (selective for μ-opioid receptors). Participants were asked to rate the efficacy of the analgesic and describe adverse events. Effective placebo analgesia was associated with increased dopamine and opioid neurotransmission in multiple brain regions. A nocebo effect was identified in 5 participants who reported increased pain intensity during placebo administration. Nocebo responders showed decreased dopamine and opioid neurotransmission in the same brain regions where increased neurotransmission was observed in placebo responders.[23]

In a study where patients reporting mild perioperative pain were given saline solution and were told that the solution produced an increased pain (nocebo hyperanalgesia), pain was abolished when proglumide was added to the solution. Proglumide is a cholecystokinin antagonist, which blocks both the CCK_A and CCK_B receptor subtypes, suggesting that nocebo hyperanalgesia is mediated at least in part by cholecystokinin.[24]

PET studies have found that administration of a placebo to people with Parkinson's disease can induce dopamine release in the striatum.[25] Furthermore, in a study of 24 participants with Parkinson's disease undergoing deep brain stimulation, the firing rate of selected neurons was changed in participants who showed a clinical response to placebo, but not in nonresponders or partial responders to placebo. Mean firing frequency decreased in subthalamic and substantia nigra pars reticulata neurons and increased in ventral anterior and anterior ventral lateral thalamus neurons. The placebo effect had a duration of no more than 45 minutes. Other parts of the brain circuitry were not measured.[26] Another study found that placebo was enhanced with preconditioning by apomorphine exposure, with the greater number of exposures to apomorphine associated with a greater change in neuronal firing rates.[27]

Endocannabinoids have a role in placebo-induced analgesia, as reported in a study analogous to the 1978 naloxone experiment that reported on the role of endorphins.[20] Placebo was effective as an analgesic against tourniquet pain after preconditioning participants to analgesia with either the opioid morphine or the nonsteroidal anti-inflammatory drug ketorolac. In these preconditioned participants, the CB1 cannabinoid receptor antagonist rimonabant reversed placebo analgesia after preconditioning with ketorolac, but did not reverse placebo analgesia in participants preconditioned with morphine.[28]

Prostaglandin levels have also been found to change in response to placebo. In an experiment,

placebo was used to treat headache caused by high-altitude (3,500 m) hypobaric hypoxia, after preconditioning by treating headache with inhaled oxygen and later giving placebo (sham) oxygen, or by preconditioning with aspirin and later giving a placebo tablet. In both scenarios, the placebos were effective for reducing headache pain, but the analgesic effect of placebo oxygen was superior to placebo aspirin. Placebo oxygen was found to specifically reduce salivary prostaglandin E_2, mimicking the therapeutic pathway of oxygen therapy, whereas placebo aspirin had a more general effect on prostaglandin synthesis, mimicking the effect of cyclooxygenase inhibition.[29]

Interaction of Psychological and Physiological Factors

Placebo and nocebo responses occur within a psychological and physiological context. This context is critical for all aspects of the response, including the neurobiological elements. The context includes characteristics of the study or treatment in which the placebo or nocebo effect is observed and characteristics of the study participant or patient, as well as other characteristics, including the environment in which the study or treatment is being conducted. The doctor–patient relationship, for example, can include trust, where untrustworthiness has been associated with increased amygdala activity, and trustworthiness can be modulated by oxytocin.[30] Trust may be a characteristic not only of the active relationship, but is powerfully influenced by personality and developmental factors that set individuals levels of trust. Similarly, hope and hopelessness have been associated with serotonergic and noradrenergic systems,[30] showing the potential for variables relevant to placebo having a direct effect on neurotransmitter systems directly implicated in mood. Also relevant to the placebo response, admiration and compassion by a participant have been found through fMRI to result in a pattern of activation within the posteromedial cortice.[31] Learned helplessness has been found to effect serotonin regulation.[32] The relationship between pain and stress and anxiety with the hypothalamic–pituitary–adrenal axis and cortisol is well established.[33]

Negative and positive expectations, which are suggested to be major drivers of the placebo and nocebo responses, have been found to induce changes in reward circuitry in the nucleus accumbens, and similarly, conditioning may induce changes in learning mechanisms.[30]

DISCUSSION

The drivers of the placebo and nocebo phenomena may be a synergy of multiple biological and psychological variables, mediated by a further multitude of contextual and individual variables. There is clear evidence of physiological factors that underpin the phenomena, as well as a contribution by psychological factors. This is further complicated by considerable inter-individual differences. Although there is consistency in the literature in terms of which pathways are implicated in placebo and nocebo responses, neurotransmitter activation does not occur with all individuals experiencing the same stimulus. Factors such as conditioning, expectancy, hope and despair, wanting to please the experimenters, treatment setting, caring nature of the clinician, and personal beliefs about medications, all play a role.

Furthermore, while the placebo and nocebo effect has been observed for treatment for a broad range of medical conditions, it has only been carefully studied in experimental models of a narrow range of conditions, especially pain and analgesia. It is possible, or even likely, that the neural pathways involved in a placebo analgesia response are different, or only partly overlapping, from the neural pathways involved in a placebo response for a different treatment. The investigation of the biological and theoretical underpinning of the placebo and nocebo phenomena is at an early stage and much additional research is required.

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CONFLICTS OF INTEREST

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REVIEW ARTICLE

Nocebo Phenomena in Medicine

Their Relevance in Everyday Clinical Practice

Winfried Häuser, Ernil Hansen, Paul Enck

SUMMARY

Background: Nocebo phenomena are common in clinical practice and have recently become a popular topic of research and discussion among basic scientists, clinicians, and ethicists.

Methods: We selectively searched the PubMed database for articles published up to December 2011 that contained the key words "nocebo" or "nocebo effect."

Results: By definition, a nocebo effect is the induction of a symptom perceived as negative by sham treatment and/or by the suggestion of negative expectations. A nocebo response is a negative symptom induced by the patient's own negative expectations and/or by negative suggestions from clinical staff in the absence of any treatment. The underlying mechanisms include learning by Pavlovian conditioning and reaction to expectations induced by verbal information or suggestion. Nocebo responses may come about through unintentional negative suggestion on the part of physicians and nurses. Information about possible complications and negative expectations on the patient's part increases the likelihood of adverse effects. Adverse events under treatment with medications sometimes come about by a nocebo effect.

Conclusion: Physicians face an ethical dilemma, as they are required not just to inform patients of the potential complications of treatment, but also to minimize the likelihood of these complications, i.e., to avoid inducing them through the potential nocebo effect of thorough patient information. Possible ways out of the dilemma include emphasizing the fact that the proposed treatment is usually well tolerated, or else getting the patient's permission to inform less than fully about its possible side effects. Communication training in medical school, residency training, and continuing medical education would be desirable so that physicians can better exploit the power of words to patients' benefit, rather than their detriment.

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Words are the most powerful tool a doctor possesses, but words, like a two-edged sword, can maim as well as heal.", Bernard Lown (e1).

Doctor–patient communication and the patient's treatment expectations can have considerable consequences, both positive and negative, on the outcome of a course of medical therapy. The positive influence of doctor–patient communication, treatment expectations, and sham treatments, termed placebo effect, has been known for many years (e2) and extensively studied (1). The efficacy of placebo has been demonstrated for subjective symptoms such as pain and nausea (1). The Scientific Advisory Board of the German Medical Association published a statement on placebo in medicine in 2010 (2).

Method

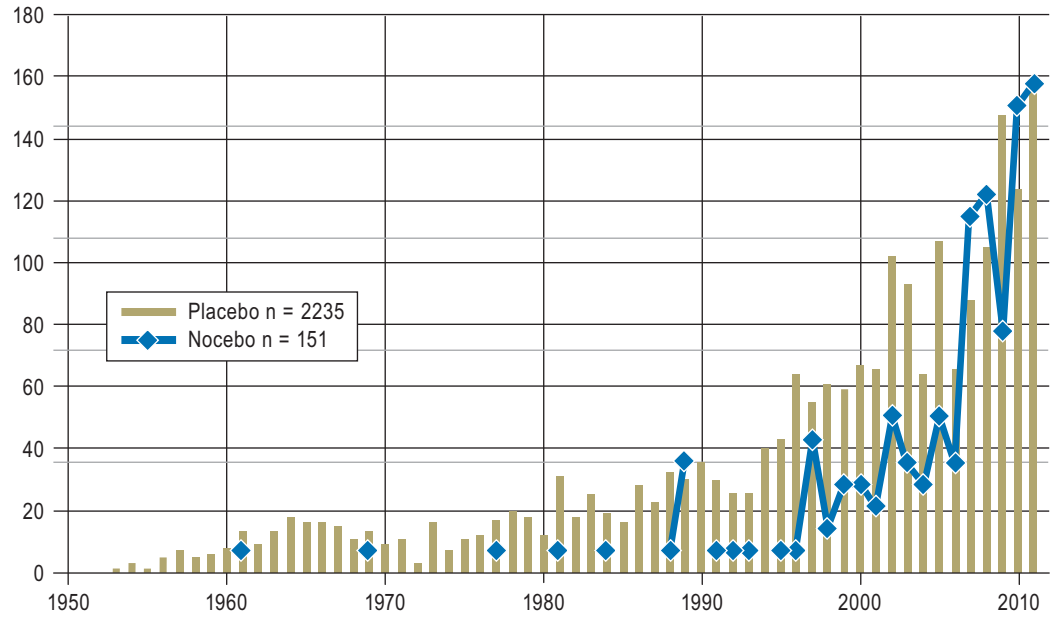
The opposite of the placebo phenomenon, namely nocebo phenomena, have only recently received wider attention from basic scientists and clinicians. A search of the PubMed database on 5 October 2011 revealed 151 publications on the topic of "nocebo," compared with over 150 000 on "placebo." Stripping away from the latter all articles in which "only" placebo-controlled drug trials were reported left around 2200 studies investigating current knowledge of the placebo effect. In comparison, the data on the nocebo effect are sparse. Of the 151 publications, only just over 20% were empirical studies: the rest were letters to the editor, commentaries, editorials, and reviews (*Figure*).

Our intention here is to portray the neurobiological mechanisms of nocebo phenomena. Furthermore, in order to sensitize clinicians to the nocebo phenomena in their daily work we present studies on nocebo phenomena in randomized placebo-controlled trials and in clinical practice (medicinal treatment and surgery). Finally, we discuss the ethical problems that arise from nocebo phenomena which may be induced by explanation of the proposed treatment in the course of the patient briefing and describe possible solutions.

Definition of nocebo phenomena

The term "nocebo" was originally coined to give a name to the negative equivalent of placebo phenomena and distinguish between desirable and undesirable effects of placebos (sham medications or other sham interventions, for instance simulated surgery). "Nocebo" was used to describe an inactive substance or

FIGURE



Number of studies on the placebo effect (olive-green bars, left ordinate) and the nocebo effect (blue diamonds, right ordinate) in PubMed between 1950 and 2011

ineffective procedure that was designed to arouse negative expectations (e.g., giving sham medication while verbally suggesting an increase in symptoms) (3).

"Placebo" and "nocebo" are meanwhile being used in another sense: The effects of every medical treatment, for example administration of drugs or psychotherapy, are divided into specific and non-specific. Specific effects are caused by the characteristic elements of the intervention. The non-specific effects of a treatment are called placebo effects when they are beneficial and nocebo effects when they are harmful.

Placebo and nocebo effects are seen as psychobiological phenomena that arise from the therapeutic context in its entirety, including sham treatments, the patients' treatment expectations and previous experience, verbal and non-verbal communications by the person administering the treatment, and the interaction between that person and the patient (4). The term "nocebo effect" covers new or worsening symptoms that occur during sham treatment e.g., in the placebo arm of a clinical trial or as a result of deliberate or unintended suggestion and/or negative expectations. "Nocebo response" is used to mean new and worsening symptoms that are caused only by negative expectations on the part of the patient and/or negative verbal and non-verbal communications on the part of the treating person, without any (sham) treatment (5).

Experimental nocebo research

Experimental nocebo research aims to answer three central questions:

- Are nocebo effects caused by the same psychological mechanisms as placebo effects, i.e., by learning (conditioning) and reaction to expectations?
- Are placebo and nocebo effects based on the same or different neurobiological events?
- Are the predictors of nocebo effects different from those of placebo effects?

Psychological mechanisms

The proven mechanisms of the placebo response include learning by Pavlovian conditioning and reaction to expectations aroused by verbal information or suggestion (6). Learning experiments with healthy probands have shown that worsening of symptoms of nausea (caused by spinning on a swivel chair) can be conditioned (7). Expectation-induced cutaneous hyperalgesia could be produced experimentally through verbal suggestion alone (8). Social learning by observation led to placebo analgesia on the same order as direct experience by conditioning (9).

Nocebo responses can also be demonstrated in patients. In an experimental study, 50 patients with chronic back pain were randomly divided into two groups before a leg flexion test: One group was informed that the test could lead to a slight increase in pain, while the other group was told that the test had no effect on pain level. The group with negative information reported stronger pain (pain intensity 48.1 [standard deviation (SD) 23.7] versus 30.2 [SD 19.6] on a 101-point scale) and performed fewer leg flexions (52.1 [SD 12.5] versus 59.7 [SD 5.9]) than the group with neutral instruction (10).

It can be concluded from these studies that both placebo and nocebo responses can be acquired via all kinds of learning. If such reactions occur in everyday clinical practice, one must assume that they arise from the patient's expectations or previous learning experiences (5).

Neurobiological correlates

A key part in the mediation of the placebo response is played by a number of central chemical messengers. Especially dopamine and endogenous opiates have been demonstrated to be central mediators of placebo analgesia. These two neurobiological substrates have also been shown to play a part in the nocebo response (hyperalgesia): While secretion of dopamine and endogenous opioids is increased in placebo analgesia, this reaction is decreased in hyperalgesia (11). Because worsening of symptoms e.g., increased sensitivity to pain is often associated with anxiety, other central processes play a part, e.g., the neurohormone cholecystokinin (CCK) in pain (12). To date, a genetic predisposition to placebo response has been demonstrated only for depression and social anxiety (e3); such a predisposition to nocebo response has so far not been shown (e4).

Interindividual variation

Sex is a proven predictor of the placebo response and also exerts some influence on the nocebo response. In the above-mentioned study on the aggravation of symptoms of nausea, women were more susceptible to conditioning and men to generated expectations (6).

Identification of predictors of nocebo responses is a central goal of ongoing investigations. The aim is to pinpoint groups at risk of nocebo responses, for example patients with high levels of anxiety, and optimize the therapeutic context accordingly (13).

Generation of nocebo responses by doctor–patient and nurse–patient communication

The verbal and non-verbal communications of physicians and nursing staff contain numerous unintentional negative suggestions that may trigger a nocebo response (14).

Patients are highly receptive to negative suggestion, particularly in situations perceived as existentially threatening, such as impending surgery, acute severe illness, or an accident. Persons in extreme situations are often in a natural trance state and thus highly suggestible (15, 16). This state of consciousness leaves those affected vulnerable to misunderstandings arising from literal interpretations, ambiguities, and negative suggestion *(Box)*.

In medical practice the assumption is that the patient's pain and anxiety are minimized when a painful manipulation is announced in advance and any expression of pain by the patient is met with sympathy. A study of patients receiving injections of radiographic substances showed that their anxiety and pain were heightened by the use of negative words such as "sting," "burn," "hurt," "bad," and "pain" when explaining the procedure or expressing sympathy (17). In another study, injection of local anesthetic preparatory to the induction of epidural anesthesia in women about to give birth was announced by saying either "We are going to give you a local anesthetic that will numb the area so that you will be comfortable during the procedure" or "You are going to feel a big bee sting; this is the worst part of the procedure." The perceived pain was significantly greater after the latter statement (median pain intensity 5 versus 3 on an 11-point scale) (18).

BOX

Unintended negative suggestion in everyday clinical practice (after 15, e5, e6)

- **Causing uncertainty**
  - "This medication may help."
  - "Let's try this drug."
  - "Try to take your meds regularly."
- **Jargon**
  - "We're wiring you up now." (connection to the monitoring device)
  - "Then we'll cut you into lots of thin slices." (computed tomography)
  - "Now we're hooking you up to the artificial nose." (attaching an oxygen mask)
  - "We looked for metastases—the result was negative."
- **Ambiguity**
  - "We'll just finish you off." (preparation for surgery)
  - "We're putting you to sleep now, it'll soon be all over." (induction of anesthesia)
  - "I'll just fetch something from the 'poison cabinet' (secure storage for anesthetics), then we can start."
- **Emphasizing the negative**
  - "You are a high-risk patient."
  - "That always hurts a lot."
  - "You must strictly avoid lifting heavy objects—you don't want to end up paralyzed."
  - "Your spinal canal is very narrow—the spinal cord is being compressed."
- **Focusing attention**
  - "Are you feeling nauseous?" (recovery room)
  - "Signal if you feel pain." (recovery room)
- **Ineffective negation and trivialization**
  - "You don't need to worry."
  - "It's just going to bleed a bit."

TABLE 1

Systematic reviews: discontinuation rates in placebo arms of randomized trials owing to adverse events

Reference	Verum	Number of studies	Discontinuation rate (%)
e9	Primary and secondary prevention of cardiovascular diseases: statins	20	4–26 *
e10	Multiple sclerosis: immune modulators	56	2.1 (95% CI: 1.6–2.7)
e10	Multiple sclerosis: symptomatic treatment	44	2.4 (95% CI: 1.5–3.3)
e11	Acute treatment of migraine	59	0.3 (95% CI: 0.2–0.5)
e11	Prevention of migraine	31	4.8 (95% CI: 3.3–6.5)
e11	Prevention of tension headache	4	5.4 (95% CI: 1.3–12.1)
22	Painful peripheral diabetic polyneuropathy	62	5.8 (95% CI: 5.1–6.6)
22	Fibromyalgia syndrome	58	9.5 (95% CI: 8.6–10.7)

CI = confidence interval; * no data on pooled discontinuation rates

The patient's expectations

Just as the announcement that a drug is going to be given can provoke its side effects even if it is not actually administered, telling headache patients that they are going to experience a mild electric current or an electromagnetic field (e.g., from cell phones) produces headaches (e7). The symptoms of Parkinson's disease patients undergoing deep brain stimulation are more pronounced if they know their brain pacemaker is going to be turned off than if they do not know (e8).

Nocebo phenomena in drug treatment

Researchers distinguish true placebo effects from perceived placebo effects. The true placebo effect is the whole effect in the placebo group minus non-specific factors such as natural disease course, regression to the mean, and unidentified parallel interventions. The true placebo effect can be quantified only by comparing a placebo group and an untreated group (19). The true nocebo effect in double-blind drug trials thus includes all negative effects in placebo groups minus non-specific factors such as symptoms from the treated disease or comorbid conditions and adverse events of accompanying medication (4). The nocebo effects in drug trials referred to below are perceived rather than "true" nocebo effects.

Adverse event profile and discontinuation rates in placebo groups of randomized trials

A systematic review showed that in randomized controlled trials (RCTs) of migraine (69 studies in total, 56 of them with triptans, 9 with anticonvulsants, and 8 with non-steroidal antirheumatic drugs), the side effect profile of placebo corresponded with that of the "true" drug being tested (20). A systematic review of RCTs of tricyclic antidepressants (TCAs; 21 studies) and selective serotonin reuptake inhibitors (SSRIs; 122 studies) revealed a significantly higher rate of adverse events in both the verum and placebo arms of the TCA trials compared to the verum and placebo arms of the SSRI trials. Patients given TCA placebos were significantly more likely to report dry mouth (19.2% versus 6.4%), vision problems (6.9% versus 1.2%), fatigue (17.3% versus 5.5%), and constipation (10.7% versus 4.2%) than patients taking SSRI placebos (21).

The side effects of medications therefore depend on what adverse events the patients and their treating physicians expect (20, 21). Rates of discontinuation owing to adverse effects of placebo in double-blind trials on patients with various diseases are presented in *Table 1*.

Problems in evaluating side effects of drugs

The methods used for recording adverse events influence the type and the frequency of effects reported: Patients specify more adverse events when checking off a standardized list of symptoms than when they report them spontaneously (21). In a large proportion of double-blind drug trials, the way in which subjective drug side effects were recorded is described inadequately or not at all (22). The robustness of the data on which summaries of product characteristics and package inserts are based must therefore be seen in a critical light.

The problems in evaluating side effects of drugs in RCTs also apply in everyday clinical practice. Is the symptom reported by the patient—nausea, for example—a side effect of medication, a symptom of the disease being treated, a symptom of another disease, or a (temporary) indisposition unconnected with either the drug or the disease?

Nocebo effects during drug treatment in everyday clinical practice

Nocebo effects have been described in *(Table 2)*:

- Drug exposure tests in the case of known drug allergy
- Perioperative administration of drugs
- Finasteride in benign prostate hyperplasia

TABLE 2

Nocebo effects in clinical studies

Reference	Diagnosis	Number of patients	Results
e12	Case series: exposure test in known drug allergy	600	27% reported adverse events (nausea, stomach pains, itching) on placebo
e13	Case series: exposure test in known drug allergy	435	32% reported adverse events (nausea, stomach pains, itching) on placebo
e14	Two RCTs: fatigue in advanced cancer	105	79% reported sleep problems, 53% loss of appetite, and 33% nausea on placebo*
e15	RCT: perioperative administration of drugs	360	Undesired effects were reported by 5–8% of patients in the sodium chloride group, 8% of patients in the midazolam-placebo group, and 3–8% of patients in the fentanyl-placebo group
e16	RCT: finasteride in benign prostate hyperplasia	107	Blinded administration of finasteride led to a significantly higher rate of sexual dysfunction (44%) in the group that was informed of this possible effect than in the group that was not informed (15%)
e17	RCT: 50 mg atenolol in coronary heart disease	96	Rates of sexual dysfunction: 3% in the group that received information on neither drug nor side effect, 16% in the group that was informed about the drug but not about the possibility of sexual dysfunction, 31% in the group that was told about both the drug and the possible sexual dysfunction
e18	RCT: 100 mg atenolol in coronary heart disease	114	Rates of sexual dysfunction: 8% in the group that received information on neither drug nor side effect, 13% in the group that was informed about the drug but not about the possibility of sexual dysfunction, 32% in the group that was told about both the drug and the possible sexual dysfunction
e19, e20	Acetylsalicylic acid versus sulfinpyrazone in unstable angina pectoris	555	Inclusion of gastrointestinal side effects in the patient briefing at two of the three study centers led to a six-fold rise in the rate of discontinuation owing to subjective gastrointestinal side effects. The study centers with and without briefing on gastrointestinal side effects showed no difference in the frequency of gastrointestinal bleeding or gastric or duodenal ulcers
23	Controlled study of lactose intolerance	126	44% of persons with known lactose intolerance and 26% of those without lactose intolerance complained of gastrointestinal symptoms after sham administration of lactose
e21	Case report from RCT of antidepressants	1	Severe hypotension requiring volume replacement after swallowing 26 placebo tablets with suicidal intent

*Worse ratings for sleep, appetite, and fatigue before the study were associated with a higher rate of reported adverse events; RCT = randomized controlled trial

- Beta-blocker treatment of cardiovascular diseases
- Symptomatic treatment of fatigue in cancer patients
- Lactose intolerance.

The lactose content of tablets varies between 0.03 g and 0.5 g. Small amounts of lactose (up to 10 g) are tolerated by almost all lactose-intolerant individuals. Therefore, complaints of gastrointestinal symptoms by lactose-intolerant patients who have been told by the physician or have found out for themselves that the tablets they are taking contain lactose may represent a nocebo effect (23).

In Germany, the *aut idem* ruling by which pharmacists may substitute a preparation with identical active ingredients for the product named on the prescription and discount agreements have led to complaints from patients and physicians of poor efficacy or increased adverse effects after switching to generic preparations. A cross-sectional survey conducted on behalf of the German Association of Pain Treatment (*Deutsche Gesellschaft für Schmerztherapie e.V.*) and the German Pain League (*Deutsche Schmerzliga e.V.*) questioned 600 patients who had been switched to an oxycodone-containing generic preparation. Ninety percent were less satisfied with the analgesic effect, and 61% reported increased pain intensity (German-language source: Überall M: *IQUISP Gutachten [Fokusgruppe Oxycodonhaltige WHOIII Opioide] Querschnittsbefragung zu den psychosozialen Folgen einer Umstellung von Originalpräparaten auf Generika bei chronisch schmerzkranken Menschen im Rahmen einer stabilen/zufriedenstellenden Behandlungssituation.* Überall M: IQUISP Expert Report [Focus Group Oxycodone-containing WHO III Opioids]: cross-sectional survey on the psychosocial consequences of substituting original preparations with generics for treatment of chronic pain in a stable/satisfactory treatment context [talk held on 8 March 2008 at a symposium sponsored by Mundipharma during the 19th German Interdisciplinary Pain Congress]).

A qualitative systematic review showed that patients with increased anxiety, depressivity, and somatization tendency are at greater risk of adverse events after switching to generic preparations (24). It must be discussed whether critical statements by medical opinion leaders (e22) and representatives of patients' self-help organizations (e23) on the substitution of powerful opioid preparations by generic equivalents might not be leading to nocebo effects. In the words of one such statement: "The consequences of substitution are always the same: more pain or more adverse events" (e23).

Expectations that a treatment will be poorly tolerated, whether based on experience or induced by information from the media or trusted third parties, may bring about nocebo effects. A systematic review and meta-analysis found a robust association between the expectation and the occurrence of nausea after chemotherapy (e24).

Ethical implications and the dilemma of the patient briefing

On one hand physicians are obliged to inform the patient about the possible adverse events of a proposed treatment so that he/she can make an informed decision (e25). On the other, it is the physician's duty to minimize the risks of a medical intervention for the patient, including those entailed by the briefing (25). However, the studies just cited show that the patient briefing can induce nocebo responses.

The following strategies are suggested to reduce this dilemma:

Focus on tolerability: Information about the frequency of possible adverse events can be formulated positively ("the great majority of patients tolerate this treatment very well") or negatively ("5% of patients report…") (4). A study on briefing in the context of influenza vaccination showed that fewer adverse events were reported after vaccination by the group told what proportion of persons tolerated the procedure well than by those informed what proportion experienced adverse events (e26).

Permitted non-information: Before the prescription of a drug, the patient is asked whether he/she agrees to receive no information about mild and/or transient side effects. The patient must, however, be briefed about severe and/or irreversible side effects (5). "A relatively small proportion of patients who take Drug X experience various side effects that they find bothersome but are not life threatening or severely impairing. Based on research, we know that patients who are told about these sorts of side effects are more likely to experience them than those who are not told. Do you want me to inform you about these side effects or not?" (5).

To respect patients' autonomy and preferences, they can be given a list of categories of possible adverse events for the medication/procedure in question. Each individual patient can then decide which categories of side effects he/she definitely wants to be briefed about and for which categories information can be dispensed with (e27).

Patient education: A systematic review (four studies, 400 patients) of patients with chronic pain showed that training from a pharmacist—e.g., general information on medicinal and non-medicinal pain treatment or on the recording of possible side effects of drugs and guidance in the case of their occurrence—reduced the number of side effects of medications from 4.6 to 1.6 (95% confidence interval of difference: 0.7–5.3) (e28).

Perspectives

Communication training with actor-patients or role-plays during medical studies or in curricula for psychosomatic basic care impart the ability to harness the "power" of the physician's utterances selectively for the patient's benefit (e29, e30). Skill in conveying positive suggestions and avoiding negative ones should also receive more attention in nurse training.

The German Medical Association's recommendations on patient briefing, published in 1990 (e25), urgently require updating. The points that need to be discussed include, for example, whether it is legitimate to express a right of the patient not to know about complications and side effects of medical procedures and whether this must be respected by the physician. Furthermore, it has to be debated whether some patients might not be left confused and uncertain by their inability to follow the legally mandatory comprehensive information on potential complications of medical treatments that is found, for example, on package inserts or multipage information and consent documents.

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KEY MESSAGES

- Every medical treatment (e.g., drug administration, psychotherapy) has specific and non-specific effects. Specific effects result from the characteristic elements of the intervention. The beneficial non-specific effects of a treatment are referred to as placebo effects, the harmful ones as nocebo effects.
- Placebo and nocebo effects are viewed as psychobiological phenomena that arise from the therapeutic context in its entirety (sham treatments, the patients' treatment expectations and previous experience, verbal and non-verbal communications by the person administering the treatment, and the interaction between that person and the patient).
- Nocebo responses may result from unintended negative suggestion by physicians or nurses.
- The frequency of adverse events is increased by briefing patients about the possible complications of treatment and by negative expectations on the part of the patient.
- Some of the subjective side effects of drugs can be attributed to nocebo effects.

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REVIEW ARTICLE

Nocebo Phenomena in Medicine

Their Relevance in Everyday Clinical Practice

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A Systematic Review of Factors That Contribute to Nocebo Effects

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Objectives: Medication side effects are common, often leading to reduced quality of life, nonadherence, and financial costs for health services. Many side effects are the result of a psychologically mediated "nocebo effect." This review identifies the risk factors involved in the development of nocebo effects. ***Method:*** Web of Science, Scopus, MEDLINE, PsycINFO, Journals@Ovid full text, and Global Health were searched using the terms "nocebo" and "placebo effect." To be included, studies must have exposed people to an inert substance and have assessed 1 or more baseline or experimental factor(s) on its ability to predict symptom development in response to the inert exposure. ***Results:*** Eighty-nine studies were included; 70 used an experimental design and 19 used a prospective design, identifying 14 different categories of risk factor. The strongest predictors of nocebo effects were a higher perceived dose of exposure, explicit suggestions that the exposure triggers arousal or symptoms, observing people experiencing symptoms from the exposure, and higher expectations of symptoms. ***Conclusions:*** To reduce nocebo induced symptoms associated with medication or other interventions clinicians could reduce expectations of symptoms, limit suggestions of symptoms, correct unrealistic dose perceptions, and reduce exposure to people experiencing side effects. There is some evidence that we should do this especially for persons with at-risk personality types, though exactly which personality types these are requires further research. These suggestions have a downside in terms of consent and paternalism, but there is scope to develop innovative ways to reduce nocebo effects without withholding information.

Keywords: inert exposure, nocebo effect, predictors, review, symptoms

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Adverse drug reactions (ADRs) are common (Davies et al., 2009), and can have serious implications in terms of patient well-being and adherence (Ammassari et al., 2001) as well as significant financial costs for health services (NICE, 2009; Rodríguez-Monguió, Otero, & Rovira, 2003). However, ADRs are not always related to the physiological action of the medication (Faasse & Petrie, 2013). Only 10.9% of reported ADRs to commonly prescribed drugs are clearly attributable to the medication (de Frutos Hernansanz et al., 1994). It is thought a nocebo effect may play a role in the formation of other apparent side effects (Barsky, Saintfort, Rogers, & Borus, 2002). As well as medication side effects, nocebo effects have been implicated in symptoms attributed to technological exposures such as electro-magnetic fields (EMF) from mobile phones and Wi-Fi (Baliatsas et al., 2012; Rubin, Cleare, & Wessely, 2008). A nocebo effect is the experience of negative symptoms following exposure to an inert substance, which are triggered or exacerbated by psychological mechanisms such as expectations (Kennedy, 1961). The name "nocebo" was created to distinguish between the desirable ("placebo") and undesirable effects of an inert exposure (Häuser, Hansen, & Enck, 2012), although in practice the distinction between undesirable and desirable is not always clear cut. For example increased alertness may be beneficial in some contexts (e.g., prior to an examination) and detrimental in others (e.g., prior to sleep).

Current literature suggests there are three main mechanisms for a nocebo effect; misattribution, expectation, and learning. Misattribution theory suggests that people misattribute preexisting symptoms to the effects of a new exposure (although some authors believe that misattribution does not technically constitute a nocebo effect, see Colloca & Miller, 2011 and Enck, Bingel, Schedlowski, & Rief, 2013). Symptoms are common in everyday life (Petrie, Faasse, Crichton, & Grey, 2014), and although often harmless and short-lived, when people are subjected to a new exposure, symptoms that were present before or occur coincidentally are available to be mistakenly attributed to it (Petrie et al., 2005; Petrie, Moss-Morris, Grey, & Shaw, 2004). Therefore factors such as high baseline symptoms or high self-awareness may serve as risk factors for nocebo effects resulting from this mechanism. Negative expectations can also mediate nocebo effects (Hahn, 1997), and may in turn arise through explicit suggestions about the effects of an exposure (Jaén & Dalton, 2014; Myers, Cairns, & Singer, 1987), or predisposing factors such as pessimism (Geers, Helfer,

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Kosbab, Weiland, & Landry, 2005). These negative expectations can make the individual more likely to attend to new or current sensations, and attribute them to the exposure (Barsky et al., 2002). The response expectancy theory suggests that it is also possible for negative expectations to act more directly, with an expectation of, for example anxiety, being itself anxiety provoking thereby directly causing the negative effect that was expected (Kirsch, 1997a, 1997b). The last mechanism, learning, can elicit nocebo effects through association or social observation. For example, if an inert stimulus has been previously paired with a symptom-inducing stimulus (Barsky et al., 2002), which may occur through conscious or nonconscious mechanisms (Stewart-Williams, 2004), or through observing someone else experience symptoms to the same exposure (Vögtle, Barke, & Kroner-Herwig, 2013).

Given the significant costs nocebo effects can have on patient quality of life and health services it is important to develop interventions to minimize these effects from occurring. Many risk factors have been implicated, but no study has systematically reviewed these to identify those which are the strongest predictors of nocebo effects; something that would assist in the development of such interventions. Instead, previous systematic reviews have focused on the magnitude of nocebo effects for a specific symptom, for example, Petersen et al. (2014) or in clinical trials of experimental medical treatments (Häuser, Bartram, Bartram-Wunn, & Tolle, 2012). One review (Symon, Williams, Adelasoye, & Cheyne, 2015) has provided a preliminary assessment of some of the risk factors involved in nocebo effects. However this "scoping review" identified only 17 papers—a limited subset of the available literature. To address this gap our systematic review aimed to identify the risk factors involved in the reporting of any symptom in response to an inert exposure. This will allow the identification of factors which appear to be consistent predictors of nocebo effects and aid in the development of evidenced-based interventions to prevent them from occurring in the future.

Method

Identification of Studies

Searches were carried out on December 11, 2014, using the following databases: Web of Science, Scopus, MEDLINE, PsycINFO, Ovid, and Global Health. The search terms consisted of "nocebo" or "placebo effect," and where available, searches were limited to studies with a human sample, with review articles restricted. The reference sections of included studies were also examined as well as papers suggested through personal contacts. No gray literature was searched and no temporal constraints were used. The review followed a previously designed, unpublished protocol.

Selection Criteria

Studies were eligible for inclusion if they met the following criteria:

- Studied a human population (healthy volunteers, patients or children were allowed).
- Used an experimental or prospective design.
- Used an inert exposure, that is, containing no pharmacological or physiological active ingredient.
- Assessed factors on their ability to predict symptom reporting, and these factors could be baseline characteristics or experimentally induced.
- Included an outcome of symptom reporting after participants received an inert exposure. Reported symptoms must not have been attributable to an active exposure (e.g., studies where an inert exposure was applied after an active exposure such as heat stimulation were excluded, as in this case the symptoms would have resulted from the heat stimulation).
- Measured symptoms via self-report or inferred through objective measures (e.g., scratching behavior). Such symptoms could be somatic, a measure of arousal or mood. Because of the difficulty in defining when an outcome is aversive or beneficial we took an inclusive approach. For example measures of alertness (where an increase could be aversive in some instances) or contentedness (where decreases might be possible) were both included.
- Published in any language.

Data Extraction

For each study included in the review, details relating to 20 issues were extracted. In summary these related to: sample characteristics, methodological design, type of exposure, experimental conditions and/or baseline risk factors, symptom measurement, statistical analysis, and results. Any non-English articles were translated. We differentiated between studies that used an experimental or a prospective design to easily identify factors implicated in nocebo effects that can be manipulated and those that naturally occur at baseline. For a copy of the data extraction sheet used, see Appendix 1 in the supplemental materials.

Quality Assessment

Eligible studies using an experimental design were assessed using the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011). For prospective studies, the CASPin International (1998) critical appraisal tool was used and adapted to give a "high," "unclear," or "low" risk of bias score, which were color coded red, orange, and green, respectively. Originally the CASP is scored with yes/no answers but this was rescored to low risk (yes) and high risk (no) as well as including an unclear risk response for when enough information was not provided, similar to the Cochrane Risk of Bias tool. As these tools had no criteria assessing sample size we looked at this separately.

Review Process

Rebecca K. Webster conducted the database searches and screened the titles and abstracts of articles to assess their potential relevance. Guidance was obtained from G. James Rubin if there was any uncertainty as to including an article for full text review. Rebecca K. Webster obtained the full articles for those citations that appeared potentially relevant and checked them against the inclusion criteria. If it was unclear whether an article met the inclusion criteria, consensus was sought from G. James Rubin and John Weinman, Rebecca K. Webster then independently extracted data for each included study and carried out the quality assessment

with guidance from G. James Rubin Because of the expected heterogeneity in the studies we did not plan for any meta-analyses and instead we used a narrative synthesis. There is no general consensus on the best way to carry out a narrative synthesis for systematic reviews (Popay et al., 2006). As such we decided to use a weight of evidence approach. To do this, we identified the strength of evidence for each risk factor based on the number of studies investigating each risk factors and their respective quality.

Results

Search Results

The database search retrieved 12,582 citations. After removing duplicates 6,585 citations remained. After screening titles and abstracts, we reviewed the full text of 88 articles relating to 96 studies. Of these, 13 studies were excluded for not investigating any risk factors for the development of symptoms, nine were excluded for using an active exposure and seven were excluded for not measuring symptoms. Sixty-six articles met the inclusion criteria. Twenty-one additional articles were identified by reference checks of included articles and through personal contacts; resulting in a total of 87 articles. Two articles reported results on two separate studies each (Walach & Schneider, 2009; Winters et al., 2001) and are referred to as "Exp 1" or "Exp 2" where necessary, leaving 87 articles reporting on 89 studies. Of these, 70 were experimental (see Table 1) and 19 prospective (see Table 2). Figure 1 provides a flow diagram of the study selection according to the Preferred Reporting for Systematic Reviews and Meta-analyses statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

Quality Assessment

Experimental studies. The quality of experimental studies was poor (see Figure 2), with the main problem being a lack of clear reporting. Thirty-six studies neglected to mention how they carried out randomization, whereas 22 studies were at high risk of bias for failing to mention whether participants were randomized or for not using randomization at all. Because of the unclear reporting of random sequence generation, the risk for allocation concealment bias followed a similar pattern. For blinding of participants and personnel, studies often failed to state whether the experimenters were blind to the manipulation that accompanied the exposure, leaving the risk of bias unclear. Only six studies used adequate blinding procedures, with 12 not using blinding at all. Sixty-five studies used self-report measures, as such blinding of the outcome assessment was judged to be unlikely to influence these results. For 52 studies, drop outs were not addressed, or if they were, they typically failed to explain how this affected the results, leaving the risk of bias unclear. Only one study had lodged a protocol in a publically accessible registry before the start of recruitment, leaving us unable to assess the risk for selective reporting for the remaining studies. As well as this we looked for justification of sample size to assess if each study was adequately powered. Again this was poorly addressed, with only 9 of the 70 studies mentioning that they carried out an a priori sample size calculation.

Prospective studies. The prospective studies performed well against the quality check (see Figure 2). All studies addressed a clearly focused issue with a standardized exposure across all participants. Studies often lacked information about how participants were recruited. However, self-report measures were widely used to minimize bias from experimenters. The identification and control of confounding factors was only deemed an issue for six studies that neglected to control for demographic factors such as gender or age and past symptom reporting. The follow-up of participants was judged to be appropriate in 16 studies. Regarding the generalizability of the findings, it was often difficult to know whether the results could be applied to the population being studied because of the insufficient information about how participants were recruited. In addition, similarly to the experimental studies, justification for sample size was limited with only one study providing an a priori sample size calculation.

Experimentally Induced Risk Factors Categories

Seventy experimental studies were included that investigated risk factors which fell into 9 different categories as discussed below (further details in supplementary Tables 3–11).

Learning. Twenty-three studies manipulated different types of learning on symptom reporting finding some evidence for its role in nocebo effects. Four of these investigated prior experience of which two lower quality studies found no significant effects (Bayer, Coverdale, Chiang, & Bangs, 1998; Dinnerstein & Halm, 1970). However, André-Obadia, Magnin, and Garcia-Larrea (2011) showed that sham rTMS tended to worsen patients' pain when following an active yet unsuccessful rTMS treatment (however caution is required as no statistical test accompanied this finding), and a high-quality study by Stegen et al. (1998) found that participants reported significantly more arousal and respiratory symptoms when completing a breathing trial with room air before a breathing trial with carbon dioxide rather than afterward. As such there is some evidence that prior experience is involved in the development of nocebo effects. Two studies of mixed quality explored the impact of implicit association supporting its role in the nocebo effect, finding that drinking sham caffeine in a coffee solution resulted in significantly more alertness, contentedness, and arousal, than drinking sham caffeine in an orange juice solution (Flaten & Blumenthal, 1999; Mikalsen, Bertelsen, & Flaten, 2001). Three studies of high quality investigated learning through the manipulation of social observation, with two finding a significant effect, broadly supporting its role in the nocebo effect. Lorber, Mazzoni, and Kirsch (2007) failed to show any main effects of observing a confederate display symptom behaviors after inhaling a sham environmental toxin which they were also exposed to. However, in a similar study, participants who observed a confederate display symptoms had significantly higher symptom ratings after inhalation than participants who did not (Mazzoni, Foan, Hyland, & Kirsch, 2010). Similarly, patients who watched a video of people scratching compared to those who saw a video of people sitting idle had higher itch and scratching behavior rating after administration of sham histamine (Papoiu, Wang, Coghill, Chan, & Yosipovitch, 2011), no results were reported for the healthy volunteers in this study.

Of the remaining 14 studies, 13 investigated learning by using classical conditioning to pair inert exposures such as odors with CO2 inhalation before presenting the inert exposures on their own (De Peuter et al., 2005; Devriese, De Peuter, Van Diest, Van de

Table 1
Summary of the Methods Used in Experimental Studies

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
André-Obadia et al. (2011)[b,d]	RCT (B)	Chronic neuropathic pain patients (45, 55.0, 37.8)	Sham rTMS	1. Prior experience: a. Sham rTMS before active rTMS (20); b. Sham rTMS after successful active rTMS (12); c. Sham rTMS after ineffective active rTMS (13)	Pain
Angelucci and Pena (1997)[d]	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	1. Arousal suggestions: a. Given coffee with no expectations (37); b. Given coffee with low arousal expectations (37); c. Given coffee with high arousal expectations (37); d. no coffee and no expectations (37)	State and trait anxiety, Suggestibility, Expectations, Gender
Bayer et al. (1991)[d]	RCT (B + W)	Unemployed Men (100, U/K, 100.0)	Sham electrical shock	1. Symptom suggestions: a. Told they would receive a safe but often painful undetectable current (60); b. Were assured there would be no shocks (40) 2. Perceived dose: a. Within each group the stimulator setting increased from 0 to 80 mA	None
Bayer et al. (1998)[a,d]	RCT (B + W)	Job seekers (62, U/K, 82.0)	Sham electrical shock	1. Prior experience: a. Exposed to two physical pain induction procedures prior to sham stimulation (32); b. Warned of pain and received sham stimulation. They were not exposed to any prior pain induction (30) 2. Perceived dose: a. Within each group the stimulator setting increased in steps of 10 every 5 minutes till it reached 50	Expectations
Benedetti et al. (1997)[d]	RCT (B)	Video assisted thoracoscopy patients (36, 53.7, 66.1)	Sham treatment	1. Symptom suggestions: a. Open injection that it would increase pain (18); b. Hidden injection (18)	None
Brodeur (1965)[d]	RCT (B)	Healthy senior students (45, U/K, 91.1)	Sham arousal capsule	1. Arousal suggestions: a. Told it was a stimulant (15); b. Told it was a tranquilizer (15); c. No suggestion (15)	None
Colagiuri et al. (2012)[d]	RCT (B)	Students experiencing sleep difficulty (82, 20.2, 22.0)	Sham sleeping pill	1. Symptom suggestions: a. Treatment might cause one side effect (29); b. Treatment might cause four side effects (23); c. No warning about side effects (30)	None
Crichton et al. (2014)[d]	RCT (B)	Students (54, U/K, 37.0)	Sham infrasound	1. Symptom suggestions: a. TV footage detailing symptomatic experiences attributed to wind farms *(27)*; b. TV footage with experts stating wind farms would not cause symptoms *(27)*	None
Dalton (1999)[d]	RCT (B)	Healthy volunteers (180, 31.7, 49.4)	Odors	1. Odors: a. Pleasant smelling methyl salicylate (60); b. neutral smelling isobornyl acetate (60); c. Foul smelling butanol (60) 2. Symptom suggestions: a. Told they would have relaxing effects (60); b. Told they were industrial solvents (60); c. Told they were approved for olfactory research (60)	Odor reactivity, Olfactory sensitivity
De Peuter et al. (2005)[d]	RCT (W)	Asthma patients and healthy controls (40, *23.9*, 52.5)	Sham inhaler	1. Conditioning: a. one sham inhaler paired with CO2 challenge; b. one sham inhaler paired with O2	Expectations, Negative affect, Clinical condition
Devriese et al. (2000)[a,d]	Non RCT (B + W)	Healthy students (56, U/K, 41.1)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 3. Timing: a. Test phase immediately after conditioning trials (28); b. Test phase one week after conditioning trials (28) 4. Generalization: a. New foul smelling odor butyric acid; b. New foul smelling odor acetic acid; c. New pleasant smelling odor citric aroma	Negative affect

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Devriese et al. (2004)[a,d]	Non RCT (B + W)	Healthy students (53, U/K, U/K)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (28); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (25) 3. Symptom suggestions: a. Given information about possible health damaging effects of chemical pollution (U/K); b. No information (U/K)	Negative affect, Perceived cue odor
Devriese et al. (2006)	RCT (B + W)	Psychology students (40, U/K, .0)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling acetic acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, acetic acid paired with room air breathing task (20); b. Ammonia paired with room air breathing task, acetic acid paired with CO2 breathing task (20) 3. Symptom suggestions: a. Given information about possible health damaging effects of chemical pollution (20); b. No information (20)	None
Dinnerstein and Halm (1970)[c,d]	RCT (B)	Male students (80, U/K, 100.0)	Sham arousal liquid	1. Arousal suggestions: a. Told it was an energizer (40); b. Told it was a tranquilizer (40) 2. Prior experience: a. Received aspirin prior to sham (40); b. Received lactose prior to sham (40)	None
Faasse et al. (2013)[b,c,d]	RCT (B)	Healthy students (60, 19.4, 43.5)	Sham anti-anxiety tablet	1. Brand suggestions: a. Branded reformulation change (20); b. Generic reformulation change (20); c. No change (20)	None
Flaten (1998)[d]	RCT (B)	Healthy students (48, U/K, 35.4)	Sham arousal drink	1. Arousal suggestions: a. Told you will feel relaxed and sleepy (16); b. Told you will feel alert and a little stress (16); c. Told you will take an inactive drug (16)	None
Flaten and Blumenthal (1999)[d]	RCT (W)	Healthy coffee drinkers (21, 24.8, 61.9)	Decaffeinated solution	1. Association: a. Orange juice; b. Decaffeinated coffee	None
Flaten et al. (1999)[d]	RCT (B)	Healthy volunteers in non-health professions (34, U/K, 54.5)	Sham arousal capsule	1. Arousal suggestions: a. The drug will make you feel relaxed (11); b. The drug will make you feel alert (12); c. You will receive capsules that contain a prescription drug (11)	None
Flaten et al. (2003)[a,b,d]	W	Coffee drinkers (20, U/K, 50.0)	Sham coffee	1. Perceived dose: a. Participants were first given one cup and then a second	Symptoms, Expectations
Gavrylyuk et al. (2010)[d]	RCT (B)	Healthy volunteers (30, 24.9, 32.0)	Saline eye drops	1. Symptom suggestions: a. Informed of pupil dilation effects (10); b. Informed of pupil constriction effects (10); c. Informed of saline eye drops (10)	None
Geers et al. (2006)[d]	RCT (B)	Healthy students (54, U/K, 31.5)	Sham over-the-counter pill	1. Likelihood suggestions: a. Told the pill had unpleasant side effects (18); b. Told they may or may not receive the active drug (19); c. Told they would ingest an inactive drug (17) 2. Self-awareness: a. Told to closely monitor feelings/bodily sensations (27); b. Not given any such instructions (27)	None
Geers et al. (2011)[d]	RCT (B)	Healthy students (102, 20.5, 21.6)	Sham caffeine capsule	1. Likelihood suggestions: a. Told it contained 250mg of caffeine (34); b. Told they may or may not be ingesting 250mg of caffeine (34); c. Not given the capsule and received no caffeine expectation (34)	Gender, Age, Caffeine consumption

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Geers, Helfer, et al. (2005)[d]	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	1. Likelihood suggestions: a. Told the pill had unpleasant side effects *(18)*; b. Told the pill would make them feel either unpleasant or was an inactive substance *(18)*; c. Told they would ingest an inactive pill *(18)* 2. Self-awareness: a. Told to attend to any symptoms experienced (27); b. Not given any such instructions (27)	Age, Gender, Optimism
Geers, Weiland, et al. (2005)[d]	RCT (B)	Healthy students (57, U/K, 35.1)	Sham caffeine pill	1. Arousal suggestions: a. Told they were given caffeine (U/K); b. No mention of caffeine (U/K) 2. Cooperation prime: a. Given a scrambled sentence test with a cooperation prime (U/K); b. Given a scrambled sentence test with a neutral prime (U/K)	Caffeine consumption
Gibbons et al. (1979)[a,d]	RCT (B)	Female students (38, U/K, .0)	Sham drug	1. Symptom suggestions: a. Told they were taking Cavanol which would produce some noticeable side effects (19); b. Told they were taking baking soda (19) 2. Self-awareness: a. Mirror was facing participants (19); b. Mirror was not facing participants (19)	None
Goldman et al. (1965)[a,b,d]	Non RCT (B)	Male veterans with schizophrenia (64, 44.0, 100.0)	Sham arousal treatment	1. Type of administration: a. Received sugar pill (32); b. Received saline injection (32) 2. Arousal suggestions: a. Told it would heighten their ward activity (32); b. Told it would lower their ward activity (32)	Attitudes towards medication
Harrell and Juliano (2009)[c]	RCT (B)	Adult non-smoking coffee consumers *(30, 22.6, 22.0)*	Sham coffee	1. Performance suggestions: a. Told caffeine enhances performance *(15)*; b. Told caffeine impairs performance *(15)*	None
Harrell and Juliano (2012)[c,d]	RCT (B)	Adult smokers (43, 28.7, 67.4)	Sham cigarette	1. Performance suggestions: a. Told cigarette enhances performance (20); b. Told cigarette impairs performance (23)	Gender
Heatherton et al. (1989)[d]	RCT (B)	Female students (59, U/K, .0)	Sham vitamin pill	1. Symptom suggestions: a. Told vitamin has been reported to make people feel hungry (19); b. Told vitamin has been reported to make people feel full (20); c. Told no further information (20)	Participant restraint
Higuchi et al. (2002)[d]	RCT (B)	Healthy volunteers (30, 21.2, 40.0)	Fragrance (Jasmine or Lavendar)	1. Arousal suggestions: a. Told it was relaxing (10); b. Told it was stimulating (10); c. No information given (10)	None
Jaén and Dalton (2014)[a,b,d]	Non RCT (B)	Asthmatics (17, 38.5, 52.9)	Sham active odor	1. Symptom suggestions: a. Labelled the odor as therapeutic (9); b. Labelled the odor as asthmogenic (8)	None
Jensen and Karoly (1991)[d]	RCT (B + W)	Students (86, U/K, 45.3)	Sham sedative pill	1. Social desirability: a. Type B personality is more positive then type A. Type B have been shown to respond more to pills *(43)*: b. Relationship between type A and B personality and response to pills is very weak *(43)* 2. Perceived dose: a. Suggestions of a high dose or low dose were counterbalanced across each group	Gender
Kaptchuk et al. (2006)	RCT (B)	Adults with distal pain in the arms (266, 36.7, 45.9)	Sham treatment	1. Type of administration: a. Received sham acupuncture (133); b. Received placebo pill (133)	None
Kirsch and Weixel (1988)[d]	RCT (B)	Student coffee drinkers (U/K, *19.3, 31.0*)	Sham coffee	1. Likelihood suggestions: a. Told they would receive coffee (U/K); b. Told they may or may not receive caffeinated coffee (U/K); c. No beverage, waited for 20 minutes (U/K) 2. Perceived dose: a. 1 tsp (U/K); b. 2 tsps (U/K); c. 3 tsps (U/K); d. 5 tsps (U/K); e. 8 tsps (U/K)	None
Kuenzel et al. (2012)[d]	RCT (B)	English speaking students (148, 21.7, 18.2)	Herbal infusion tea	1. Arousal suggestions: a. Told it would make them feel relaxed (45); b. Told it would make them feel active (53); c. No information given (50)	None

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Lorber et al. (2007)[d]	RCT (B)	Students without upper respiratory conditions (86, U/K, 40.7)	Sham environmental toxin	1. Social observation: a. Told inhaled substance has been reported to produce symptoms and observed a female confederate inhale and display symptoms (U/K); b. As above but no observation of confederate (U/K); c. Did not inhale the substance and observed a female confederate inhale and display symptoms (U/K); d. As above but no observation of confederate (U/K)	Gender
Lotshaw et al. (1996)[d]	RCT (B)	Male student coffee drinkers (*50*, U/K, 100.0)	Sham coffee	1. Arousal suggestions: a. Told coffee received decaffeinated *(25)*; b. Told decaffeinated received decaffeinated *(25)*	None
Mazzoni et al. (2010)[d]	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Social observation: a. Observed a male/female confederate inhale the substance and display symptoms *(60)*; b. Did not observe a male or female confederate inhale the substance and display symptoms *(60)*	Personality, Gender, Gender of model
Meulders et al. (2010)[a,d]	Non RCT (B + W)	Healthy adults (58, 22.0, 48.3)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (29); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (29)	Ability to predict which odor produced the most symptoms
Mikalsen et al. (2001)[d]	RCT (W)	Student coffee drinkers (21, 25.9, 66.7)	Sham coffee	1. Arousal suggestions: a. Told it was caffeine; b. Told it was not caffeine 2. Association: a. Given in a juice solution; b. Given in a coffee solution	None
Mrňa and Skiřvánek (1985)[a,b,d]	W	Healthy volunteers (21, 17.0, 47.6)	Sham arousal drug	1. Arousal suggestions: a. Told it was a new doping drug undetectable by anti-doping tests; b. Told it was to relax pre-restart states	Prior placebo response
Neukirch and Colagiuri (2014)[a,d]	RCT (B)	Students with sleep difficulty (91, 21.3, 33.0)	Sham sleep medication	1. Symptom suggestions: a. Warned about an increase/decrease in appetite and received placebo treatment (24); b. Warned about the side effect but received no treatment (23); c. Not warned about the side effects and received placebo treatment (22); d. Not warned about the side effects and received no treatment (22)	None
Nevelsteen et al. (2007)[d]	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. Performance suggestions: a. Told magnetic fields enhance cognitive performance (15); b. Told magnetic fields impair cognitive performance (15); c. Told magnetic fields have no effect on cognitive performance (14); d. Not exposed to sham magnetic field and received no information (15)	State-trait anxiety, Depression, Positive and Negative affect, Sensitivity to anxiety, Vigilance, Comfort under helmet
Ossege et al. (2005)	RCT (B)	Healthy volunteers (60, *27.6*, 40.0)	Sham drug	1. Likelihood suggestions: a. Misleading information that is was an active medication (30); b. 50% chance that it was a placebo or active medication (30)	None
Papoiu et al. (2011)[d]	RCT (W)	Healthy volunteers and patients with atopic dermatitis (25, U/K, 44.0)	Sham histamine	1. Social observation: a. Watched a 5 minute video of people scratching their left forearm; b. Watched a 5 minute video of the same persons in the scratching video but sitting idle.	Gender
Penick and Fisher (1965)[a,b,c,d]	W	Healthy medical students (14, U/K, U/K)	Sham arousal drug	1. Arousal suggestions: a. Told they would receive a stimulant drug; b. Told they would receive a sedative drug	None

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Pennebaker and Skelton (1981)[d]	RCT (B)	Students (38, U/K, 31.6)	Ultrasonic noise	1. Symptom suggestions: a. Told it would increase skin temperature (13); b. Told it would decrease skin temperature (12); c. Told it would have no effect on skin temperature (13)	None
Put et al. (2004)[a,b,c,d]	W	Asthma patients (32, 40.0, 50.0)	Sham inhaler	1. Symptom suggestions: a. Told it would have no effect on breathing; b. Told it was a bronchoconstrictor; c. Told it was a bronchodilator	Negative affect, Social desirability
Read and Bohr (2014)[a,b,c,d]	Non RCT (B)	Volunteers without photosensitive epilepsy (177, 25.3, U/K)	Sham 3D TV	1. Symptom suggestions: a. Told it was 3D and wore passive 3D glasses (22); b. Told it was 3D and wore active no shuttering 3D glasses (33); c. Told it was 2D and did not wear glasses (122)	Gender
Schneider et al. (2006)[c,d]	RCT (B)	Healthy Adults (45, 31.0, 22.2)	Sham coffee	1. Arousal suggestions: a. Told they were to consume decaffeinated coffee (15); b. Told they were to consume regular coffee (15); c. Informed they would receive no beverage and no instructions (15)	None
Schweiger and Parducci (1981)[d]	RCT (B)	Students (34, U/K, 52.9)	Sham electric current	1. Symptom suggestions: a. Told a low current would be delivered, too mild to be felt but had produced mild headaches in the past (17); b. Told current would be too weak to be felt, but some people develop mild headaches as a side effect (17)	None
Slánská et al. (1974)[a,d]	Non RCT (B)	Medical students (33, U/K, U/K)	Salt solution	1. Arousal suggestions: a. Told it was a stimulant (17); b. Told it was a sedative (16)	Stability – instability, Activity – passivity, Submissive-dominance, Rationality-sensuousness, Introversion-extraversion
Stegen et al. (1998)[d]	RCT (W)	Healthy psychology students (72, U/K, 48.6)	Breathing trial with room air	1. Conditioning: a. Room air breathing trial before 7.5% CO2 challenge; b. Room air breathing trial after 7.5% CO2 challenge	Negative affect
Szemerszky et al. (2010)[a,b,c,d]	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. Perceived dose: a. Told it would be weak; b. Told it would be strong	Gender, Expectations, IEI-EMF scores, State anxiety, Dispositional optimism, Somatization, Somatosensory amplification, Motivation
Tippens et al. (2014)[d]	RCT (B)	Obese adults (79, 49.4, 10.4)	Sham weight loss supplement	1. Likelihood suggestions: a. Told they would be given an active weight loss supplement (27); b. Told they would be randomly assigned to either the active or placebo supplement (28); c. Only received lifestyle education (24)	None

(*table continues*)

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Van den Bergh et al. (1999)[a,d]	Non RCT (B + W)	Healthy students (64, U/K, 25.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (32); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (32)	None
Van den Bergh et al. (1995)[a,d]	Non RCT (B + W)	Healthy students (28, U/K, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14)	Negative affect
Van den Bergh et al. (1997)[a,d]	Non RCT (B + W)	Psychosomatic patients (28, 36.0, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14) 3. Generalization: a. New foul smelling odor Ichytol; b. New pleasant smelling odor Rose	Gender, State and trait anxiety, Blunting behavior
Van den Bergh et al. (1998)[d]	RCT (B + W)	Healthy adults (56, 42.5, 50.0)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Self-awareness: a. Told to count lower tones and disregard higher tones (28); b. Told to ignore tones (28) 3. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 4. Generalization: a. New foul smelling odor Ichytol; b. New pleasant smelling odor Rose	Gender
Van Diest et al. (2006)[d]	RCT (B + W)	Students (28, U/K, 21.4)	Odors	1. Odor: a. Foul smelling ammonia; b. Foul smelling acetic acid 2. Conditioning: a. Ammonia paired with hypocapnic over breathing trial, acetic acid paired with normocapnic over breathing trial (13); b. Ammonia paired with normocapnic over breathing tria, acetic acid paired with hypocapnic over breathing trial (15) 3. Type of breathing: a. Test odors given with normocapnic breathing trial (U/K); b. Test odors given with spontaneous breathing (U/K)	None
Walach and Schneider (2009) Exp 1	RCT (B)	Healthy adult coffee drinkers (60, 32.3, 23.3)	Sham coffee	1. Likelihood suggestions: a. Told it was caffeine (15); b. Told it could be placebo or caffeine (15); c. Told it could be placebo or caffeine (15); d. Received no beverage (15)	Expectations
Walach and Schneider (2009) Exp 2	RCT (B)	Healthy adult coffee drinkers (*30, 29.9, 33.3*)	Sham coffee	1. Arousal suggestions: a. Told it was caffeine *(15)*; b. Received no beverage *(15)*	Expectations
Walach et al. (2001)	RCT (B)	Coffee drinkers (157, 28.1, 34.0)	Sham coffee	1. Likelihood suggestions: a. Told they would receive a placebo (41); b. Told they would receive coffee (39); c. Told they may receive real coffee or decaffeinated coffee (39); d. No substance or instruction given (38) 2. Experimenter expectations: a. Experimenter told the physiological effects from a caffeine placebo are real (proplacebo) (U/K); b. Experimenter told the effects of caffeine placebos are just due to artifacts (antiplacebo) (U/K)	Expectations

Table 1 (*continued*)

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Experimental risk factor(s) and conditions (*n*)	Baseline risk factors
Walach et al. (2002)	RCT (B)	Coffee drinkers (159, 25.5, 58.0)	Sham coffee	1. Symptom suggestions: a. Received an information leaflet describing the pharmacological effects of caffeine (U/K); b. Received no further information (U/K) 2. Likelihood suggestions: a. Told they would receive a placebo (39); b. Told they would receive coffee (40); c. Told they may receive real coffee or decaffeinated coffee (40); d. No substance or instruction given (40)	None
Winters et al. (2001) Exp 1[a,d]	Non RCT (B)	Psychology students (50, U/K,U/K)	Ammonia	1. Conditioning: a. Odor + CO2 trials and room air trials (10); b. Odor trials and CO2 trials (10); c. Odor trials, CO2 trials, odor + CO2 trials, room air trials (10); d. odor trials, room air trials (10); e. CO2 trials, room air trials (10)	None
Winters et al. (2001) Exp 2[a,d]	Non RCT (B)	18–30 year olds (40, U/K,U/K)	Odors	1. Odor: a. Foul smelling ammonia (20); b. Pleasant smelling niaouli (20) 2. Conditioning: a. Odor + CO2 trials and room air trials (20); b. Odor trials and CO2 trials (20)	None
Winters et al. (2003)[d]	Non RCT (B + W)	18–30 year olds (32, U/K,15.6)	Odors	1. Odor: a. Foul smelling ammonia; b. Pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (16); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (16) 3. Verbal suggestions of symptoms: a. Given leaflet describing widespread chemical pollution of the environment is a potential cause of multiple chemical sensitivity (16); b. No information given (16)	None
Wise et al. (2009)[c]	RCT (B)	Patients with poor asthma control (241, 39.0, *29.5*)	Sham asthma drug	1. Symptom suggestions: a. Emphasized benefit of treatment and described potential side effects (121); b. Expressed uncertainty about improvement following treatment and did not describe potential side effects (120)	None
Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	1. Symptom suggestions: a. Watched a documentary concerning the potential adverse health effects of Wi-Fi (76); b. Watched a BBC News report concerning the security of the internet and mobile phone data (71)	State anxiety, Age, Gender, Level of education, Personality
Zimmermann-Viehoff et al. (2013)[b,d]	RCT (B)	Healthy Caucasians (92, 24.5, 41.3)	Sham arousal oral spray	1. Symptom suggestions: a. Told it contained a drug to increase blood pressure (33); b. Told it contained a drug to decrease blood pressure (29); c. Told it was a placebo (30)	None

Note. RCT = randomized controlled trial; Non RCT = nonrandomized controlled trial; B = between subjects design; W = within subjects design; U/K = unknown; *italicized* = not directly given but has been extrapolated from the available data; rTMS = repetitive transcranial magnetic stimulation; EMF = electromagnetic field; tsp = teaspoon; IEI-EMF = idiopathic environmental intolerance attributed to electromagnetic fields; CO2 = carbon dioxide; O2 = oxygen.
[a] High-risk random sequence generation bias. [b] High-risk allocation concealment bias. [c] High-risk blinding of participants and personnel bias. [d] Did not mention an a priori sample size calculation.

Table 2
Summary of the Methods Used in Prospective Studies

Reference and quality	Study design	Population (*N*, mean age, %male)	Inert exposure	Baseline risk factor(s)
Bogaerts et al. (2010)[e]	P	Female patients with medically unexplained dyspnea and healthy controls (58, U/K, .0)	Breathing trial with room air	State anxiety, Negative affect, Clinical condition
Casper et al. (2001)[e]	P	Nonpsychotic major depressive patients (876, U/K, 42.8)	Sham fluoxetine treatment	Gender, Depression severity
Danker-Hopfe et al. (2010)	P	Villages in Germany with weak RF-EMF sources (397, U/K, 49.1)	Sham EMF	Bad sleep quality, General fear/anxiety towards risks of RF-EMF, Fear/anxiety towards base station, Preoccupation with EMF, Visibility of the base station
Davis et al. (1995)[a,d,e]	P	Healthy adults (27, U/K, 55.6)	Sham anti-depressant pill	Neuroticism, Somatosensory amplification
de la Cruz et al. (2010)[e]	P	Patients with cancer related fatigue (105, U/K, 40.0)	Sham treatment	Anxiety, Nausea, Sleep, General health, Well-being, Cognitive status, Age, Education level
De Peuter et al. (2007)[e]	P	Asthma patients (30, 38.0, 26.7)	Sham histamine inhalation	Negative affect
Drici et al. (1995)[b,e]	P	Healthy volunteers (52, 23.5, 50.0)	Sham paracetamol eye drop	Employment, Type A Personality, Type B Personality
Fillmore and Vogel-Sprott (1992)[e]	P	Male students (56, U/K, 100.0)	Sham coffee	Symptom expectations
Goetz et al. (2008)[e]	P	Parkinson's patients with dyskinesia (484, U/K, U/K)	Sham medication	Age, Gender, Dyskinesia severity, UPDRS motor score, Daily L-dopa dose, Dyskinesia duration, Adverse events, Severity of adverse events, Geographical site of enrolment, Study (1 or 2)
Köteles and Babulka (2014)[a,d,e]	P	Adult volunteers (33, 37.7,15.2)	3 types of Essential oils (Randomized to 1)	Expectations, Pleasantness of odor
Liccardi et al. (2004)[b,e]	P	Patients with ADRs (600, 42.0, 30.3)	Sham allergen pill	Gender, Hospital centre
Link et al. (2006)[a,b,c,d,e]	P	Students (36, 22.7, 44.0)	Sham herbal supplement	Expectations, State anxiety, Social desirability
Lombardi et al. (2008)[a,d,e]	P	Patients with ADRs (435, 39.7, 32.0)	Sham allergen pill	Gender, Age, Atopic status, Severity of previous reaction, Type of previous reaction
Molcăn, Heretik, Novotrý, Vajidičková, and Zucha (1982)[b,e]	P	Medical students (48, U/K, 52.1)	Sham arousal pill	Expectations, State anxiety, Trait anxiety
Stegen et al. (2000)[a,b,d,e]	P	Healthy psychology students (44, U/K, 27.3)	Breathing trial with room air	Negative affect, Social desirability
Strohle (2000)[e]	P	Healthy adults and patients with panic disorder (U/K, *33.5, 56.6*)	Sham panic disorder trigger	Gender, Clinical condition
Sullivan et al. (2008)[c,e]	P	Patients with neuropathic pain (24, 54.7, 62.5)	Sham cream treatment	Pain catastrophizing
Vase et al. (2013)[e]	P	Patient with pain due to tooth removal (U/K, *25.5, 47.5*)	Sham acupuncture	Expectations
Wendt et al. (2014)[e]	P	Healthy males (24, 25.0, 100.0)	Sham immunosuppressive capsule	Genes

Note. P = prospective design; U/K = unknown; *italicized* = not directly given but has been extrapolated from the available data; ns = nonsignificant; UPDRS = unified Parkinson's disease rating scale; RF-EMF = radio frequency electromagnetic fields; EMF = electromagnetic fields; ADRs = Adverse drug reactions.
[a] High-risk for selection bias. [b] High-risk for confounding factors. [c] High-risk for insufficient follow-up. [d] High-risk for low generalizability. [e] Did not mention an a priori sample size calculation.

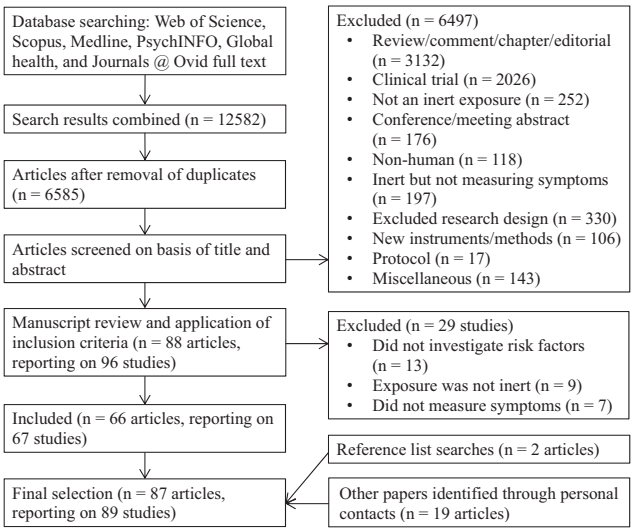

Figure 1. Flow diagram of the selection process of studies including the number of events and reasons for exclusion.

Woestijne, & Van den Bergh, 2006; Devriese et al., 2000; 2004; Meulders et al., 2010; Van den Bergh et al., 1999; Van den Bergh, Kempynck, van de Woestijne, Baeyens, & Eelen, 1995; Van den Bergh, Stegen, & Van de Woestijne, 1997, 1998; Van Diest et al., 2006; Winters et al., 2001 Exp 1 and 2; Winters et al., 2003). Six studies of mixed quality found significant effects of classical conditioning and although seven found no main effect of conditioning on symptom reporting, six of these were of lower quality. As such there is some evidence for the role of classical conditioning in nocebo effects, and that this learning effect can be generalized to new odors (Devriese et al., 2000; Van den Bergh et al., 1997, 1998). However, odor type alone without classical conditioning is not enough to elicit symptoms as demonstrated in this group of studies and the remaining study in this category (Dalton, 1999).

Perceived dose. Six studies manipulated participant perceptions of the dose of the exposure that they received. Four of these found significant effects with three being of higher quality, broadly supporting a link between higher perceived dose and nocebo effects. Only two studies found no significant effects of dose related to decaffeinated coffee consumption (Flaten, Aasli, & Blumenthal, 2003) or taking a sham sedative pill (Jensen & Karoly, 1991). The remaining four all demonstrated significant main effects: Increasing the setting on a sham shock generator increased pain intensity ratings in two studies (Bayer, Baer, & Early, 1991; Bayer et al., 1998), tension scores increased as a function of perceived dose following decaffeinated coffee consumption in one study (Kirsch & Weixel, 1988), and in a final study being told that a sham EMF exposure would be strong resulted in a higher overall symptom scores compared to being told the exposure would be weak (Szemerszky, Köteles, Lihi, & Bardos, 2010).

Self-awareness. Four studies manipulated self-awareness during exposure. Three higher quality studies found no significant effects with only one lower quality study reporting an effect. As such there is little evidence that self-awareness increases the likelihood of a nocebo effect. Both Geers, Helfer, et al. (2005) and Geers, Helfer, Weiland, and Kosbab (2006) showed no significant main effects of instructing participants to attend to any symptoms or sensations they experienced. Using a distraction task also did not have a significant effect on symptom reporting (Van den Bergh et al., 1998). Gibbons, Carver, Scheier, and Hormuth (1979), however, did find a significant main effect, with participants facing a mirror reporting less perceived arousal than participants not facing a mirror following ingestion of a sham drug.

Type of administration. Two studies of mixed quality tested whether type of administration affects symptom reporting, finding no evidence for a link with nocebo effects. There was no difference in symptom reporting between a sham pill and either a saline injection (Goldman, Witton, & Scherer, 1965) or sham acupuncture (Kaptchuk et al., 2006).

Verbal suggestions on performance. Three studies manipulated verbal suggestions about the effect an inert exposure would have on performance. Two higher quality studies found no significant effects with only one lower quality study reporting an effect. As such there is little evidence that suggesting an exposure impairs performance increases the likelihood of a nocebo effect. Both Harrell and Juliano (2009) and Nevelsteen, Legros, and Crasson (2007) found no significant main effects of suggesting sham coffee or sham EMF would enhance or impair performance on a task on any of their symptom measures, respectively. However, smokers told that a sham cigarette would impair performance had significantly more craving symptoms than those who were told it would enhance performance (Harrell & Juliano, 2012).

Verbal suggestions of likelihood of exposure. Nine studies manipulated suggestions about the likelihood that an exposure would occur. All studies were of higher quality with four finding

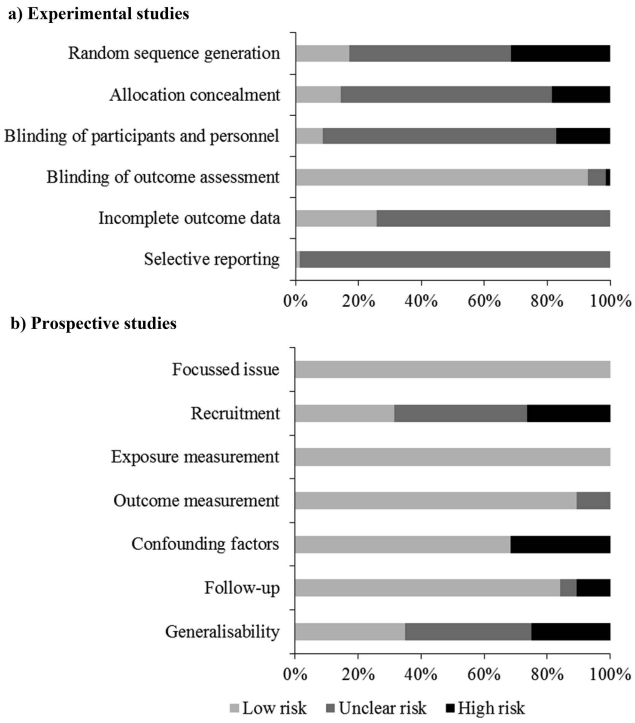

Figure 2. Quality assessment of experimental and prospective studies.

significant effects and five finding nonsignificant effects. In other words, there was mixed evidence for the role of likelihood suggestions in nocebo effects. The studies used a mixture of conditions in which participants were either told they would receive an active exposure (deception), might receive an active or inactive exposure (double-blind), would receive an inactive exposure (open) or nothing (control). Five of the studies found no significant main effects (Geers, Helfer, et al., 2005; Geers et al., 2006; Ossege et al., 2005; Walach, Schmidt, Dirhold, & Nosch, 2002; Walach & Schneider, 2009 Exp 1). Geers, Wellman, Fowler, Rasinski, and Helfer (2011), however, found that participants reported significantly more side effects in response to a sham pill when given deceptive information, compared with double-blind or control information. In addition, participants given deceptive or double-blind suggestions had a significantly higher increase in alertness following ingestion of sham coffee (Kirsch & Weixel, 1988) and a significantly higher number of adverse events following a sham weight loss supplement (Tippens et al., 2014) than participants in the control condition. For Walach, Schmidt, Bihr, and Wiesch (2001) participants told they would receive an inactive exposure scored higher on general wellbeing than those who received no substance or instruction.

Verbal suggestions of arousal. Sixteen studies manipulated suggestions about the effect an inert exposure would have on arousal. Thirteen studies showed a significant effect, with 10 of these being of higher quality. This strongly supports a link with nocebo effects. Only three studies revealed no main effects (Brodeur, 1965; Kuenzel, Blanchette, Zandstra, Thomas, & El-Deredy, 2012; Penick & Fisher, 1965). The remaining 13 all demonstrated significant effects. Participants given stimulant suggestions compared to sedative suggestions had higher tension scores and were more lively after administration of a sham drug (Flaten, Simonsen, & Olsen, 1999; Mrna & Skrivanek, 1985), and had higher scores of stress, arousal, alertness, friendliness and aggressiveness, and lower fatigue scores after ingestion of an inert drink (Dinnerstein & Halm, 1970; Flaten, 1998; Slánská, Tikal, Hvizdosova, & Benesova, 1974). Higuchi, Shoji, and Hatayama (2002) demonstrated lower stress and stimulant symptoms for participants given relaxing suggestions compared to no information for lavender and jasmine fragrances respectively. Goldman et al. (1965) found that more patients reported suggested drug effects in a sedative condition than in a stimulant condition. The remaining studies found a significant increase in caffeine related symptoms (Geers, Weiland, Kosbab, Landry, & Helfer, 2005; Lotshaw, Bradley, & Brooks, 1996), and alertness (Schneider et al., 2006; Walach & Schneider, 2009 Exp 2) and a significant decrease in calmness (Mikalsen et al., 2001) for participants told they would receive caffeine compared to participants who were told they would not receive caffeine or who received no beverage. Finally, Angelucci and Pena (1997) found that participants given coffee with low arousal expectations had significantly lower alertness compared to participants given coffee with no expectations, high arousal expectations, or no coffee at all.

Verbal suggestions of symptoms. Twenty-one studies manipulated suggestions about what symptoms to expect from an inert exposure. Thirteen found a significant effect, with 11 of these being of higher quality, broadly supporting a link with nocebo effects. Of the 21 studies, eight reported no significant main effects (Devriese et al., 2004, 2006; Heatherton, Polivy, & Herman, 1989; Jaén & Dalton, 2014; Schweiger & Parducci, 1981; Walach et al., 2002; Winters et al., 2003; Witthöft & Rubin, 2013). For the remaining 13 studies, Benedetti, Amanzio, Casadio, Oliaro, and Maggi (1997); Crichton, Dodd, Schmid, Gamble, and Petrie (2014); Wise et al. (2009) and Pennebaker and Skelton (1981) found significantly higher symptoms scores for those warned about side effects compared to those not warned after administration of sham treatment, infrasound, and ultrasonic noise, respectively. Dalton (1999), Neukirch and Colagiuri (2015), and Put et al. (2004) found that participants' symptoms were significantly consistent with the warning they received about an odor, sham sleep medication, and sham inhaler, respectively. Three studies demonstrated that participants experienced significantly more symptoms when informed about side effects to a sham drug (Gibbons et al., 1979; Zimmermann-Viehoff et al., 2013) or saline eye drops (Gavrylyuk, Ehrt, & Meissner, 2010) compared with being informed it was a placebo. Similarly both Bayer et al. (1991) and Read and Bohr (2014) established significantly higher symptoms scores for those informed they would receive an active compared to an inactive exposure. Colagiuri, McGuinness, Boakes, and Butow (2012), however, found the opposite; participants not warned about the side effects experienced more and a greater severity of side effects than those warned about one or four side effects.

Miscellaneous. Six studies looked at factors that did not fit into the above categories. There was no significant effect of manipulating participants to cooperate (Geers, Weiland, et al., 2005) or the experimenters' expectations of participants' symptoms (Walach et al., 2001). However, Faasse, Cundy, Gamble, and Petrie (2013) found that manipulating tablet brand to make participants think they had changed to a generic version resulted in a significantly higher number of symptoms compared with participants told that they were still taking the original branded tablet, although this study was of lower quality than the others in this group. Jensen and Karoly (1991) have shown that manipulating social desirability so that participants think responding to the pill is more socially desirable results in significantly higher symptom scores. Type of breathing has also been shown to affect symptom reporting with normocapnic overbreathing resulting in higher respiratory symptoms compared with spontaneous breathing (Van Diest et al., 2006). Lastly, a conditioned odor results in more symptoms if the odor is presented immediately rather than a week after conditioning trials (Devriese et al., 2000).

Baseline Risk Factors Categories

Nineteen prospective studies and also 33 experimental studies which assessed baseline risk factors were included which fell into six different categories as discussed below (further details in supplementary Tables 12–17).

Demographics. Twenty studies looked at the risk of demographic characteristics, finding no demonstrable evidence for their role in nocebo effects. Five of these investigated age and found it did not predict any symptom outcomes (de la Cruz, Hui, Parsons, & Bruera, 2010; Geers, Helfer, et al., 2005; Goetz et al., 2008; Lombardi, Gargioni, Canonica, & Passalacqua, 2008; Witthöft & Rubin, 2013). As four of these studies were of higher quality, this is good evidence that age is not linked with the development of nocebo effects. Eighteen studies (Angelucci & Pena, 1997; Casper,

Tollefson, & Nilsson, 2001; Geers, Helfer, et al., 2005; Geers et al., 2011; Goetz et al., 2008; Harrell & Juliano, 2012; Jensen & Karoly, 1991; Liccardi et al., 2004; Lombardi et al., 2008; Lorber et al., 2007; Mazzoni et al., 2010; Papoiu et al., 2011; Read & Bohr, 2014; Strohle, 2000; Van den Bergh et al., 1997, 1998; Witthöft & Rubin, 2013) looked at gender and only four reported significant results suggesting women are more susceptible to nocebo effects than men (Casper et al., 2001; Liccardi et al., 2004; Strohle, 2000; Szemerszky et al., 2010). Of the remaining 14 showing nonsignificant effects, 12 were of high quality, suggesting there is very little evidence for the role of gender in nocebo effects. The effects of level of education (de la Cruz et al., 2010; Witthöft & Rubin, 2013) were equivocal in two high quality studies, whereas employment (Drici, Raybaud, Delunardo, Iacono, & Gustovic, 1995) was not a significant predictor.

Clinical characteristics. Fourteen studies investigated clinical characteristics, finding mixed evidence for a link with nocebo effects. Six studies of high quality looked at the effect of baseline symptom scores, finding mixed evidence for a link with nocebo effects. Two found no significant effects (André-Obadia et al., 2011; Casper et al., 2001). For the other four, results were mixed. Danker-Hopfe, Dorn, Bornkessel, and Sauter (2010) and de la Cruz et al. (2010) found that higher symptom scores at baseline predicted higher symptom scores after exposure to sham EMF and treatment respectively, whereas Flaten et al. (2003) and Goetz et al. (2008) found the opposite after drinking decaffeinated coffee and taking sham medication for Parkinson's respectively. Six studies of high quality looked at the effect of type of clinical condition, with five finding a significant effect. They showed that suffering from a condition that is exacerbated by the suggested sham exposure significantly increased symptom reporting compared to healthy volunteers, strongly supporting a link with nocebo effects. Nevelsteen et al. (2007) found that depression did not predict symptoms in response to a sham magnetic field. However, De Peuter et al. (2005); Papoiu et al. (2011); Strohle (2000) and Bogaerts et al. (2010) showed that suffering from atopic dermatitis, panic disorder, asthma, or medically unexplained dyspnea resulted in significantly more symptoms in response to sham histamine, sham panic disorder trigger, sham inhaler, and breathing trials with room air, respectively, compared with healthy volunteers. In addition, Szemerszky et al. (2010) found that the level of perceived sensitivity to EMFs was positively correlated with symptom scores after sham EMF exposure. The remaining two studies looked at previous drug reactions finding weak evidence for a link with nocebo effects. Lombardi et al. (2008) found no significant effects of type or severity of previous drug reaction on symptoms in response to a sham allergen pill. However, a higher quality study by Mrňa and Skiřvánek (1985) found the reaction to another sham drug was significantly correlated with perceived drug effect.

Expectations. Thirteen studies looked at the effect of participant expectations on symptom reporting, broadly supporting a link with nocebo effects. Eleven of these studies looked at participants' symptom expectations, of which five higher quality studies revealed no significant effects (Angelucci & Pena, 1997; Molcăn et al., 1982; Walach et al., 2001; Walach & Schneider, 2009 Exp 1 and 2). The remaining six studies demonstrated that expectations of symptoms significantly predicted (Fillmore & Vogel-Sprott, 1992; Köteles & Babulka, 2014; Vase et al., 2013) or correlated (De Peuter et al., 2005; Flaten et al., 2003; Szemerszky et al., 2010) with symptom reporting. Five of these studies were of higher quality therefore broadly supporting a link with nocebo effects. Three studies also looked at expectations in terms of the substance taken finding weak evidence for its role in nocebo effects. Link, Haggard, Kelly, and Forrer (2006) found that participants who believed they had taken an active pill reported more symptoms than those who thought they had a taken a sham pill, however this was a low quality study. Higher quality studies by Bayer et al. (1998) and Walach et al. (2001) also investigated this but found no significant effects.

Anxiety. Nine studies looked at the influence of anxiety on symptom reporting, finding weak evidence for a link with nocebo effects. Six studies of mixed quality looked at state anxiety (Bogaerts et al., 2010; Link et al., 2006; Molcăn et al., 1982; Nevelsteen et al., 2007; Szemerszky et al., 2010; Witthöft & Rubin, 2013) but only Nevelsteen et al. (2007) found a significant effect, with state anxiety predicting physical symptom scores. Molcăn et al. (1982) and Nevelsteen et al. (2007) found no significant effects of trait anxiety. Angelucci and Pena (1997) found combined state and trait anxiety scores significantly predicted anxiety, but did not report results for state and trait anxiety separately. However, no such effect of combined state and trait anxiety was found on symptom reporting to an odor (Van den Bergh et al., 1997), although this was a lower quality study. Finally, a high quality study by Danker-Hopfe et al. (2010) found that anxiety toward a local base station predicted subjective sleep quality after sham EMF exposure.

Personality. Twenty-two studies looked at different aspects of personality as predictors of symptoms. Twelve studies showed significant effects of personality of which only three were of low quality as such finding evidence broadly supporting a link with nocebo effects. There were no significant effects of suggestibility (Angelucci & Pena, 1997), sensitivity to anxiety (Nevelsteen et al., 2007), restraint (Heatherton et al., 1989), or social desirability (Link et al., 2006; Put et al., 2004; Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2000). However, studies did show significant effects of the following on at least one symptom outcome: Type A personalities reported more side effects than Type B (Drici et al., 1995); pain catastrophizing positively correlated with side effect reports (Sullivan, Lynch, Clark, Mankovsky, & Sawynok, 2008); blunting behavior predicted symptom reporting (Van den Bergh et al., 1997); positive affect and vigilance predicted symptom scores (Nevelsteen et al., 2007); "frail and submissive" personality correlated with the exposures perceived effect (Slánská et al., 1974); somatization and motivation predicted symptom score (Szemerszky et al., 2010); and modern health worries and somatosensory amplification predicted symptom scores (Witthöft & Rubin, 2013). There was mixed evidence for the role of negative affect (Bogaerts et al., 2010; De Peuter et al., 2005, 2007; Devriese et al., 2000, 2004; Nevelsteen et al., 2007; Put et al., 2004; Stegen et al., 1998, 2000; Van den Bergh et al., 1995), neuroticism (Davis, Ralevski, Kennedy, & Neitzert, 1995; Mazzoni et al., 2010), and pessimism (Geers, Helfer, et al., 2005; Szemerszky et al., 2010).

Miscellaneous. Thirteen studies looked at baseline factors which did not fit into the above categories. These included caffeine consumption (Geers, Weiland, et al., 2005; Geers et al., 2011), olfactory sensitivity (Dalton, 1999), perceived cue odor (Devriese

et al., 2004), visibility of a mobile phone base station and preoccupation with EMF (Danker-Hopfe et al., 2010), geographical site of enrolment (Goetz et al., 2008), hospital center (Liccardi et al., 2004), stress experienced while wearing a helmet delivering sham EMF (Nevelsteen et al., 2007), ability to predict which odor produced the most symptoms (Meulders et al., 2010), and risk perception (Nevelsteen et al., 2007), which had no significant effects. Köteles and Babulka (2014), however, found that odor pleasantness predicted perceived change in alertness for eucalyptus oil. In addition, odor reactivity predicted symptom responding to odors (Dalton, 1999) and high regard for medications positively correlated with perceived drug effect (Goldman et al., 1965). Mazzoni et al. (2010) found that if the gender of the model matched the participant this predicted symptom development in social observation studies. Nevelsteen et al. (2007) found that less comfort under the helmet delivering the sham EMF predicted symptoms. Finally, Wendt et al. (2014) reported that significantly more symptoms were reported in val/val homozygous carriers compared to val 158/Met 18 and Met/Met 158 homozygous carriers after sham treatment.

Interactions Between Risk Factor Categories

As well as investigating the main effects of each risk factor, some studies assessed the interactions between risk factors, as displayed in the last column of Tables 3 through 17. Those risk factors which were implicated often in these interactions were factors such as "likelihood suggestion" which interacted with: "pessimism"—participants given deceptive suggestions report more symptoms compared to those told it was an inactive pill, if they were pessimists (Geers, Helfer, et al., 2005); "self-awareness"—participants given deceptive suggestions reported more symptoms when asked to monitor their bodily sensations (Geers et al., 2006); and "perceived dose"—tension increased with increasing coffee dose for those given deceptive suggestions, but decreased with increasing coffee dose when given double-blind suggestions (Kirsch & Weixel, 1988).

In addition, "classical conditioning" showed interactions with "odor"; pairing an odor with CO2 elicited symptoms to the odor alone, only if the odor was foul smelling (Devriese et al., 2000; Van den Bergh et al., 1995, 1997; Winters et al., 2003). This interaction between "classical conditioning" and "odor" was also found to more likely occur among people with high "negative affect" (Devriese et al., 2000) and those manipulated to have higher "self-awareness" (Van den Bergh et al., 1998). Negative affect also interacted with "symptom suggestions," with higher obstruction and dyspnea symptom scores after suggestions of bronchoconstriction compared to bronchodilation for a sham inhaler if participants had high negative affect (Put et al., 2004). An interaction was also found with "prior experience," with high negative affect participants reporting more arousal and symptoms on the whole to a room-air breathing trial when this preceded rather than followed a CO2 breathing trial (Stegen et al., 1998).

As well as interacting with negative affect, symptom suggestions interacted with other factors. These included the following: "self-awareness," participants reported more symptoms when told they were taking an active drug with side effects if they were not facing a mirror (Gibbons et al., 1979); "odors," more symptom reports following suggestion of symptoms if the odor was unpleasant (Dalton, 1999); "classical conditioning," higher total, respiratory, cardiac, and unclassified symptom scores following exposure to an odor previously paired with CO2 if participants received symptom suggestions (Winters et al., 2003); and "state anxiety," higher total and head/concentration symptoms following symptom suggestions if participants had high anxiety (Witthöft & Rubin, 2013).

Discussion

Summary of Main Results

From the 89 studies that met our inclusion criteria, 14 categories of risk factor for a nocebo effect were identified, including nine experimentally induced risk factor categories and six baseline risk factor categories (miscellaneous categories were present for both experimental and prospective studies). Of these categories, "learning/social observation," "perceived dose," "verbal suggestions of arousal and symptoms," and "baseline symptom expectations" appeared to be the strongest predictors of nocebo effects. There was some evidence for the role of "personality" in nocebo effects; however which facets of personality are more strongly linked with nocebo effects needs further research. In addition, although not strong predictors on their own, learning/classical conditioning, likelihood suggestion, self-awareness, and negative affect consistently interacted with other risk factors.

Given the proposed psychological mechanisms behind nocebo effects it is perhaps unsurprising that these factors have been consistently identified in the literature. Specifically looking at the expectation mechanism, it is intuitive that verbal suggestions of symptoms can generate expectations of these effects leading to symptom reporting. In support of this, participants' own baseline expectations can trigger symptoms, while perceived dose presumably affects symptom reports through a mediating effect of expectations, with a higher dose associated in a participant's mind with a stronger effect. This could also explain the significance of medication brand, with branded medication being generally expected by the public to be better quality than generic unbranded medication and therefore less likely to cause side effects (Faasse et al., 2013). Expectations could also explain why four studies which measured symptom reports both for prewarned and nonwarned symptoms found stronger effects for symptoms that had previously been suggested (Faasse et al., 2013; Gibbons et al., 1979; Lorber et al., 2007; Mazzoni et al., 2010). It also explains why no effect was found for performance suggestions, as this should not directly influence expectations of symptoms from the exposure.

It is important not to overemphasize the nature of our results with respect to expectation, however. In particular, it was striking that type of administration and verbal suggestions of the likelihood of exposure did not appear to be relevant despite both supposedly raising expectations of symptoms. Possibly, the influence of these factors on expectations is weaker than might be thought. Alternatively, methodological factors may account for the lack of effect. For example, both studies assessing type of administration used patient samples (Goldman et al., 1965; Kaptchuk et al., 2006). Given their greater experience with medical procedures, merely changing an intervention from a pill to an injection may not have triggered a substantial change in expectations. For three of the likelihood suggestion studies (Walach et al., 2001, 2002; Walach

& Schneider, 2009 Exp 1) it was suggested that the absence of an effect could have been because of cultural differences, with the caffeine effect stereotype not as strong in Germany as it is in the U.S.A.

The overall support for the role of expectations identified in our review still allows for at least two "submechanisms" to exist. The first is a role for attentional bias and symptom detection (Hahn, 1997). The second is a more direct effect, where-by expectations affect emotional state (Kirsch, 1997b; Stewart-Williams, 2004). For example, Kirsch (1997b) pointed out that the expectation of anxiety is likely to be anxiety provoking, thereby directly causing the outcome. This could explain the strong results seen for manipulating verbal suggestions of arousal on symptom reporting, as the expectation of arousal or relaxation is itself likely to be arousing or relaxing. However, there does need to be a degree of caution in interpreting these results on arousal as they could be interpreted as part of the placebo response.

With regard to misattribution as a mechanism, the evidence from the studies that investigated self-awareness as a risk factor did not support this, with the two most directly relevant studies that instructed participants to monitor for any sensations failing to find an effect. Equally, for the six studies investigating the effect of baseline symptoms on symptom reporting the results were mixed providing inconclusive support for misattribution. However, five studies (Bogaerts et al., 2010; De Peuter et al., 2005; Papoiu et al., 2011; Strohle, 2000; Szemerszky et al., 2010), showed that suffering from a condition with symptoms similar to those being induced was a predictor of symptom reporting. As such, although the mechanism remains plausible, further evidence is required to clarify its importance.

For the learning mechanism support was found from studies investigating the risk factor "association," with the taste of decaffeinated coffee being enough to elicit caffeine related symptoms (Flaten & Blumenthal, 1999; Mikalsen et al., 2001). For prior experience, the results were weak but this could have been attributable to a lack of experience as this manipulation was typically a one off event. However, there was evidence for the role of social observation, with two of three studies showing a significant effect. In addition, support for learning was seen in the studies using classical conditioning, which involved a number of trials. Almost half of the studies showed that conditioning CO2 inhalation with any odor is enough to elicit symptoms to the odor itself, and a reliable finding among the studies was that this was especially the case if the odor was unpleasant.

For baseline risk factors, we found no evidence of any effects of gender. However, since conducting the literature search, one additional study that would have met the inclusion criteria has become apparent and which is relevant here. This study by Faasse, Grey, Jordan, Garland, and Petrie (2015) investigated the risk factor of observing a female confederate display symptoms, demonstrating a significant effect on symptom reporting in females. It is interesting to note that Lorber et al. (2007), who also studied social observation, also only found a significant effect in females. One possibility is that it may be something inherent to social observation that makes females more vulnerable to nocebo effects. Other demographic factors such as age, employment status or level of education were also not risk factors. Interestingly, anxiety did not come out as a strong predictor despite the role it could play through misattribution (generating physical symptoms that are available to be misattributed) and expectations (apprehension of symptoms). One possible explanation for this advanced by Szemerszky et al. (2010) is that scores of anxiety could reach a ceiling effect due to advance information about the risks of taking part in the study. For other baseline risk factors, many different types of personality were implicated such as: Type A personality (Drici et al., 1995), lower positive affect, vigilance (Nevelsteen et al., 2007), pessimism, motivation to cooperate, somatization, somatosensory amplification, modern health worries (Szemerszky et al., 2010; Witthöft & Rubin, 2013), and neuroticism (Davis et al., 1995). A lack of consistency in the personality traits studied makes it difficult to interpret these findings, but many would seem to fit with expectation and/or misattribution mechanisms.

Nocebo effects have occasionally been referred to as the 'evil twin' of placebo effects. If true, one would expect the risk factors for a nocebo effect to be the inverse of the risk factors for a placebo effect. At a first look the mechanisms supported in our review do appear to be similar to those previously identified for placebo effects, albeit acting in the opposite direction. For example, the expectancy mechanism has been implicated for placebos through factors such as verbal suggestions, and participants' own baseline expectations which lead to positive expectations for pain or symptom relief (Benedetti et al., 2003; Kam-Hansen et al., 2014; Price et al., 1999; Vits et al., 2013). In addition, learning mechanisms such as prior experience of pain relief, social observation, or conditioning people to experience pain relief results in subsequent placebo responses (Colloca & Benedetti, 2006, 2009; Suchman & Ader, 1992). It also seems that opposite personality characteristics also predict placebo responding for example, optimism (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007) as opposed to pessimism. One notable exception, however, would be the misattribution of preexisting symptoms, as logically this can only be relevant for nocebo: one cannot misattribute the absence of preexisting symptoms to an exposure. However, it is possible one could misattribute and fixate on a coincidental decline in symptoms after taking a sham tablet, and misattribute their improved wellbeing to the tablet.

Quality of Original Research

It is possible that some of our conclusions may be attributable to differences in quality between those studies that found an effect and those that did not. We did not observe any clear trend for lower quality studies to report more or fewer significant results than higher quality studies. However, on the whole the quality of the studies included in this review was limited because of poor reporting of key issues in experimental research such as randomization, allocation concealment, blinding, and not registering a study protocol before initiating recruitment. Prospective studies had fewer quality concerns, however given that experimental studies allow the control of more variables the results of these have more weighting than those from the prospective studies. It is also worth noting that almost half of studies did not mention receiving ethical approval. In an area of research requiring deception, or at least withholding information to deliberately cause symptoms, this is surprising. There is scope for future researchers to improve the methodological rigor of this field. Another surprising limitation of many of the studies included in this review was the lack of a priori sample size calculations. Only 10 of 89 studies included in this

review mentioned carrying out a sample size calculation in order to make sure the sample was adequately powered to test their research question(s). As such, we could not assess the quality of studies based on their sample size in the large majority cases. Although it would have been useful to score each study for their strength of evidence, because of this lack of clear reporting and the heterogeneity across studies it was too hard to quantify the strength of each study using the same scale.

Quality of This Review

A strength of this review is that we did not include studies in which participants were exposed to an active exposure capable of eliciting symptoms through physiological mechanisms (e.g., experiments altering the information given to participants about a genuine medication). Such studies do not assess the pure nocebo effect, described as the undesirable effects experienced from an inert exposure (Kennedy, 1961) and can prove more difficult to interpret (Neukirch & Colagiuri, 2015).

Our search resulted in a large number of results. As the term 'nocebo' is still not widely used and may be preferentially used by those studies identifying a significant increase in symptoms in their participants, we deliberately adopted a broader search strategy than that used in previous reviews, for example, Petersen et al. (2014). Despite this, it is not certain that every study that met the inclusion criteria has been included, especially as nearly a quarter of included studies were identified through personal contacts. This inconsistent use of terminology makes the nocebo literature difficult to search and will continue to limit reviews in this area. We could have included terms such as 'adverse effects or negative outcome' in the search strategy but the number of results would be unmanageable as it would include many clinical trials that would not meet our inclusion criteria. On Medline alone, such search terms return over 97,000 results. This is also one of the reasons why we did not simply use 'placebo' as one of the search terms—every study which described itself as "placebo-controlled" would be returned.

In addition to limitations resulting from our search strategy, it is possible that some studies could have been falsely rejected after title and abstract screening (e.g., the main purpose of the study may have been on the placebo effect and therefore only placebo and not nocebo findings were reported in the abstract). We suspect that this is unlikely to have occurred often, however. In order to have been included such studies would have had to (a) manipulated factor(s) to affect nocebo responding or (b) looked at baseline measures as predictors of nocebo responding, which many do not do. Many studies which looked at the placebo effect passed through abstract screening as they mentioned participants experiencing negative symptoms or patients feeling worse after placebo exposure. However, going through the full manuscript the majority of these studies would not explore the possible reasons why, for example, baseline predictors. Therefore we feel this is not something to be too concerned about.

In addition studies published in non-European languages may have been less likely to have been identified as well as studies that were not reported in the conventional peer-reviewed literature.

Other limitations of the review reflect the way we grouped the results. We aggregated studies based on the independent variable. Because of this and because there are no direct replications each risk factor grouping contains several different outcomes. It is possible that an interaction exists between independent and dependent variables: for example, some outcomes may be more susceptible to the effects of changes in expectations than others. Unfortunately, we did not have enough data to explore this in depth.

Similarly as this review focused on identifying all the possible risk factors of nocebo effects that have been investigated in the literature, we included studies with different research populations, for example, students, healthy volunteers and patients. As such there could be differences between the groups in terms of which mechanisms are more likely to be at play. For example, it is likely the misattribution mechanism is more important for the development of nocebo effects in patient samples than healthy volunteers. However, looking at studies that had a patient sample we should interpret the results of those that just focused on baseline disease measures as support of the misattribution mechanism with caution. These studies did not measure actual baseline symptoms or emotions which are more likely to be subject to the misattribution mechanism, rather than disease status.

Finally, the interaction between the mechanisms, outcomes, and mode of delivery may also be important, but could not be explored in detail given the data available to us. For example, different forms of sham intervention for example, sham tablets versus sham caffeine versus sham EMF, may be more or less likely to trigger certain psychological mechanisms, and be more or less likely to affect certain outcomes, see Szemerszky, Dömötör, Berkes, and Köteles (2016).

Implications for Clinical Practice and Research

Our results suggest clinicians keen to reduce side effects induced by any nocebo effect associated with their interventions could (a) identify patient expectations of the adverse effects of an intervention and provide reassurance if these seem excessive, (b) avoid giving suggestions of side effects associated with the intervention, (c) down-play the dose that is being provided, and (d) reduce patient exposure to other patients experiencing side effects. Wells and Kaptchuk (2012) suggest the use of contextualized informed consent, whereby doctors should identify high-risk patients and tailor the medication side effect information so that these patients only receive drug specific side effect information, which is less susceptible to the nocebo response. Our review supports this and suggests that such tailoring may be especially required for those who have at-risk personality types. Clearly, these suggestions also have a downside, however, as they reduce informed consent and patient autonomy by restricting the information that is being provided. Alternative ways to reduce nocebo effects while maintaining the ability of a patient to give full informed consent are required. There is scope for researchers to develop innovative ways to reduce nocebo effects that does not require withholding of information. This has been shown by Crichton and Petrie (2015), who found that informing participants about nocebo effects effectively reduced symptoms to infrasound noise. In addition Bingel and the Placebo Competence Team (2014) provides some suggestions on how to avoid nocebo effects which are supported by this review such as improving the communication in patient information leaflets to make them more patient-orientated and reduce negative expectations of potential adverse effects.

Additional research should also aim to replicate risk factors which have so far received limited research, such as the more rarely investigated personality characteristics. It would also be advisable to look again at the risk factor 'type of administration' in a healthy volunteer sample and to assess this manipulation on expectations to explore possible mechanisms. It is also time for authors to use consistent terminology allowing easier identification of papers, and to enhance the quality of their research in this area. Simple acts such as being more explicit about randomization and blinding procedures and publishing protocols will enhance the transparency of the research in this area while also helping to alleviate some of the controversy surrounding nocebo research.

Conclusions

This review found that there is a mix of factors which predict whether someone will experience a nocebo effect. Given the implications nocebo effects have on patients' quality of life and the health costs they create, it is important for research to start developing interventions to prevent nocebo effects from occurring while still trying to uphold informed consent. This systematic review provides a useful starting point for researchers to develop evidenced based interventions designed to negate nocebo effects, while also highlighting areas that need further investigation and improvement.

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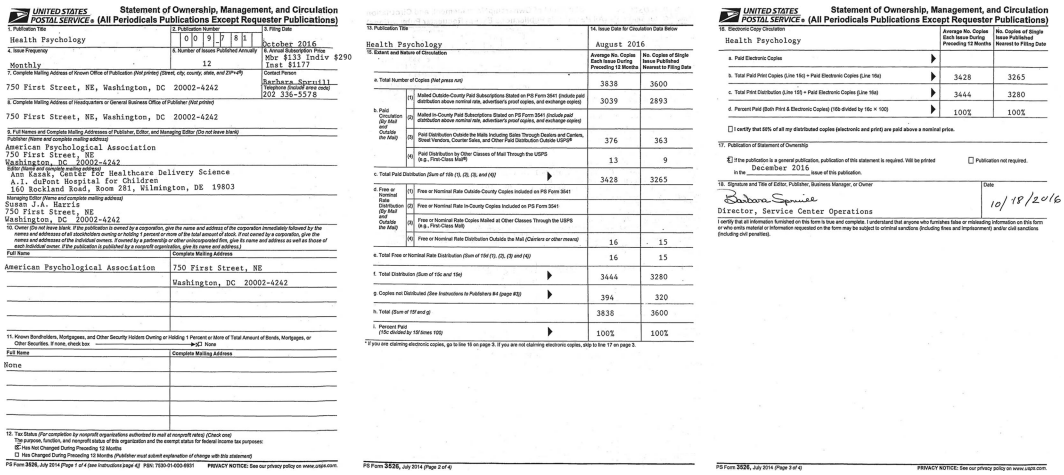

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Nocebo Effect of Informed Consent in Interventional Procedures

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Placebo and nocebo effects have recently emerged as an interesting template to appreciate some of the intricate underpinnings of the mind-body interaction. A variety of psychological mechanisms, such as expectation, conditioning, anxiety modulation, and reward, have been identified, and a number of neurochemical networks have been characterized across different conditions.[1] The nocebo effect, the mirror phenomenon to the placebo effect, occurs when the expectation of a negative outcome precipitates the corresponding symptom or leads to its exacerbation.[2] Unlike the placebo effect, there has been much fewer studies on the nocebo effect. A PubMed keyword search on "placebo" returned 185,249 entries, whereas that of "nocebo" returned only 334 entries. This editorial aims at revealing the potential conflict between nocebo and informed consent in interventional pain management and discussing possible strategies to minimize potentially harmful nocebo effects.

HISTORICAL ASPECT OF INFORMED CONSENT

In ancient Greece, patient participation in medical decision making was considered undesirable. It was generally accepted that the physician's primary task was to inspire the confidence of the patient. Any disclosure of possible difficulties might, therefore, erode the patient's trust.[3] During medieval times, doctors were encouraged to use their conversations with patients as an opportunity to offer comfort and hope, while emphasizing the need for the doctor to be manipulative and deceitful. It was widely held that for the treatment to be effective the authority must be coupled with obedience.[4]

During the Era of Enlightenment, new views emerged such that patients had the capacity to listen to the doctor; however, it was still felt that deception was necessary to facilitate patient care.[3] During the 1800s the medical profession was split over whether to disclose a dire prognosis to a patient. However, most physicians of the time argued against informing patients of their condition.[4]

The doctrine of assault and battery has its roots in early English Common Law. Common Law is the combination of customs, traditions, and case law. This Doctrine forms the basis for the possible "injury" or "liability" incurred from surgery without proper consent.[3] As the concept of informed consent gained popularity during the 20th century, the courts extended the English Common Law Tort doctrine of negligence to the field of surgery by equating negligence with breach of duty and breach of duty with an incomplete patient consent. The failure of a physician to provide adequate information to the patient about his or her own treatment is interpreted by the courts as a breach of duty by the physician.[4]

MODERN FORM OF INFORMED CONSENT

During the last few decades, the way in which medicine is practiced has changed dramatically. The previous paternalistic approach, which emphasized beneficence to the exclusion of other principles, particularly autonomy, has been largely eroded. Unfortunately, however, physicians are not always able to determine their patients' best interests.[5] The case of Schoendorff v. Society of New York Hospital in 1914 has had the most impact on the doctrine of informed consent, in which the patient with a tumor underwent an operation to which he had not agreed.[3] In this case, Justice Benjamin Cardozo summarized "Every human being of adult years in sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patients consent commits a battery for which he is liable in damages."[3]

In recent years, along with the increasing popularity of shared decision making in health-care delivery, more patients have become interested in embracing their roles in making decisions regarding their own health.[6] Informed consent is the process by which a person authorizes medical treatment after discussing with clinicians the nature, indications, benefits, and risks of treatment.[6] Information to be discussed includes diagnosis, procedure, available alternatives, potential outcomes of each option, risks and benefits of each alternative, and the values of each potential outcome.

ORIGIN OF NOCEBO EFFECT

The nocebo effect was first named by Kennedy[7] as "Placebo reaction" in 1961, subsequently elaborated by Kissel and Barrucand.[8] The nocebo hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause sickness in the expectant.[9] Two variants of these nocebo responses exist: one is characterized by new symptoms or a symptom aggravation associated with drug or placebo intake, although the chemical agent itself is not able to trigger these symptoms. Another variation of nocebo responses is the reduced efficacy of clinical interventions due to negative expectations or prior experiences.[10]

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Nocebo effects exist and operate during routine treatments, negatively affecting clinical outcomes. Nocebo effects are the direct result of the psychosocial context or therapeutic environment on a patient's mind, brain, and body, involving multiple factors, such as verbal suggestions and past experience.[11] Negative information and prior unsuccessful therapies may be particularly important in mediating undesirable outcomes to routine therapy. Therefore, consideration of nocebo effects in the context of patient-clinician communication and disclosure of interventional procedures may be valuable in both minimizing the nocebo component of a given therapy and improving procedural outcomes.

Nocebo effects can modulate the outcome of a given therapy in a negative way, as do placebo effects in a positive way. Importantly, these effects operate in the absence of a traditional placebo, forming part of everyday treatments.[11] To this extent, a balance must exist between communicating important clinical information and ensuring that every attempt is made to minimize negative instructions and a negative therapeutic context. This fine balance must take into consideration the patient's autonomy to make a decision based on all relevant information, with attempts to reframe how information may be delivered in a nondeceptive, yet reassuring way.[11]

PROPOSED MECHANISM OF NOCEBO EFFECT

The psychological mechanism of nocebo is thought to involve negative expectations and anxiety.[12,13] Although conditioning paradigms are more powerful in triggering placebo effects, both verbal suggestion and learning induce similar effects on nocebo development.[14] Cholecystokinin has also been shown to be involved in the hyperalgesic nocebo response.[15] Further, Scott et al[16] showed that, although placebo responses were associated with greater dopamine and opioid activity, nocebo responses were associated with deactivation of dopamine and opioid release, demonstrating involvement of the brain circuitry implicated in the reward response and motivated behavior.

Taken together, the underlying mechanisms of nocebo responses are much less well understood than those of placebo responses. In particular, the contribution of similar overlapping and distinct trajectories mediating nocebo versus placebo responses requires further investigation.[10]

CONFLICT OF CONCERN OF NOCEBO EFFECT AND INFORMED CONSENT

The principle of informed consent obligates physicians to explain possible side effects when prescribing medications or performing interventional procedures. This disclosure may itself induce adverse effects through expectancy mechanisms—that is, nocebo effects—contradicting the principle of nonmaleficence. Rigorous research suggests that providing patients with a detailed enumeration of every possible adverse event can actually increase side effects.[17]

One of the primary missions of physicians, dating back to Hippocrates, is the principle of nonmaleficence, Primum non nocere: "Above all do no harm." At the same time, the pinnacle of modern bioethics is informed consent, respect for person, and transparency.[17]

The relevant parallel dilemma is when the harmfulness of the nocebo effect may outweigh the good in proper disclosure of medical information to the patient, and where the duty to inform may therefore be suspended.[2] In view of the nocebo effect of informed consent, the harm in point does not exist; rather, the physician risks creating it by merely mentioning its potentiality. Moreover, this harm can be biologically real and cannot be dismissed as "merely psychological." This raises a different, new moral dilemma, which demands a search for a new moral balance between respect for autonomy and paternalistic nonmaleficence, and which ethicists are called upon to investigate.[2] This is of special importance with respect to the clinical practice of informed consent, where the very disclosure of potential side effects or complications can bring them about through a nocebo effect.

STRATEGIES TO MINIMIZE NOCEBO EFFECT

Wells and Kaptchuk[17] advocate that the perceived tension between balancing informed consent with nonmaleficence might be resolved by recognizing that adverse effects have no clear black or white "truth." They believe informing a patient about side effects is not a mere presentation of "facts" but is an important component of the art of medicine and requires the practitioner's clinical judgment. They have proposed a pragmatic approach for providers to minimize nocebo responses while still maintaining patient autonomy through "contextualized informed consent," an ethical procedure in which the disclosed information is tailored in a way that reduces expectancy-induced side effects while still respecting patient autonomy and truth-telling.[17]

These differences in reported adverse effects indicate that the way in which adverse events are presented affects not only risk perception but, more importantly, clinical outcomes. Rather than merely delivering detailed lists of specific adverse effects, clinicians should incorporate in their communication positive framing and percentage formats as opposed to negative framing and frequency format, thus possibly reducing nocebo effects by minimizing attention on the negative aspects of the treatment.[11]

Studies have shown that pain increases when harsher words are used to describe an upcoming experience. For example, 1 study showed that the use of the word "pain" resulted in patients reporting more pain than use of the phrase "cool sensation,"[18] whereas another study found that saying "you will feel a bee sting" before injection of a local anesthetic resulted in more pain than saying that the anesthetic will "numb the area [so that] you will be comfortable during the [following] procedure."[19] Pain interventionists may need to pay special attention to which words to choose when describing interventional pain procedures to patients in the process of obtaining consent approval as well during procedures. It may be a good idea to explain to the patients more about how the procedures will be done, the mechanism of the action of the selected procedures, and how successful they are in other people, and of course a confident, competent, and compassionate bedside manner will always help.

In summary, clinicians' efforts should be devoted to avoiding instilling negative expectations during the informed consent process, procedural information, and follow-up assessments so that the most effective patient-clinician communication can be pursued while unwarranted and untenable nocebo responses can be avoided.[11] In particular, description of procedures, a common interaction from doctors such as interventional pain practitioners, requires understanding of the potential of nocebo-mediated responses and their implications.

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The nocebo effect in the context of statin intolerance

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Abstract: The nocebo effect, the inverse of the placebo effect, is a well-established phenomenon that is under-appreciated in cardiovascular medicine. It refers to adverse events, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention or a nonmedical situation. These expectations can be driven by many factors including the informed consent form in a clinical trial, warnings about adverse effects communicated by clinicians when prescribing a drug, and information in the media about the dangers of certain treatments. The nocebo effect is the best explanation for the high rate of muscle and other symptoms attributed to statins in observational studies and clinical practice, but not in randomized controlled trials, where muscle symptoms, and rates of discontinuation due to any adverse event, are generally similar in the statin and placebo groups. Statin-intolerant patients usually tolerate statins under double-blind conditions, indicating that the intolerance has little if any pharmacological basis. Known techniques for minimizing the nocebo effect can be applied to the prevention and management of statin intolerance.

Characteristics of the nocebo effect

In 1985, Cairns et al[1] found that aspirin 325 mg qid significantly reduced total and cardiac mortality in a randomized placebo-controlled trial in patients with unstable angina, whereas the uricosuric agent sulfinpyrazone was ineffective. The investigators subsequently noted[2] that the frequency of minor gastrointestinal (GI) adverse events (AEs) in the study population (all patients regardless of treatment allocation) was much greater in 2 centers they denoted A and B, than in center C, as summarized in Table 1. Even more striking, discontinuations of blinded study medication due to minor GI AEs were 6 fold greater in centers A and B, compared with center C.

All participating hospitals were university affiliated and in Ontario. Study procedures were carried out in the same way by all 3 centers using a common procedures manual, including a uniform query for AEs. However, because of local ethical review committee requirements, the consent form differed among centers with regard to adverse effects. In centers A and B, the relevant section read "Side effects are not anticipated beyond occasional GI irritation and, rarely, skin rash." In center C, the consent form read "Sulfinpyrazone and aspirin are generally well tolerated … Occasionally a patient taking sulfinpyrazone or aspirin may develop a tendency to bleed but the risk of serious hemorrhage is extremely unlikely." Thus, study participants in centers A and B were informed of the potential for GI irritation, but at center C, they were not. The investigators concluded that this was the probable source of the differences in GI AEs.

To the best of our knowledge, this report[2] is the first convincing evidence of the nocebo (*Latin: I will harm*) effect in cardiovascular medicine. The nocebo effect (or phenomenon) is the inverse of the placebo effect; it refers to

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Table 1 Adverse events (AEs) in 555 patients with unstable angina allocated to aspirin, sulfinpyrazone, aspirin + sulfinpyrazone, or placebo[2]. All randomized patients included, irrespective of treatment group allocation

Centers (hospitals)	A (4)	B (3)	C (1)	χ^2	*P*
N	313	86	156		
GI AEs in consent form	Yes	Yes	No		
Minor GI AEs	143 (46%)	32 (37%)	25 (16%)	39.8	<.001
Major GI AEs*	8 (2.6%)	1 (1.2%)	6 (3.8%)	1.6	NS
DC due to minor AE†	61 (19%)	15 (17%)	5 (3%)	22.8	<.001
DC due to major AE	27 (9%)	7 (8%)	11 (7%)	3.1	NS

DC, discontinued; GI, gastrointestinal; NS, not significant.
*For example, GI bleeding, peptic ulcer.
†All due to GI AEs.

AEs, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention, or a nonmedical situation. These expectations can be driven by many factors beyond the informed consent form in a randomized controlled trial (RCT), including warnings about adverse effects communicated by clinicians when prescribing a drug,[3,4] information on the Internet and in social media,[5] health scares propagated by broadcast and print media,[6] and simply observing the symptoms and behavior of others.[7,8] Just as an ineffective treatment can be subjectively effective in an uncontrolled setting due to the placebo effect, an innocuous treatment can be subjectively toxic due to the nocebo effect.[6,9] The placebo and nocebo effects reflect normal human neuropsychology and not drug efficacy or toxicity.

The differences reported by Myers et al[2] were not randomized comparisons, but there have since been many studies randomizing subjects to receive different information with follow-up for subsequent AEs. One of the few reports[10] involving a cardiovascular treatment stemmed from the perception at the time of the study that beta blockers commonly cause erectile dysfunction. A total of 96 male patients with hypertension or angina pectoris and normal sexual function completed a multidimensional quality of life questionnaire designed to assess the presence of erectile dysfunction (International Index of Erectile Function). They were then all treated with atenolol 50 mg daily, randomized into 3 groups of 32 receiving different information about the drug. The first group did not know what drug they were taking, the second knew but were not informed about the potential adverse effects, and the third knew they were taking atenolol and were further informed that atenolol could cause erectile dysfunction. The language used was "… it may cause erectile dysfunction but this is uncommon."

At the end of the 90-day treatment period, the same questionnaire was administered again. Erectile dysfunction was reported by 1 patient (3.1%) in the group blinded to treatment, 5 (15.6%) in the group that knew they were taking atenolol but were not informed about side effects, and 10 (31.2%) in the group that was informed about sexual dysfunction potentially attributable to atenolol ($P < .01$ for the informed patient group vs the blinded group). The authors concluded that erectile dysfunction in their study was psychogenic. This conclusion is supported by a review[11] of beta blocker RCTs, which concluded that these drugs rarely cause erectile dysfunction, contrary to widespread belief at the time.

Several reviews[3,7,12,13] have summarized studies reporting the nocebo effect in mostly noncardiovascular contexts. The most common manifestation of the nocebo effect is pain of various kinds, with or without other symptoms. Pain may be heightened because of negative expectations about a treatment or situation,[14] and it can be experienced in the total absence of a noxious stimulus, as in mass psychogenic illness, which is the most dramatic manifestation of the nocebo effect.[15] As shown by functional MRI, negative expectations that heighten pain lead to increased activity of regions involved in pain processing, including the prefrontal cortex, anterior cingulate cortex, and insula.[14] The nocebo phenomenon is thus well established. It hinders effective therapy, especially in the age of the Internet and social media, where misinformation can proliferate.

The nocebo phenomenon in randomized controlled trials vs observational studies

It is widely accepted that a well-performed double-blind RCT provides high-quality evidence because it is the most reliable way to evaluate the benefit, safety, and tolerability of a treatment.[16,17] Double-blind RCTs have the great advantage that bias is controlled (providing the blind remains secure), and the only factor (other than random error) determining the outcome of a properly performed RCT is allocation to the test treatment or the control. Because placebo and nocebo effects depend on expectations, they affect all blinded treatment arms equally.[16,17] The main disadvantage of large RCTs is that they are difficult to carry out, require a long time to complete, and are often very costly.

Observational studies can be useful to detect adverse effects that are too rare to be reliably apparent in RCTs,

particularly when the background incidence is very low.[18] Before 2010, when simvastatin 80 mg was shown in an RCT to cause myopathy (unexplained muscle pain or weakness with creatine kinase >10X ULN) including rhabdomyolysis much more frequently than simvastatin 20 mg,[19] this rare adverse effect had been recorded in statin RCTs, but the numbers were too small for statistically significant differences, so its detection was essentially observational. In this case, observational data were reliable because the background incidence of idiopathic rhabdomyolysis is extremely low, so that any case occurring during statin therapy without another known cause is likely to be causally related to the statin. Cerivastatin was withdrawn from the market in 2001 because observational data derived from post-marketing surveillance revealed that the risk of rhabdomyolysis was much higher than that with other statins.[20]

Because the comparisons made in observational studies are not randomized, all observational studies, whether controlled or not, are at risk of confounding.[16,18] Evaluation of the contribution of placebo or nocebo effects is rarely possible. Statistical adjustment can reduce the risk of confounding but not eliminate it. There are numerous instances of observational findings later refuted by RCTs. In cardiovascular medicine, among the best known is estrogen therapy to reduce coronary heart disease (CHD) risk in post-menopausal women, which was strongly supported by numerous epidemiologic studies[21,22] and subsequently largely refuted by RCTs.[23–25] Another example relates to supplementation with the antioxidant vitamin E, which was associated with a reduced risk of cardiovascular events in several observational studies.[26] RCTs subsequently found no suggestion of cardiovascular benefit.[26,27] These examples and many others show that observational studies should be interpreted cautiously.[16,18]

Surveys and clinical practice medical records provide uncontrolled observational data. In contrast to double-blind RCTs, which measure only the pharmacologic properties of a drug (beneficial or adverse), these methods provide information on the net effect of the pharmacologic properties of the drug combined with background symptoms and any placebo or nocebo effect, subject to confounding factors such as recall or selection bias, if any. Surveys and medical records can provide information on AEs associated with a treatment but are of limited value for evaluating the causal relationship between the event and the treatment.

Statin intolerance in the clinic

Statin intolerance is a recent concept. The first statin, lovastatin, was introduced in 1987,[20] but the first article with "statin intolerance" in the title did not appear until 2005. A Medline search returns 9 such articles before the end of 2010 and 44 from 2011 until March 2016. Before the current decade, statins (other than cerivastatin) were generally regarded as a safe and well-tolerated class of drugs with a favorable benefit risk relationship.[20,28–30]

One in 4 Americans aged older than 40 years, about 25 million people, take a statin.[31] Statin therapy is a long-term endeavor, sometimes lifelong. As with any chronic therapy intended to prevent adverse outcomes rather than treat symptoms, adherence can be problematic.[32] Compounding the problem, a significant minority of patients report AEs during treatment with statins, which may lead to discontinuation. In a retrospective cohort study in eastern Massachusetts, 18,778 (17%) of 107,835 statin-treated patients had a statin-associated AE.[33] Of these, 11,124 (10%) patients discontinued their statin, at least temporarily, and were thus intolerant. From a multinational survey of 810 statin prescribers—mainly cardiologists—Hovingh et al[34] estimated an overall average of 6% as the percentage of patients who are statin intolerant (defined as unable to tolerate the recommended statin dose). The range was wide, even within Western Europe, where the percentage was 2% in Italy, Spain, and Sweden, 4% in Germany, 6% in France, and 11% in the United Kingdom. English-speaking countries (Australia, Canada, the United Kingdom, and the United States) all reported percentages of 8% to 12%, with the 12% US value similar to the 10% reported previously by Zhang et al.[33] Cultural factors, including local language media misinformation that can create the nocebo effect, likely play a role in this distribution. The most common complaints of statin-intolerant patients are related to muscle, occurring in 64% in an international survey,[34] and over 90% in a specialist lipid clinic.[35] In the study by Zhang et al the percentage of patients who discontinued statins because of muscle symptoms is not provided; however, of 18,778 patients with AEs, of whom 11,124 discontinued their statin, 27% had myalgia.[33] Overall, perhaps about half of all statin discontinuations caused by AEs are due to muscle symptoms. Taking 10% as an overall average for the percentage of patients who are statin-intolerant and one half as the proportion in whom the intolerance is caused by muscle symptoms, roughly 5% of all statin-treated patients are intolerant due to muscle symptoms. These symptoms are rarely accompanied by significant elevations in creatine kinase (CK) or other objective changes,[35] and no pathophysiological explanation for muscle symptoms during statin therapy has been found.[36] As discussed in the following section, RCTs demonstrate that muscle and other intolerable symptoms are generally not caused by the statin.

Statin intolerance in randomized controlled trials

In contrast to the substantial AE rate under the uncontrolled open-label conditions of clinical practice, in randomized placebo-controlled trials, the incidence of muscle symptoms[37] and of discontinuations due to any AE[38] are consistently similar in the patient group allocated to the

statin and the group allocated to placebo.[37] Recently, the HOPE 3 investigators reported a small excess of patients with muscle symptoms in patients allocated to rosuvastatin 10 mg daily compared with placebo (5.8% vs 4.7%, respectively, $P = .005$), but no significant difference in the number of patients permanently discontinuing study treatment because of these symptoms (1.3% vs 1.2%, respectively).[39] Meta-analyses of placebo-controlled studies have shown no significant difference between statin and placebo in the rates of muscle symptoms.[40,41] Table 2 summarizes AEs pooled from 17 placebo-controlled trials with atorvastatin (the statin most commonly prescribed) across the 10- to 80-mg dosage range. Table 2 is reproduced from the US LIPITOR (atorvastatin) prescribing information and therefore has been reviewed and approved by the US Food and Drug Administration, which had access to the raw data. The 20-mg and 40-mg doses were used in few studies, so data with these doses are sparse and less reliable. There is no suggestion that atorvastatin increases the incidence of any of these AEs, including muscle symptoms. Indeed, there is a trend to fewer AEs with the maximal 80-mg dose compared with lower doses and placebo. This may reflect the play of chance and the fact that most studies did not include all doses.

Randomized controlled trials in statin-intolerant patients

The first study specifically in statin-intolerant patients was a proof-of-concept N-of-1 placebo-controlled study in 8 patients.[42] No difference between statin and placebo was observed. ODYSSEY ALTERNATIVE[43,44] was an RCT in 361 patients with statin intolerance due to muscle symptoms that included a rechallenge over 24 weeks with atorvastatin 20 mg, with the PCSK9 inhibitor alirocumab and ezetimibe as comparators in a parallel design. In an exploratory analysis, there was no significant difference in withdrawal due to muscle AEs, which were recorded in 16% of patients allocated to alirocumab, 20% to ezetimibe, and 22% to atorvastatin ($P > .20$); 82%, 75%, and 75% of study participants in these 3 groups, respectively, did not have an AE of any type causing discontinuation.

In the most recent and largest rechallenge RCT in statin-intolerant patients, GAUSS-3,[45,46] 491 patients with well-documented statin intolerance were randomly allocated to atorvastatin 20 mg or placebo for 10 weeks or until they experienced intolerable muscle symptoms. After a 2-week washout period, they were crossed over to the other treatment for an additional 10 weeks or until the onset of intolerable muscle symptoms. This sequence comprised Phase A of the study, the results of which were subject to an exploratory analysis without predefined methods in the statistical analysis plan.[46]

Overall, 133 patients (27.1%) experienced intolerable muscle-related symptoms while taking both treatments or had no symptoms on either treatment. Intolerable symptoms were experienced by 209 patients (42.6%) on atorvastatin but not placebo, and 130 (26.5%) on placebo but not atorvastatin. Taking the results at face value, the excess of 79 of 491 (16%) participants relative to placebo could represent patients whose muscle symptoms were due to the pharmacologic properties of atorvastatin. Symptoms in the remaining 84% can be accounted for by the nocebo effect.

Before settling on this conclusion, it should be noted that the GAUSS-3[46] results contain features that complicate interpretation. Most obviously, in the first period, the Kaplan–Meier cumulative probability curves do not start to separate until at least 50 days after randomization (period length was 70 days). Muscle symptoms causing statin intolerance can occur at any time but typically arise within the

Table 2 Adverse events as listed in the LIPITOR (atorvastatin) US prescribing information

	Any dose	10 mg	20 mg	40 mg	80 mg	Placebo
Adverse reaction*	N = 8755	N = 3908	N = 188	N = 604	N = 4055	N = 7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

Clinical adverse reactions occurring in ≥2% in patients treated with any dose of LIPITOR and at an incidence greater than placebo regardless of causality (% of patients).

*Adverse reaction > 2% in any dose greater than placebo.

first few weeks of treatment.[36] Of the 262 patients in GAUSS-3 who reported intolerable symptoms during period 1, about 70% had reported these symptoms by 50 days after randomization. This is consistent with the findings of a retrospective cohort study in a US specialist lipid clinic, in which 52% of patients who could not tolerate a statin (due to muscle symptoms in over 90%) reported symptoms within the first month of therapy.[35] Therefore, if atorvastatin could produce reproducible muscle symptoms in these statin-intolerant patients, the excess over placebo in intolerable symptoms should have been substantial in the early weeks after randomization. But the period 1 Kaplan–Meier cumulative probability curves are virtually superimposable up to 50 days.

In GAUSS-3, the muscle symptom end point is purely subjective, and intolerable muscle symptoms on at least 2 statins was an entry criterion. In this situation, maintaining the blind is crucial, as without it virtually all subjects would report muscle symptoms on atorvastatin but not placebo, but in any study, participants may self-unblind if given the opportunity.[47,48] Crossover designs are particularly vulnerable because all subjects have access to the 2 dosage forms and can compare them.[47] In GAUSS-3, participants had the ability to self-unblind either by obtaining a lipid profile outside the study or by removing the overencapsulation from a dose of study medication.[48] Some participants may have felt that a placebo-controlled rechallenge questioned the credibility of their symptoms or exposed them to the potential embarrassment of being found intolerant of placebo, either of which would have created a motive for self-unblinding. In addition, only patients who in phase A had experienced intolerable symptoms on atorvastatin but not placebo could enter phase B of the study, in which they would be randomly allocated to either the PCSK9 inhibitor evolocumab or ezetimibe for 24 weeks, followed by open-label evolocumab in phase C for 2 years. The mean baseline low-density lipoprotein cholesterol in GAUSS-3 was very high—5.5 mmol/L (212 mg/dL), one third had CHD, and all subjects believed they could not tolerate a statin. Some sites may have been able to offer another evolocumab study to participants in GAUSS-3 not proceeding to phases B and C, but participants at other sites who wanted to be sure of access to evolocumab (in phase C) would have had an additional motive to self-unblind. This triad of a crossover design, unusual motivating factors, and a purely subjective end point is not present in most RCTs (for which the overencapsulation method used in GAUSS-3 may suffice). Self-unblinding would most likely commence toward the end of the period 1, when participants who had not yet reported intolerable symptoms might well have started to have doubts about their ability to distinguish atorvastatin from placebo before the period ended. This would create bias that can explain the delayed separation of the Kaplan–Meier curves toward the end of period 1, a phenomenon that is otherwise not easily explained, and the continuing separation in period 2. Therefore, bias caused by self-unblinding explains the results of phase A in GAUSS-3 at least as plausibly as an appreciably greater frequency of intolerable muscle symptoms on a statin compared to placebo, a phenomenon never previously demonstrated. Future rechallenge studies in statin-intolerant patients should use designs that minimize incentives and opportunities to unblind and should avoid overencapsulation by contracting with a statin manufacturer to use established tablet matching techniques that minimize the risk of unblinding.[47] It is easier to make a placebo tablet matching simvastatin, which is tasteless, than atorvastatin, which is bitter.

As previously noted (under "Statin intolerance in the clinic" section), the incidence of statin intolerance due to muscle symptoms in statin-treated patients appears to be roughly 5%. If the 16% excess in the statin-intolerant patients studied in GAUSS-3 could be shown to accurately reflect intolerance with a pharmacologic basis, as opposed to self-unblinding, then the incidence of discontinuation of statin therapy due to muscle AEs caused by the statin would be about 1% in unselected patients. A difference between statin and placebo in discontinuations due to AEs has not been observed in earlier clinical trials[38] or the recent HOPE 3 study,[39] as previously noted. A new UK National Institute for Health Research N-of-1 study in 200 patients[49] may shed more light on statin intolerance under double-blind conditions.

Taken together, GAUSS 3, ODYSSEY ALTERNATIVE, and the small N-of-1 study of Joy et al[42] provide evidence that intolerance usually depends on patients knowing they are taking a statin.[37,50,51] Added to the massive amount of information provided by cardiovascular outcome and other statin RCTs, these rechallenge studies provide further evidence that the predominant cause of statin intolerance is the nocebo effect, which is totally dependent on patient awareness of a treatment and its potential adverse effects. Under double-blind conditions, patients do not know what they are taking (as long as the blind is secure), so expectations are the same regardless of treatment allocation; the nocebo effect can increase the frequency of an AE in the study population[2,10] but cannot cause differences between the treatment and control groups.

The nocebo effect and statin intolerance in the clinic

Muscle symptoms are subjective and common in untreated middle-aged or elderly patients. In the Heart Protection Study,[52] which compared simvastatin 40 mg and placebo in over 20,000 patients during a follow-up period of 5 years, participants were directly questioned at every visit about muscle symptoms (in addition to the standard general query for AEs typically used in clinical trials). At each visit, about 6% of patients in both groups reported muscle symptoms, and 32.9% and 33.2% reported these symptoms at least once during the trial in the simvastatin and placebo groups, respectively. The Heart Protection

Study illustrates the high prevalence of muscle symptoms in middle-aged to elderly people who are taking a placebo, are queried at regular intervals about muscle symptoms, and have been informed that a statin can cause muscle injury.

The risk of myopathy and rhabdomyolysis is prominent in statin patient information leaflets, and clinicians warn patients to report muscle symptoms; furthermore, Internet searches bring up mainly disturbing misinformation about statin adverse effects. This is the fate of many advances in medicine, such as vaccination programs and fluoridation of water.[5] Aggravating this problem, there is an inbuilt bias in news outlets and social media; "Statins have very few adverse effects" is not newsworthy, but "Cholesterol drugs taken by millions are dangerous" often is. These influences appear to have set up a powerful belief system. Therefore, some patients will expect muscle and other symptoms[6,9] and may associate background symptoms with their statin use—the nocebo effect. Furthermore, normal healthy people can experience pain in the absence of any painful stimulus, as previously noted.

In recent years, various objections have been raised to the reassuring adverse effect profile demonstrated in statin RCTs, which include over 170,000 patients followed for several years.[30] Some have argued that the statin trials do not reflect clinical practice and therefore fail to reliably assess adverse effects.[53–56] For example, the NLA Task Force on Statin Safety has written[55] "One of the major limitations of using randomized controlled trials (RCTs) for the evaluation of safety is that the populations studied are very restricted in their study entry characteristics and often patients with multiple comorbidities and previous statin intolerance are excluded. Thus there is limited generalizability of patients in RCTs compared with the general clinical population, which tends to have more comorbidity and frailty."

We disagree. We have previously challenged the argument that any exclusion of patients with statin intolerance casts doubt on the tolerability data in RCTs.[38] Also, while it is true that individual statin RCTs, in common with RCTs in general, had inclusion and exclusion criteria, over 170,000 patients[30] have participated in the statin RCTs and among them are large numbers with multiple comorbidities. Table 3 summarizes discontinuation rates due to any AE in 8 large cardiovascular outcome trials with statins comprising over 45,000 participants, many female or elderly, with complex medical histories including one or more of CHD, stroke, diabetes, chronic kidney disease, and heart failure. Taking the participants in the cardiovascular outcome RCTs with statins as a whole, the entry characteristics were very broad. Consequently, there is no good reason not to generalize these RCT results to clinical practice.

In any double-blind RCT, the difference between the active and placebo treatments in discontinuation rates due to any AE is a good measure of tolerability. The discontinuation rates in the broad array of patient types summarized in Table 3 were consistently similar in participants allocated to statin and placebo, and withdrawal due to any AE in the 8 studies pooled was 8.0% (1814/22,714) and 8.1% (1843/22,715) in patients allocated to statin and placebo, respectively. Thus, there was no intolerance in these studies, not because of the characteristics of the participants, whose comorbidities were at least that of patients in most clinical practices, but because statins are well tolerated when treatment is blinded.

The authors[53–56] dismissing statin RCTs appear not to have considered the possibility that the nocebo effect could lead to high rates of subjective AEs attributed to statins in uncontrolled observational studies, in contrast to RCTs, which consistently show little difference between statin and placebo. This is not surprising because there are few reports of the nocebo effect in cardiovascular medicine. A Medline search on March 19, 2016 using the terms "nocebo" and "cardiovascular" in any field revealed only 6 publications. Substituting "pain" for "cardiovascular" returned 151 publications. As far as we are aware, the first explicit mention of the nocebo effect in the context of statins was in a review of AEs in statin RCTs by Finegold et al.[57]

Although most cases of statin intolerance can be adequately explained by the nocebo effect, it remains a clinical problem. Virtually all patients and some clinicians are convinced that the intolerance has a pharmacologic basis. In a typical scenario, a clinician prescribes a statin, the patient returns complaining of muscle symptoms with no obvious cause, the clinician or patient stops the statin, and the symptoms resolve. This sequence of events convinces the patient that the symptoms are caused by the statin, especially if symptoms recur during rechallenge. But this scenario is readily explained by the nocebo effect, and there is no reason for the clinician to invoke drug toxicity that somehow fails to appear in RCTs.[37,38] However, this does not make the symptoms any less relevant.

Although the nocebo effect reflects normal human neuropsychology, very few patients will accept that their symptoms are psychogenic; any such suggestion is stigmatizing for many people and should generally be avoided. This is seen most clearly when the nocebo phenomenon is manifested in a group setting as mass psychogenic illness; those affected often vigorously reject any psychological explanation.[15] On the other hand, knowing that purely subjective symptoms during statin therapy are unlikely to be caused by the statin helps the clinician to preempt statin intolerance and to deal with it if it does occur, as discussed in the following section.

Devoting effort to restarting treatment with a statin is important because the only class of lipid-lowering agent capable of matching the efficacy of high-intensity statin therapy is the PCSK9 inhibitors, but as of April 2016, these lack cardiovascular outcome and long-term safety data. In addition, atorvastatin 80 mg, the maximum dose of the most commonly prescribed generic statin and capable of producing a mean reduction in low-density lipoprotein

Table 3 Discontinuation due to any adverse event (AE) in randomized double-blind placebo-controlled cardiovascular outcome trials of statins in patients with advanced disease

Trial*	N	Drug, dose (mg)	Duration (y)†	Patient type	Age (y)†	% Female	Discontinuation due to AEs (%)	
							Statin	Placebo
4S	4444	S 20-40	5.4	CHD	59	19	5.7	5.7
HPS	20,536	S 40	4.9	Mixed‡	64	25	4.8	5.1
ALERT	2102	F 40-80	5.1	Renal transplant	50	34	14.8	16.3
4D	1255	A 20	4.0	Diabetes on dialysis	66	46	11.8	8.2
SPARCL	4731	A 80	4.9	Stroke/TIA§	63	40	17.5	14.5
CORONA	5011	R 10	2.7	Heart failure	73	24	9.6	12.1
GISSI-HF	4574	R 10	3.9	Heart failure	68	23	4.6	4.0
AURORA	2776	R 10	3.8	Hemodialysis	64	38	14.9¶	16.8¶
Total	**45,429**						**8.0**	**8.1**

A, atorvastatin; CHD, coronary heart disease; F, fluvastatin; HPS, Heart Protection Study; R, rosuvastatin; S, simvastatin; TIA, transient ischemic attack.

*Trials are listed in order of publication date of the main results.

†Mean or median.

‡65% CHD, 16% cerebrovascular disease, and 29% diabetes.

§69% stroke and 31% TIA.

¶Included end point events.

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cholesterol of about 55%, is obtainable for less than $100 per year of treatment in the United States. The US list price of both marketed PCSK9 inhibitors, alirocumab and evolocumab, was over $14,000 per year of treatment at launch in 2015.

Minimizing the nocebo effect during statin therapy

Prevention of statin intolerance is better than cure. The prescribing information for all statins advises warning patients about the risk of myopathy (unexplained muscle pain or weakness with CK >10X ULN), including rhabdomyolysis, and to promptly report unexplained muscle symptoms. Because warning patients about a subjective AE can substantially increase the risk that it will occur,[2,4,6,10,58,59] the frequency of subjective AEs can be strongly influenced by clinician–patient communication.[3,4,9,59] The goal of the nocebo-conscious clinician is to avoid creating negative expectations and to counter any that already exist. Therefore, it is important to emphasize to the patient that myopathy including rhabdomyolysis is rare, occurring in less than 1 in 1000 patients, and to put this very small risk in the context of the proven substantial benefits of statins. Patients starting a statin can be reminded that muscle aches and pains are very common background symptoms in middle-aged and older people. They can also be informed that in the event of any new muscle symptoms with no reason such as vigorous exercise, a simple blood test can determine whether the statin is the likely cause (if CK is >5X ULN) or far more commonly not (if CK is <3X ULN). Clinicians can also advise patients that statins are safe medicines in clinical use for nearly 30 years, and that statins as a common cause of muscle and other symptoms is a recent myth perpetuated on the Internet and elsewhere.

The nocebo minimization approach summarized here is very different from the advice of the National Lipid Association Statin Intolerance Panel, whose recommendations to patients include "About 1 in 10 people who try taking a statin will report some kind of intolerance, most commonly muscle aches in the legs, trunk, or shoulders and upper arms….".[56] This is more explicitly negative than the patient information examples provided at the beginning of this article,[2,10] which produced large nocebo effects. Patients need to know about proven serious adverse effects, as described in the *Patient Counseling* or equivalent section of the prescribing information; what other patients report is not useful.

In patients stopping their statin because of subjective AEs (such as muscle symptoms without a significant elevation of CK), rechallenge is usually successful,[33] although not necessarily with the same statin or at the same dose. Patient expectations are critical.[6] Communicating an optimistic outlook[3,9] can reverse or reduce the effect of previous negative expectations.[5] Patients need to know that intolerance is a soluble problem that responds to therapy adjustments. It is also useful to remind the patient of the proven cardiovascular benefits of statins and to explore any ambivalence about the need to take a statin. Knowing the value of a treatment reduces the nocebo effect.[9] There is some evidence[60] that the nocebo effect is attenuated if a choice of treatments is available, so it may be worth asking a patient agreeing to rechallenge, which option he or she prefers—switching to a different statin,

lowering the dose of the existing statin, or just giving the statin another try at the same dose.

In summary, the nocebo effect is a well-established phenomenon that is under-appreciated in cardiovascular medicine. It is the best explanation to account for the high rate of muscle and other symptoms attributed to statins in observational studies and clinical practice, in contrast to RCTs where muscle symptoms, and rates of discontinuation due to any AE, are consistently similar in the statin and placebo groups. Statin-intolerant patients usually tolerate statins under double-blind conditions, indicating that the intolerance has little if any pharmacologic basis. Known techniques for minimizing the nocebo effect can be applied to the prevention and management of statin intolerance.

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Fright factors about wind turbines and health in Ontario newspapers before and after the Green Energy Act

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In this article, we analyse coverage of the health effects of wind turbines in Ontario newspapers relative to the Green Energy Act using published risk communication fright factors. Our aim was to provide insights into the health risk information presented in newspapers serving Ontario communities where wind turbines are located. We selected five geographically discontinuous wind energy installations in Ontario and their surrounding communities based on 2006 Canadian Census data. We identified the newspapers serving each community and searched for articles from May 2007 to April 2011 on wind turbine technology and human health, identifying a total of 421 articles from 13 community and 4 national/provincial newspapers. We found that most newspaper articles included the fright factor of 'dread' (94%) and well over half (58%) included the fright factor of 'poorly understood by science'. 'Involuntary exposure' and 'inequitable distribution' were fright factors occurring in somewhat fewer than half of the newspaper articles (45% and 42%, respectively). Of note was that four of the fright factors – 'dread', 'poorly understood by science', 'inequitable distribution' and 'inescapable exposure' – occurred more frequently in community newspaper articles than in national/provincial ones ($p < 0.001$). Although the total number of occurrences of each fright factor increased following the Green Energy Act, only 'dread' ($p < 0.05$) and 'poorly understood by science' ($p < 0.01$) increased significantly. We conclude that Ontario newspapers contain fright factors in articles about wind turbines and health that may produce fear, concern and anxiety for readers.

Keywords: risk communication; public health; mass media; wind turbines

Introduction

The Government of Ontario, Canada has established goals for reducing greenhouse gas emissions through the Climate Change Action Plan (MOE 2010). Part of this plan involves phasing out coal-fired power plants and supporting renewable energy technologies, such as wind, solar, hydro, biomass and biogas. The objective of this programme is to double the amount of electricity from renewable sources by 2025, positioning Ontario as one of the top energy producers in North America. By implementing the Green Energy Act in 2009, the province streamlined the approval process for many renewable energy technologies, notably wind energy installations. As a result, the number of wind turbines in Ontario increased from 10 in 2003 to almost 700 currently in place or planned (MOE 2010). The rapid and substantial increase in the number of wind turbines has caused concerns among individuals and community organisations, in part due to potential health effects.

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The health impact of wind energy installations has become a widely debated political issue in Canada (Knopper and Ollson 2011, Watson *et al.* 2012) and elsewhere (Pedersen 2011). In 2010, the Ontario Chief Medical Officer of Health concluded that the current scientific literature does not demonstrate a causal link between exposure and direct health effects (CMOH 2010). However, there are anecdotal reports which indicate a possible relationship between exposure and health effects such as dizziness, headaches and sleep disturbance (Pierpont 2009, Knopper and Ollson 2011). People living near wind turbines have reported prolonged annoyance and psychosocial stress, which may physically manifest as adverse health effects (Pedersen and Waye 2004). Media triggers, including conflicting opinions, high exposure and human interest through identification of victims, have made the potential public health risk of wind turbines a newsworthy story (Bennett 2010).

The public often gathers information relating to health consequences of environmental exposures from news reports, rather than more science-based sources such as health care practitioners (Lundgren and McMakin 2009, Riesch and Spiegelhalter 2011). However, many newspaper editors consider stories for publication in terms of economic, political or cultural relevance rather providing information about public health (Hillier 2006, McCarthy *et al.* 2008). Public perceptions of health risk can be influenced by the way the media frames and covers a risk story, especially how and what elements are reported (Rowe *et al.* 2000). Several factors including message content, tone of delivery, expert sources and information accuracy influence whether the public attends to, understands and acts on risk information (McCarthy *et al*. 2008). A diagnostic checklist of fright factors has helped to explain why some environmental health risks are more likely to trigger alarm, anxiety or outrage than others, independently of scientific estimates of their seriousness (Bennett 1999). Media stories that contain a large number of these fright factors provoke a strong public reaction (Bennett 2010). These fright factors have been shown in newspaper coverage of human papillomavirus (HPV) vaccination, avian flu, biosolids and genetically modified crops (Burke 2004, Goodman and Goodman 2006, Abdelmutti and Hoffman-Goetz 2009, Fung *et al.* 2011).

In the present study, we analysed newspaper coverage of the health effects of wind turbines in Ontario newspapers using a published typology of fright factors (Bennett 1999). Our aim was to provide insights into the public newspaper discourse about health risks from exposure to wind turbines using select Ontario communities. We chose Ontario, Canada as a case study because of recent major policy legislation on alternative energies, including wind turbines, known as the Green Energy Act. We did not evaluate the biological evidence for or against health effects of wind turbines but rather the occurrence of fright factors linked to possible health effects of wind installations.

Methods

We identified 37 wind turbine installations prior to September 2011 in Ontario using the CANWEA database (CANWEA 2011). From this list, three large and two small wind energy installations, which began operation between 2006 and 2009, were selected: large installations were Melanchton Phase II, Ontario Wind Power Farm and Prince Wind Farm with 88, 110 and 126 turbines, respectively; small installations were Dunnville Wind Turbine and Proof Line Wind Turbine with one and four turbines, respectively. We selected these turbines because they were geographically discrete, represented a diverse set of communities in Ontario and reflected differing magnitudes of installations throughout the province. Maps identifying the location of each of these wind energy

developments can be found on the CANWEA database (http://www.canwea.ca/farms/index_e.php). We generated a list of communities within a 50 km radius of each installation using 2006 Canadian Census subdivisions maps. In addition, large urban centres (Toronto and Hamilton), which were located just beyond the 50 km radius, were included because of their potentially high influence on the public agenda about wind turbines and health. The approximate population of census subdivisions for Melancthon Phase II was 2,600,000 (including Toronto), for Ontario Wind Power Farm was 85,000, for Prince Wind Farm was 95,000, for Dunnville Wind Turbine was 750,000 (including Hamilton) and for Proof Line Wind Farm was 460,000. We identified the newspapers distributed in each census subdivision through the Canadian Newspaper Association database (CCNA 2011). Seventeen newspapers were included, with four considered national/provincial and thirteen considered community based on geographic reach, circulation size and frequency of publication (Table 1). The four national/provincial newspapers included the *Globe and Mail*, *National Post*, *Toronto Star* and *Hamilton Spectator*. The *Globe and Mail* and *National Post* are generally considered to be national newspaper sources because several editions are published across Canada. However, we used only 'Ontario' editions for this study. The *Toronto Star* and *Hamilton Spectator* are considered provincial newspapers, with the majority of their readership based in Toronto and Hamilton, respectively, and the remainder spread throughout neighbouring major cities.

Newspapers were searched using the LexisNexis database and individual newspaper websites from May 2007 to April 2011 (2 years before to approximately 2 years after the introduction of the Green Energy Act in May 2009). The following search terms alone and in combination were used to identify articles: (wind turbine* or wind farm* or wind energy or wind power or windmill* or green energy or renewable energy or turbine* or alternative power) and (health* or noise or vibration* or stress* or sleep* or flicker* or mood* or illness* or mental* or joint pain). Articles were excluded if they were duplicates, outside of date range, did not contain the terms 'health' and 'wind turbine' or 'wind farm' or contained 'health' not related to humans (such as economic health).

We undertook a directed content analysis to develop the coding instrument based on the fright factors that affect the public's perception of risk (Hsieh and Shannon 2005). This approach is guided by a structured process in which existing theory is used to identify key concepts or variables as coding categories. We developed operational definitions for each of the fright factors used in this study, and examples of their application to newspaper articles on wind turbines and health can be found in Table 2. We also coded articles by newspaper name, newspaper type (national/provincial, local), article date, article type (article, letter to editor, editorial/column), article main focus (human health, other) and number of references to health. We classified the main focus of an article as 'human health' if the article made a reference to health three or more times and as 'other' if human health was mentioned fewer than three times in the article. The 'other' category included topics such as the economy, politics and the environment.

One author coded all of the articles. However, to ensure reliability of data extraction, a randomly selected subset of 100 articles was coded by two independent readers, and inter-rater reliability was calculated. Cohen's kappa ranged from 0.813 to 1.00, with an average of 0.920, indicating excellent agreement for each variable. The readers/coders resolved discrepancies through discussions which informed the coding process.

We generated descriptive statistics (frequencies, means and percentages) on the fright factors mentioned in the articles (SPSS v20, SPSS Inc., Chicago, IL) and analysed differences in the frequency of fright factors across newspaper type and relative to the Green Energy Act using chi-square. We used Student's *t*-test to analyse the number of

Table 1. Summary of newspapers included in study.

Newspaper name	Category	Geographical distribution (census subdivisions)	Circulation size (Canadian Newspaper Association annual circulation for 2010)
Globe and Mail	National/ provincial	All	317,781 (daily)
Toronto Star	National/ provincial	All	292,003 (daily)
National Post	National/ provincial	All	158,250 (daily)
Hamilton Spectator	National/ provincial	All	91,716 (daily)
Orangeville Banner	Community	Melancthon, Shelburne, Southgate, Orangeville, Grey Highlands, Amaranth, Mulmur, Caledon	42,508 (twice weekly)
Orangeville Citizen	Community	Melancthon, Shelburne, Southgate, Orangeville, Grey Highlands, Amaranth, Mulmur, Caledon	14,412 (weekly)
Hanover Post	Community	Hanover, Brockton	14,868 (weekly)
Kincardine News	Community	Kincardine	2,838 (weekly)
Lucknow Sentinel	Community	Huron-Kinloss	1,412 (weekly)
The Owen Sound Sun Times	Community	Owen Sound	12,505 (daily)
Shoreline Beacon	Community	Arran-Elderslie, Saugeen Shores	3,765 (weekly)
Lakeshore Advance	Community	Lambton Shores, South Huron, North Middlesex	1,254 (weekly)
Sault Star	Community	Prince, Sault Ste. Marie, Rankin 15D, Garden River 14, Elliot Lake, Algoma	13,851 (daily)
Londoner	Community	London	145,200 (weekly)
Sarnia Observer	Community	Sarnia, Plympton-Wyoming	13,029 (daily)
Sarnia and Lambton This Week	Community	Sarnia, Plympton-Wyoming	39,296 (weekly)
St. Catharines Standard	Community	St. Catharines	19,388 (daily)

Table 2. Diagnostic fright factors and application to wind turbine news media.

Fright factors (Bennett 1999, 2010)	Examples of application to wind turbine media coverage
Involuntary exposure	Location of wind turbine not under influence of community or nearby residents
Inequitably distributed	Wind turbines present in certain communities and absent in others
Inescapable by taking personal precautions	Unable to avoid vibration/noise/flicker unless physically distant from wind turbine
Cause hidden or irreversible damage	Some effects of low frequency vibration and noise (such as infrasound) cannot be seen or heard
Pose particular danger to small children or pregnant women	Potential effect of wind turbines on learning and behaviour of children, long-term fertility unknown
Arousing dread due to death, illness or injury	Threat of long-term illness unknown. Chronic migraines may increase risk of other health problems
Damage to identifiable victims	Specific cases of residents leaving homes within close proximity to turbine
Poorly understood by science	Lack of studies on health effects relating to wind turbine exposure
Subject to contradictory statements from responsible sources	Municipal governments/councils conflict with provincial governments (such as moratoriums)
Arises from unfamiliar or novel source	Not applicable
Result from man-made sources	Not applicable

mentions of health in each article by newspaper type and accepted. A p-value of <0.05 indicated that differences were not the product of chance.

We used a cluster analysis (SAS v9.2, SAS Institute Inc., Cary, NC) to identify distinct community subgroups based on demographic variables from the 2006 Canadian Census; these variables were population density, population with post-secondary education, house value and median income, which broadly reflected 'urban' and 'rural' community characteristics. The cluster technique groups communities that share similar socioeconomic and demographic characteristics. Classifying communities into various subgroups allowed us to determine whether the content of newspaper articles on wind turbines and health varied based on characteristics of the readership.

Findings

Coverage by newspaper and region

There were 421 newspaper articles retrieved from 17 newspapers. Of these, 150 articles were from 4 national/provincial newspapers and 271 articles were from 13 community newspapers. The number of newspaper articles about wind turbines and health published from each newspaper type increased substantially over time. In the national/provincial newspapers for full years of coverage, the number of articles were 13 in 2008, 52 in 2009 and 40 in 2010 ($X^2 = 22.8$, df = 2, $p < 0.001$). Also of note is that for the 4 months of data collection in 2011 (January–April), there were 34 articles on wind turbines and health appearing in the national/provincial newspapers. In the local newspapers, the number of articles on wind turbines and health also increased: 15 in 2008, 90 in 2009 and 107 in 2010 ($X^2 = 67.83$, df = 2, $p < 0.001$). For the 4-month period of January–April 2011, there were 49 articles on wind turbines and health in the local newspapers. The increase in newspaper articles over time was greater in community newspapers compared to national/provincial newspapers ($X^2 = 9.63$, df = 4, $p < 0.05$).

There were differences in news coverage based on wind energy development size. The small wind energy developments included in this study, Dunnville and Proof Line, accounted for 15% ($n = 42$) of the community newspaper coverage collected on wind turbines and health. The large wind energy developments, in contrast, contributed 85% ($n = 229$) of the community newspaper coverage on wind turbines and health.

Prevalence of fright factors

The most common fright factors linking wind turbine exposure to human health were 'dread', 'poorly understood by science', 'involuntary exposure' and 'inequitable distribution' occurring in 94% ($n = 394$), 58% ($n = 242$), 45% ($n = 188$) and 42% ($n = 177$) of articles, respectively. In the following extracts, we present illustrative examples of newspaper coverage highlighting the four most prominent fright factors.

Dread

We identified the fright factor 'dread' as a negative, loaded or fear-evoking description of health-related signs, symptoms or adverse effects of wind turbine exposure.

> Extract from *Lucknow Sentinel* (community newspaper), May 2009: In a recent interview…all made it clear that the [family's] environments had two changes occur simultaneously in November of 2007 [when the Ripley industrial wind turbine project was installed]. First there

was a change in the hydro configuration to their homes enabling electrical pollution to enter via a cross contamination from the wind turbine high voltage collection lines. The second change was the repetitive sound, both low frequency and audible from the blades of the industrial turbines that began rotating close to and above the height of their homes. Since these two changes, all began experiencing sleep deprivation, humming in the head and ears, stress, anxiety, heart palpitations, increased blood pressure, vibrations in the chest, earaches, headaches, an increased sensitivity to noise and sore eyes. It gets worse when the winds increase.

Extract from *Hanover Post* (community newspaper), Jan 2011: Stelling's comments, and a two-page letter he read to council outlining results of studies about adverse health issues resulting from the low frequency noise emitted by the turbines and suggestions that turbines have setbacks from 1 to 4.3 km from any residences, drew loud applause from those in attendance.

Poorly understood by science

We identified the fright factor 'poorly understood by science' as the need for a health study, the unknown effects or outcomes on health or the implementation of a moratorium until health effects are better studied.

Extract from *Sarnia & Lambton County this Week* (community newspaper), Oct 2008: The residents, 180 of [whom] signed a petition presented to council, are hoping the municipality will do a health study before making a decision about the project.

Extract from *Lucknow Sentinel* (community newspaper), Feb 2011: 'We haven't had the opportunity to do a lot of scientific research around the large-scale, very large-sized turbines that are generally the type most projects are installing,' Gillespie said.

Involuntary exposure

We operationalised the fright factor 'involuntary exposure' as a stated or implied statement that wind turbine placement was beyond the control of an individual or municipality, or that the Green Energy Act removed municipal rights over land development:

Extract from *Lakeshore Advance* (community newspaper), March 2009: They are just being whipped into place without due diligence, and now our Premier has decided to take out the role of the municipalities. Instead of working with them to solve issues, he is rolling over them.

Extract from *Kincardine News* (community newspaper), Aug 2010: The lakeshore community of Point Clark does not want to see this project move forward, but instead of the company demonstrating why it should be allowed to build, or recommending where the best place would be, the decisions have already been made and the public's opinion isn't a factor in determining where the turbines are erected, at all.

Inequitable distribution

We judged that the fright factor 'inequitable distribution' was present if the newspaper article mentioned (directly or indirectly) the risk of health effects from wind turbines increased with proximity or was higher in one group compared to another.

Extract from *Kincardine News* (community newspaper), Aug 2010: In the Ripley area, Lynn said 10%, or about 35 people living within the wind development area, have said they suffer as a result of proximity to the turbines.

Extract from *Lakeshore Advance* (community newspaper), Sept 2010: During a question-and-answer period, McMurtry agreed with one participant's assertion the projects are going

> up in rural Ontario, because urban residents are supporting the Green Energy Act without understanding its long-term impacts. 'Make no mistake about it. This is a targeting of rural Ontario.'

The other five fright factors occurred less frequently in the newspaper articles: 'identifiable victims' in 19% of articles (n = 80), 'inescapable' in 15% of articles (n = 64), 'contradictory statements from reliable sources' in 9% of articles (n = 39), 'damage to future generations' in 6% of articles (n = 23) and 'hidden or irreversible damage' in 3% of articles (n = 12). In the following extracts, we present illustrative examples newspaper coverage highlighting these less common fright factors linking wind turbines and human health.

Identifiable victims

We identified the fright factor 'identifiable victims' as occurring in newspaper articles if there was a reference to a named individual who was affected by wind turbines.

> Extract from *Kincardine News* (community newspaper), April 2009: 'I consider myself a green person, but there's controversy on how green (wind turbines) actually are,' said Norma Schmidt of Bruce Twp. who lives west of Underwood and came to protest because of the perceived health impacts it has had on her and her family. With wind turbines erected around her property, she and her husband Ron have experienced sleeping problems and headaches since the commissioning of the project.
>
> Extract from *the Owen Sound Sun Times* (community newspaper), July 2009: 'We can't live in our house anymore. We bought a house and moved to Kincardine. My son and daughter-in-law and two-year-old who live on a different farm... the wind company is paying for them to stay in Kincardine,' said Glen Wild, one of a half-dozen speakers at a public information session on the dangers of living too close to wind turbines.

Inescapable

We identified the fright factor 'inescapable' if a newspaper article stated that an individual or family was unable to modify their exposure to the health risk or were forced to leave their home.

> Extract from the *Londoner* (community newspaper), Dec 2010: As more wind farms are built, more stories are emerging of farmers having to leave their homes because of health issues attributed to wind turbines.
>
> Extract from *Toronto Star* (national/provincial newspaper), Jan 2011: Too many Ontario families have already been made ill and forced to flee from their homes as a result of hastily developed wind energy projects with inadequate setbacks.

Contradictory statements

We identified the fright factor 'contradictory statements' as occurring in newspaper articles which emphasised that experts (such as medical health officers and government officials) were on opposite sides of the issue.

> Extract from *Globe and Mail* (national/provincial newspaper), Jan 2011: To support his client's case in court, Mr. Gillespie will present evidence from three physicians who say turbine noise and vibration can cause high stress, sleep deprivation and headaches among people who live near them. The government argues, in a document filed with the court, that

the doctors' conclusions are suspect, and that it reviewed all the literature available on the issue, and held public consultations before creating the guidelines.

Extract from *Toronto Star* (national/provincial newspaper), Jan 2011: Their case was bolstered last May after the provincial medical officer of health, Dr. Arlene King, issued a report saying no scientific evidence exists to show that wind turbines harm human health. (Dr.) McMurtry countered that this is because no one has ever conducted a proper study - which is why he wants one.

Damage to future generations

Newspaper articles that contained the fright factor 'damage to future generations' had statements which identified the health of pregnant women, infants, children or teenagers as being adversely influenced by wind turbine exposure.

Extract from *Lucknow Sentinel* (community newspaper), May 2009: 'We have taken three-year-old Keiara to the emergency room 10 times with problems and Dr. McMurtry said my daughter shouldn't be there (at their home in the Ripley Wind Project). Melissa as well because she is pregnant,' said Kent Wylds.

Extract from *Toronto Star* (national/provincial newspaper), April 2010: They claim the turbines cause low-frequency noise and have sickened 106 Ontario residents, causing a variety of health ailments ranging from hypertension to sleeplessness and nosebleeds in children.

Hidden or irreversible damage

We recognised the fright factor 'hidden or irreversible damage' as being present in newspaper articles which stated that individuals did not know the source of their symptoms or that exposure to wind turbines may result in lasting health effects.

Extract from *Lucknow Sentinel* (community newspaper), June 2009: Krogh compared the situation to discovering the harmful effects of tobacco adding that there is no long-term investigation into the effects of wind turbines in 10 to 20 years.

Extract from *Kincardine News* (community newspaper), Feb 2011: Remember thalidomide and second-hand smoke, both perceived as acceptable at one time until science proved otherwise. Unfortunately this approach is being taken again with the blind acceptance of wind farms in close proximity to humans.

The fright factors of 'dread', 'poorly understood by science', 'inequitable distribution' and 'inescapable' occurred more frequently in community newspapers than in national/provincial ones ($X^2 = 12.11$, df = 1, $p < 0.001$; $X^2 = 36.19$, df = 1, $p < 0.001$; $X^2 = 15.45$, df = 1, $p < 0.001$; $X^2 = 17.61$, df = 1, $p < 0.001$, respectively). National/provincial and community differences in the occurrence of the four most common fright factors are shown in Figure 1. The remaining, less prevalent fright factors are shown in Figure 2. Article focus (human health vs. other) differed between newspapers, with community newspapers focused more on human health than national/provincial newspapers ($X^2 = 36.193$, df = 1, $p < 0.001$). There was an average of 5.01 ± 3.9 (SD) mentions of health per article from community newspapers and 2.53 ± 2.4 (SD) mentions per article from national/provincial newspapers ($t = 8.0$, df = 416, $p < 0.001$).

Influence of the Green Energy Act

The number of occurrences of each fright factor increased after the Green Energy Act, with dread and poorly understood by science increasing significantly ($X^2 = 4.76$, df = 1,

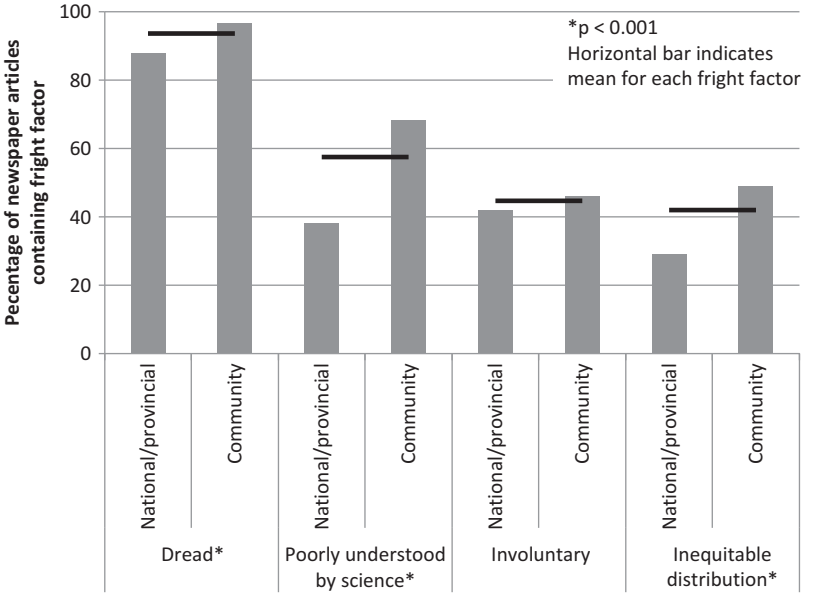

Figure 1. Presence of most commonly mentioned fright factors in Ontario newspaper articles.

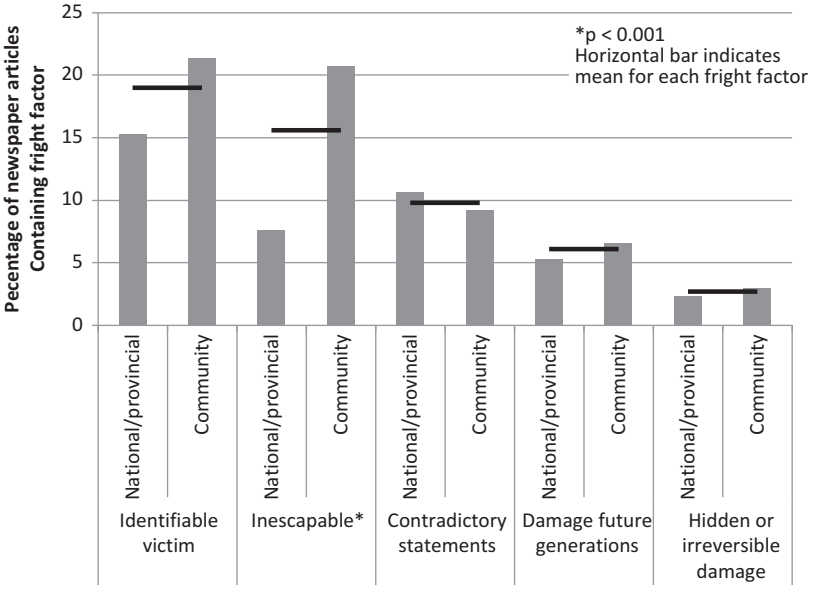

Figure 2. Presence of less commonly mentioned fright factors in Ontario newspapers articles.

$p < 0.05$ and $X^2 = 7.66$, df = 1, $p < 0.01$, respectively). The fright factor identifiable victims occurred less often after the Green Energy Act ($X^2 = 25.35$, df = 1, $p < 0.001$) (Table 3). Both community and national/provincial newspapers were more likely to focus on human health following compared to before the Green Energy Act ($X^2 = 19.36$, df = 1, $p < 0.001$).

Table 3. Presence of fright factors before vs. after the Green Energy Act in Ontario.

	Before Green Energy Act (total number of articles = 99)		Following Green Energy Act (Total number of articles = 322)			
Fright factor	Number of articles with fright factor	Percentage of articles with fright factor	Number of articles with fright factor	Percentage of articles with fright factor	Chi-square	*p*-value
Arousing dread	88	88.9	306	95.0	4.759	0.029
Poorly understood by science	45	45.5	197	61.2	7.662	0.006
Involuntary exposure	46	46.5	142	44.1	0.171	0.679
Inequitable distribution	38	38.4	139	43.2	0.711	0.399
Identifiable victim	36	36.4	44	13.7	25.348	0.001
Inescapable	14	14.1	50	15.5	0.113	0.737
Contradictory statements	8	8.1	31	9.6	0.215	0.643
Damage to future generations	8	8.1	15	4.7	1.717	0.190
Hidden or irreversible damage	2	2.0	10	3.1	0.322	0.570

Cluster analysis

To explore whether community characteristics influenced the occurrence of fright factors in newspaper articles about wind turbines and health, we conducted a cluster analysis based on demographic census characteristics. Three subgroups were identified: Cluster 1 characteristics included communities with higher population density (>400 persons/km^2), education levels above the provincial mean, average house values between $300,000 and $400,000 and a median income of $61,000; examples of communities in Cluster 1 included Toronto, Hamilton, Sarnia, Orangeville and Kincardine. Cluster 2 included communities with a lower population density (<400 persons/km^2), education levels below the provincial average, average house values between $100,000 and $200,000 and a median income of $30,000. Examples of communities in Cluster 2 included Hanover, Owen Sound, Arran-Elderslie, Elliot Lake and Algoma. Together, these two clusters accounted for almost 60% of the variation in demographic characteristics of census subdivisions. A third cluster capturing four communities did not have a distinct census profile, explained only 20% of the variation in demographic characteristics and was excluded from further analysis. Within the two clusters, we identified the community newspaper with the largest number of articles and compared these for type and prevalence of fright factors. The representative community newspaper for Cluster 1 was the *Kincardine News* (n = 53), and the representative community newspaper for Cluster 2 was *the Owen Sound Sun Times* (n = 72).

None of the fright factors occurred significantly more often in the representative community newspapers as a function of the community cluster characteristics. However, 'involuntary exposure' tended to be mentioned more often in articles from Cluster 2 (n = 34) compared with Cluster 1 (n = 16) (X^2 = 3.69, df = 1, p = 0.055). With respect to timing relative to the Green Energy Act, newspaper articles from Cluster 2 had a significantly greater number of occurrences of the fright factor 'involuntary exposure' after vs. before the Green Energy Act (n = 30 vs. n = 4) (X^2 = 5.26, df = 1, p < 0.05). In the following extracts, we present illustrative examples newspaper coverage highlighting 'involuntary exposure' in Cluster 2 both before and after the Green Energy Act.

Before the Green Energy Act

> Extract from *the Owen Sound Sun Times*, March 2009: The primary issues of concern for Grey Highlands are that the act will remove local planning control over renewable energy projects as well as concerns over health issues and loss of property values.
>
> Extract from *the Owen Sound Sun Times*, April 2009: Protesters questioned how much wind generation is actually reducing greenhouse gas emissions and raised concerns about the visual impact on the landscape and the loss of local control over projects if the provincial Green Energy Act is made law.

After the Green Energy Act

> Extract from *the Owen Sound Sun Times*, Oct 2009: Municipalities with projects in their areas know, firsthand, how much trouble they are. When they tried to stop existing projects from expanding, they were taken to the Ontario Municipal Board where they were told they had to allow turbines because the provincial government said so.
>
> Extract from *the Owen Sound Sun Times*, March 2011: The minister addressed concerns raised by critics of the government's renewable energy policies contained in the Green Energy and Green Economy Act which takes away planning approval powers by local and county councils and replaces it with a poorly-defined consultation process.

Discussion

A content analysis of newspaper media is a convenient, low-cost and non-intrusive technique used to build understanding of how the public interprets health risk when risk perception surveys are not available (Driedger 2007, Mistry and Driedger 2012). In the study on which this article is based, we used systematic counting and recording to produce a quantitative description of fright factor content on wind turbines and health in Ontario newspaper articles relative to a major policy initiative. To our knowledge, no previous media analysis has documented the issue of wind turbines and health. The study of these results may help to fill gaps in the literature regarding newspaper media framing of wind energy and health.

Of the fright factors associated with environmental risks and human health (Bennett 1999), we found the most commonly reported were 'dread', 'poorly understood by science', 'involuntary exposure' and 'inequitable distribution'. The high number of citations for 'dread' and 'poorly understood by science', which we identified, is consistent with the literature on perceived risk associated with other technologies – electromagnetic fields (EMFs), power lines, cell phone radiofrequencies and cell phone base towers (Slovic 2000, Frick *et al.* 2002, Cousin and Siegrist 2011, Khiefets *et al.* 2010). The rapid rate of change in many technological sectors has made it difficult to characterise and study exposures prospectively, resulting in a knowledge deficit in both scientific and lay communities (Slovic 1987). The combination of dread and unknown consequences, when associated with technology, may lead to greater risk perceptions and result in stigmatisation and avoidance (Finucane *et al.* 2000). This effect may be exaggerated when coupled with frequent and dramatic news media coverage.

Local conditions, and their consequences, are experienced more directly by local media than national media (Viswanath *et al.* 2008). Therefore, our finding that both fright factors of 'dread' and 'poorly understood by science' were identified more frequently in community compared with national/provincial newspaper articles is not surprising. The audience for community newspapers generally have closer ties with local reporters, and expect information that affects their daily quality of life (Kaniss 1991). Subscribers to community newspapers are more likely to be local residents who live in a closer proximity to wind turbines. Thus, there may be an association between how often the fright factors 'dread' and 'poorly understood by science' were mentioned in the articles and the physical proximity of community residents to the actual wind energy installations; these fright factors were increasingly likely to occur in newspaper articles when the risk of exposure to wind turbines was greater. This potential relationship between locality of wind turbines, resident responses and public media discourse is an area for future research.

The fright factors of 'involuntary exposure' and 'inequitable distribution' were present in about half of the articles, with community newspapers emphasising inequitable distribution more often than national/provincial newspapers. This finding may reflect wind turbine locations in rural areas where community newspapers feature prominently. National/provincial newspapers, in contrast, are generally published in cities more distant from wind energy installations. Therefore, residents of rural areas might have a higher exposure than urban populations to the potential health risk of wind turbines. This represents an inequitable distribution of risk and may enhance and reinforce perceived risk among Ontario residents located near wind energy developments. Whether the perception of inequitable risk by local residents parallels the occurrence of this fright factor in the community newspaper reports remains to be determined.

A major function of the Green Energy Act was to streamline the approval process for wind energy installations in Ontario. This removed the ability of municipal governments to control the location of renewable energy sources in their communities. We expected to see an increase in the reporting of the fright factors 'involuntary exposure' and 'inequitable distribution'. However, only 'dread' and 'poorly understood by science' were reported more often after the Green Energy Act. Although our data do not indicate why the newspaper reporting of the fright factor 'poorly understood by science' increased after the Green Energy Act, this may reflect public dissatisfaction with the level of scientific evidence regarding wind turbines and potential health effects. Of note is that public calls for scientific study have been successful in altering behaviours towards other environmental and technological health risks, such as cell phones on airplanes, pesticides in schools and polyvinyl chloride children's toys (Kriebel *et al.* 2001). We also found a decreased prevalence in newspaper articles of the fright factor 'identifiable victims', following the Green Energy Act. The drop in the occurrence of this fright factor may be due to a greater collective voice and mobilisation of community groups, rather than concerns expressed by individuals. For example, the largest wind turbine opposition group in Ontario was established in late 2008 and has since grown to about 60 grassroot organisations (WCO 2011).

We used cluster analysis to study geographic variations in public health (Pedigo *et al.* 2011). Our intention was to contrast the prevalence of fright factors in newspaper articles in different communities. Following the Green Energy Act and extrapolating from a representative newspaper in each cluster with the greatest number of articles, Cluster 2 ('rural communities') had more articles linked to the fright factor of 'involuntary exposure' than did Cluster 1 ('urban communities'). The excerpts from the representative Cluster 2 newspaper showed that 'involuntary exposure' almost exclusively refers to the loss of municipal control over the placement of wind energy developments after the implementation of the Green Energy Act. Residents of rural communities may also feel disproportionately affected by legislation that removes municipal control, leading to feelings of powerlessness and a decreased ability to regain this control compared with urban communities.

The significant increase in news articles on wind turbines and potential health effects over time suggests that this topic is newsworthy. An increase in news coverage of an issue can result in audience negativism independent of the nature of the risk itself, and repeated public reactions to media can itself induce health consequences (Mazur and Lee 1993, Young *et al.* 2008). This is especially true of public exposure to new health information, which has been shown to increase health concerns for up to 2 weeks after the receipt of the information (Cousin and Siegrist 2011). Alternatively, an increase in newspaper coverage of an issue can lead to positive health behaviours, such as reporting on the H1N1 outbreak and increased demand for diagnostic testing (Olowokure *et al.* 2012). The increased frequency of newspaper coverage that focuses on human health reflects not only greater public discourse about health effects of wind turbines but a growing influence of the media in this debate.

The study on which this article is based had limitations. Our results and conclusions were restricted to a select number of Ontario newspapers, a handful of wind energy installations in the province, and did not reflect risk information presented in other important media outlets such as television or the internet. Newspaper articles were also retrieved through an online database, and manually searching newspaper websites and archives, which could potentially have biased their collection. The search string used to collect articles from the online database included terms such as illness and stress, which

may have biased our results to overrepresent negative news articles. However, the inclusion of these terms was necessary to capture the complete public discourse on health effects of wind turbines for the time period studied. A potential bias in this study is that more than half of the newspapers were owned by a single publisher. Although there is a variety of evidence to suggest that collective media ownership does not result in concentration of media content (Soroka 2002), there was still the possibility that newspaper coverage might reflect specific editorial agendas and selection bias rather than community concerns. We excluded duplicate articles from our analysis, which eliminated the potential syndication of stories across newspapers from the same publisher. Moreover, although each newspaper included in the study was publically available, they were generally sold individually or by subscription. Only those residents with the financial ability to purchase newspapers would have consistent exposure to fright factors embedded within news articles. We also recognise that there is the potential to miss relevant themes in the public discourse about wind turbines and health in Ontario because of the closed coding methods used. Although outside of the scope of this study, a qualitative analysis of these newspaper articles may identify several important emergent themes and contribute to building theory for future risk perception research. For example, the theme of political lobbying may be identified in a preliminary reading of the text, and further examined to reveal subthemes (Crabtree and Miller 1999).

Conclusion

Ontario newspaper articles on wind turbines and health contained a large number of fright factors, especially 'dread' and 'poorly understood by science', which both increased in frequency after the introduction of a major policy initiative and occurred more often in community relative to national/provincial newspapers. The information presented in mass media can affect public opinion related to wind turbines and influence the acceptance or resistance to renewable energy technology programmes in Ontario and potentially elsewhere (Dearing and Rogers 1996). Newspapers reporting of health concerns have widespread influence on the uptake of health campaigns, such as the HPV vaccination programme (Abdelmutti and Hoffman-Goetz 2009) and on consumer behaviours, such as purchasing genetically modified foods (Frewer *et al.* 2002). Findings from this content analysis represent a first step in documenting possible effects of newspaper reporting on the issue of wind turbines and health effects on individual, social or cultural norms (Riffe *et al.* 1998). Similar quantitative content analyses have contributed to understanding the public discourse about health risks in Canadian newspapers (Rachul *et al.* 2011, Holton *et al.* 2012). We suggest that other methodological approaches (for example, surveys or interviews) will be necessary to make inferences and predications about the effects of exposure to fright factors in the media on public perceptions on health risks from wind turbines.

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The Pattern of Complaints about Australian Wind Farms Does Not Match the Establishment and Distribution of Turbines: Support for the Psychogenic, 'Communicated Disease' Hypothesis

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Abstract

Background and Objectives: With often florid allegations about health problems arising from wind turbine exposure now widespread, nocebo effects potentially confound any future investigation of turbine health impact. Historical audits of health complaints are therefore important. We test 4 hypotheses relevant to psychogenic explanations of the variable timing and distribution of health and noise complaints about wind farms in Australia.

Setting: All Australian wind farms (51 with 1634 turbines) operating 1993–2012.

Methods: Records of complaints about noise or health from residents living near 51 Australian wind farms were obtained from all wind farm companies, and corroborated with complaints in submissions to 3 government public enquiries and news media records and court affidavits. These are expressed as proportions of estimated populations residing within 5 km of wind farms.

Results: There are large historical and geographical variations in wind farm complaints. 33/51 (64.7%) of Australian wind farms including 18/34 (52.9%) with turbine size >1 MW have never been subject to noise or health complaints. These 33 farms have an estimated 21,633 residents within 5 km and have operated complaint-free for a cumulative 267 years. Western Australia and Tasmania have seen no complaints. 129 individuals across Australia (1 in 254 residents) appear to have ever complained, with 94 (73%) being residents near 6 wind farms targeted by anti wind farm groups. The large majority 116/129(90%) of complainants made their first complaint after 2009 when anti wind farm groups began to add health concerns to their wider opposition. In the preceding years, health or noise complaints were rare despite large and small-turbine wind farms having operated for many years.

Conclusions: The reported historical and geographical variations in complaints are consistent with psychogenic hypotheses that expressed health problems are "communicated diseases" with nocebo effects likely to play an important role in the aetiology of complaints.

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Introduction

The attribution of symptoms and disease to wind turbine exposure is a contentious "modern health worry" [1] which has seen increasing attention from governments, their regulatory agencies and courts after organised opposition to wind farms, predominantly in Anglophone nations. Two broad hypotheses have been advanced about those reporting symptoms they attribute to exposure to wind turbines.

1. both audible noise and sub-audible infrasound generated by wind turbines can be directly harmful to the health of those exposed.
2. psychogenic factors – including nocebo responses to the circulation of negative information about their putative harms – are likely to be relevant to understanding why of those exposed, only small proportions claim to be adversely affected.

The evidence for a physical basis for these symptoms remains largely anecdotal. There has been a profusion of claims mostly by wind farm opponents about harms to exposed humans and animals (currently numbering 223 different diseases and symptoms) [2]. Despite this, 18 reviews of the research literature on wind turbines and health published since 2003 [3–20] have all reached the broad conclusion that the evidence for wind turbines being directly harmful to health is very poor. These suggest that only small minorities of exposed people claim to be annoyed by

wind turbines – typically less than 10% [14]. They conclude that the relationship between wind turbines and human responses is "influenced by numerous variables, the majority of which are non-physical" [14].

Variables associated with wind turbine annoyance include pre-existing negative attitudes to wind farms [14], including their impact on landscape aesthetics [21], having a "negative personality" [22], subjective sensitivity to noise [14], and being able to see wind turbines [5,23]. Similarly, deriving income from turbines [24] or enjoying reduced power bills can have an apparent "protective effect" against annoyance and health symptoms [18]. Such factors, which are similar to characteristics of other psychogenic illnesses ("New Environmental Illnesses" [25] and "Modern Health Worries" [26]) were found to be more predictive of symptoms than objective measures of actual exposure to sound or infrasound [14].

A large literature on nocebo effects exists about reported pain [27], but these effects have also been documented for other imperceptible agents such as electro-magnetic and radio frequency radiation [28–30]. Perceived proximity to mobile telephone base stations and powerlines, lower perceived control and increased avoidance (coping) behaviour were associated with non-specific physical symptoms in a study which found no association between reported symptoms and distance to these sources of electromagnetic radiation [31].

The psychogenic theory about wind turbine "illness" is supported by a recent New Zealand study [32], in which healthy volunteers exposed to both sham and true recorded infrasound who had been previously given information about possible adverse physiological effects of infrasound exposure reported symptoms aligned with that information. The adverse effects information provided to subjects was sourced from anti wind farm internet sites which the authors concluded indicated "the potential for symptom expectations to be created outside of the laboratory, in real world settings."

A psychogenic contagion model may be applicable to this phenomenon. Mass Psychogenic Illness (MPI) is described [33–35] as a constellation of somatic symptoms, suggestive of an environmental cause or trigger (but with symptoms without typical features of the contaminant, varying between individuals, and not related to proximity or strength of exposure) which occurs between two or more people who share beliefs related to those symptoms and experience epidemic spread of symptoms between socially connected individuals. The rapid development of fear and anxiety is key to the transmission of disease by disruption of behaviour and activities of those involved. Transmission or contagion is increased by the general excitement related to the phenomenon, including media reports, researcher interest, and labeling with a specific clinical diagnostic term.

Boss' review of factors promoting mass hysteria noted that "media reports are used as cues by potential cases for appropriate illness behavior responses and can initially alarm those at risk …Too often, it is the media-created event to which people respond rather than the objective situation itself … Development of new approaches in mass communication, most recently the Internet, increase the ability to enhance outbreaks through communication." [33].

While modern wind farms have operated since the early 1980s [36], the earliest claims alleging that wind turbines might cause health problems in those exposed appear to date from 2003 (see below); this increased rapidly after 2008, following publicity given to a self-published book, "Wind Turbine Syndrome" [37], by US physician Nina Pierpont, whose partner edits a virulent anti wind farm website [38]. Google Trends data of web-based searches for "Wind turbine noise", "Wind Turbine Syndrome" and "wind turbine health" show that "noise" began to appear from 2007 and that "syndrome" and "health" began to track together from 2008, suggesting the book generated this sudden interest in the phenomenon, rather than riding a wave of interest. Furthermore, a 2007–11 Ontario study of newspaper coverage of wind farms showed that 94% of articles featured "dread" themes [39].

"Labeling" of an illness is one of the key features associated with spread of mass psychogenic illness, along with community and media interest [33]. There have been three attempts to popularise portentous quasi-scientific names for health problems said to be caused by wind turbines: Wind Turbine Syndrome, Vibro Acoustic Disease [40] and Visceral Vibratory Vestibular Disturbance [41], although none of these have gained scientific acceptance as diagnostic terms. As described earlier, many features of MPI apply to Wind Turbine Syndrome. Furthermore, the most reported symptoms in over one third of all MPIs of nausea/vomiting, headache, and dizziness [33], are also frequently featured as common symptom complaints arising with wind turbines, suggesting these symptoms may be plausibly explained as psychogenic.

Wind farm opponent groups have been very active in the last five years in three Australian states (Victoria, NSW and South Australia) publicising the alleged health impacts of turbines. This has created insurmountable problems for researching the psychogenic and nocebo hypotheses using either cross-sectional or prospective research designs because it is unlikely that any communities near wind farms now exist which have not been exposed to extensive negative information. For this reason, audits of the history of complaints are essential because they allow consideration of whether health and noise complaints arose during years prior to the "contagion" of communities with fearful messages about turbines.

To date, there has been no study of the history and distribution of noise and health complaints about wind turbines in Australia. The two theories (the "direct effects" and the "psychogenic"), would predict differing patterns of spatial and temporal spread of disease. We sought to test 4 hypotheses relevant to the psychogenic argument.

1. Many wind farms of comparable power would have no history of health or noise complaints from nearby residents (suggesting that exogenous factors to the turbines may explain the presence or absence of complaints).
2. Wind farms which have been subject to complaints would have only a small number of such complaining residents among those living near the farms (suggesting that individual or social factors may be required to explain different "susceptibility").
3. Few wind farms would have any history of complaints consistent with claims that turbines cause acute health problems (suggesting that explanations beyond turbines themselves are needed to explain why acute problems are reported).
4. Most health and noise complaints would date from after the advent of anti wind farm groups beginning to foment concerns about health (from around 2009) and that wind farms subject to organised opposition would be more likely to have histories of complaint than those not exposed to such opposition (suggesting that health concerns may reflect "communicated" anxieties).

Table 1 sets out both the predictions of the "direct effects" model of causation, and the observed findings of our historical

Table 1. Prediction of "direct effects" model versus observations explained by psychogenic model.

Key hypotheses re distribution of complainants	Characteristic	Predictions of Direct Effects Model	Observations with Psychogenic Model
Spatial (geographic)	Distribution of wind farms with complaints	All wind farms (especially those with >1 MB turbines) should have complainants	Inconsistent distribution associated with presence or absence of anti wind farm activity
	Proportion of complainants residing around wind farms	Only in those "susceptible" but should be similar across all wind farms	Generally very low, but higher at wind farms targeted by anti wind farm groups
Temporal	Timing and latency of first complaints	Turbine exposure followed by both acute (immediate) and chronic health effects	Absence of or long delays in reporting acute effects common

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review of the distribution and timing of complaints, which are more consistent with a psychogenic model.

Methods

Information on the commencement of turbine operation, the number of turbines operating, average turbine size and the megawatt (MW) capacity of each wind farm was located from public sources such as wind farm websites.

Wind farm operators have clear risk management interest in any reactions of nearby residents to the farms they operate. In the planning, construction and power generation phases of wind farm operation they monitor local community support and complaints submitted to them, in news media and via any complaint notifications from local government. In Victoria, companies are required by law to register all complaints with the state government. In September 2012 all wind farm owners in Australia were asked to provide information on:

- the actual or estimated number of residents within a 5 km radius of each wind farm they operated. Google Maps and census data were also used to obtain this data (see below).
- whether the company had received or was aware of any health and/or noise complaints, including sleeping problems, that were being attributed to the operation of their wind farms.
- the number of individuals ("complainants") who had made such complaints (direct complaints to the companies, those voiced in local media, to local government or state or national enquiries).
- the date at which the first complaint occurred.
- whether there had been any anti wind farm activity in the local area such as public meetings addressed by opponents, demonstrations or advertising in local media.

Any documentation of complaints such as internet links or news clips about public was requested. Companies were explicitly asked to de-identify any private complaints which could identify those complaining, unless these complaints had been made public by the complainants.

It is possible that wind companies may nonetheless be unaware of some health and noise complaints about their operations or that they might downplay the extent of complaints and provide underestimates of such complaints. To corroborate the information on the number of complainants provided by the companies, we therefore reviewed all 1,594 submissions made to three government enquiries on wind farms: the 2011–2012 Senate enquiry into the Social and Economic Impact of Rural Wind Farms (1,818 submissions) [42]; the 2012 NSW Government's Draft NSW Planning Guidelines for Wind Farms (359 submissions) [43]; and the Renewable Energy (Electricity) Amendment (Excessive Noise from Wind Farms) Bill 2012 (217 submissions) [44]. We searched all submissions for any mentions by residents living in the vicinity of operating wind farms (as opposed to those being planned) of their health or sleep being adversely affected or that they were annoyed by the sound of the turbines.

We also searched daily media monitoring records supplied to the Clean Energy Council by a commercial monitoring company from August 2011 (when the monitoring contract began) until January 2013. This monitoring covered print news items, commentary and letters published in Australian national, state and regional newspapers mentioning any wind farm, as well as television and radio summaries about all mentions of wind farms. It was important to use this source of monitoring rather than use on-line databases like Factiva, as the latter do not cover all small rural news media which is where much coverage of debate about rural wind farms was likely to be found.

Finally, a pre-print of this paper was published on the University of Sydney's e-scholarship repository on March 15 2013. In the next six months the paper was opened over 10,800 times, making it the most opened document among 7761 in that repository across these 4 months. This generated considerable correspondence, and in one case (Hallett 2), information was provided about extra complainants who had complained via a legal case. These were then included.

In reviewing the submissions and media monitoring, only complaints from those claiming to be personally affected by the operation of an existing wind farm in Australia were noted. Expressed concerns about possible future adverse effects or that wind turbines *could* be harmful were not classified as evidence of personal experience of harm or annoyance. There were many of these. Third party statements, such as comments about unnamed neighbours with problems, were not accepted as evidence of harm.

Where the numbers of complainants determined from this corroborative public source searching exceeded the numbers provided to us by the wind companies, we chose the larger number. Where the numbers determined from public sources were less, we used the larger number provided by the companies. Our estimate of the number of complainants thus errs on the least conservative side. Nearly all those who publicly complained did not seek anonymity, being named in media reports or not electing to have their parliamentary submissions de-identified. However, we have chosen not to list their names in this report.

The companies provided estimates of the number of residents currently living within 5 km of each wind farm. Some companies

Table 2. Complainant numbers at 51 Australian wind farms, 1993–2013.

Wind farm name (state) *owner*	Installed Capacity (MW)+(number of turbines)+average turbine size MW	Date commenced operation & total years (to Dec 2012)	Approx. population within 5 km	Health or noise complainants (Y/N) & number (persons unless specified)	Date of first complaint (months since opened)	Local or visiting opposition group activity?
A: Farms with total >10 MW capacity						
Albany/Grasmere (WA) *Verve*	35.4 (18) 1.96	Oct 2001 (11y 2m)	200	N	–	N
Bungendore/Capital/ Woodlawn (NSW) *Infigen*	189 (90) 2.1	Nov 2009 (3y 1m)	76 houses 198	Y:10	Dec 2009 (1 m)	Y
Canunda (SA) *International Power*	46 (23) 2.0	Mar 2005 (7y 10m)	20 houses 52	N	–	N
Cape Bridgewater (Vic) *Pacific Hydro*	58 (29) 2.0	Nov 2008 (4y 1m)	68 houses 177	Y:6	2 Feb 20110 (16m)	Y
Cape Nelson South (Vic) *Pacific Hydro*	44 (22) 2.0	Jun 2009 (3y 6m)	170 houses 425	Y:2	10 Feb 2010 (8m)	Y
Cathedral Rocks (SA) *TRUenergy, Acciona & EHN*	66 (33) 2.0	Sep 2005 (7 y 3 m)	0	N	–	N
Challicum Hills (Vic) *Pacific Hydro*	52.5 (35) 1.5	Aug 2003 (9 y 4 m)	55 houses 143	N	–	N
Clements Gap (SA) *Pacific Hydro*	56.7 (27) 2.1	Feb 2010 (2 y 10 m)	41	Y:3	On-going from earlier	Y
Codrington (Vic) *Pacific Hydro*	18.2 (14) 1.3	Jun 2001 (11 y 6 m)	50	N		N
Collgar/Merriden (WA) *Collgar*	206 (111) 1.85	May 2011 (1 y 7 m)	15	N	–	N
Cullerin Range (NSW) *Origin*	30 (15) 2.0	Jul 2009 (3 y 5 m)	50	N	–	N
Emu Downs (WA) *APA*	80 (48) 1.66	Oct 2006 (6 y 2 m)	50	N	–	N
Gunning/Walwa (NSW) *Acciona*	46.5 (31) 1.5	May 2011 (1 yr 7 m)	25 houses 65	Y:1	Jan 2012 (8 m)	N
Hallett 1/Brown Hill (SA) *AGL*	95 (45) 2.11	Sep 2008 (4 y 3 m)	120	N		Y
Hallett 2/Hallett Hill (SA) *AGL*	71.4 (34) 2.1	Mar 2010 (2 y 9 m)	120	Y:13*	On-going from earlier	Y
Hallett 4/North Brown Hill (SA) *AGL*	132 (63) 2.1	May 2011 (1 y 7 m)	200	Y:1	On-going from earlier	Y
Hallett 5/Bluff Range (SA) *AGL*	53 (25) 2.1	Mar 2012 (9 m)	140	Y:1	Apr 2012 (1 m)	Y
Lake Bonney (SA) *Infigen*	278.5 (112) 2.8	Mar 2005 (7 y 9 m)	255	Y:2	June 2012 (7 y 3 m)	N
MacArthur (Vic) *AGL/ Meridian*	420 (140) 3.0	Sep 2012 (3 m)	15	Y:8 houses = 21	2 days after 2/140 turbines commenced operation	Y
Mortons Lane (Vic) *CGN Wind Energy Ltd*	19.5 (13) 1.5	Dec 2012	14 houses 36	N	–	N
Mt Millar (SA) *Meridian*	70 (35) 2.0	Feb 2006 (6 y 10 m)	10 houses 26	N	–	N
Oaklands Hill (Vic) *AGL*	67.2 (32) 2.1	Feb 2012 (10 m)	250	Y:6	On-going from earlier	Y
Snowtown (SA) *Trust Power*	100.8 (47) 2.14	Nov 2008 (4 y 1 m)	4 houses 10	N	–	N
Starfish Hill (SA) *Ratch*	34.5 (23) 1.5	Sep 2003 (9 y 3 m)	200	N	–	N
Toora (Vic) *Ratch*	21 (12) 1.75	Jul 2002 (10 y 5 m)	674	Y:2	Early (precise date not known)	Y
Walkaway (Alinta) (WA) *Infigen*	89.1 (54) 1.65	Apr 2006 (6 y 8 m)	3 houses 8	N	–	N

Table 2. Cont.

Wind farm name (state) *owner*	Installed Capacity (MW)+(number of turbines)+average turbine size MW	Date commenced operation & total years (to Dec 2012)	Approx. population within 5 km	Health or noise complainants (Y/N) & number (persons unless specified)	Date of first complaint (months since opened)	Local or visiting opposition group activity?
Waterloo (SA) *TRUenergy*	111 (37) 3.0	Dec 201 (2 y)	75 houses 195	Y:11	Feb 2011 (2 m)	Y
Wattle Point (SA) *AGL Hydro*	91 (55) 1.65	Nov 2005 (7 y 1 m)	560	N	–	N
aubra (Vic) *Acciona*	192 (128) 1.5	Mar 2009 (3 y 10 m)	283 houses 736	Y:29	13 Mar 2009 (immediate)	Y
Windy Hill (Qld) *Ratch*	12 (20) 0.6	Feb 2000 (12 y 10 m)	200	Y:1	Early (precise date not known)	N
Wonthaggi (Vic) *Transfield*	12 (6) 2.0	Dec 2005 (7 y)	6900	Y:~10	Feb 2006 (2 m)	Y
Woolnorth:Bluff Point (Tas) *Roaring 40 s & Hydro Tas.*	65 (37) 1.76	Aug 2002 (10 y 4 m)	NI	N	–	N
Woolnorth:Studland Bay (Tas) *Roaring 40 s & Hydro Tas.*	75 (25) 3.0	May 2007 (5 yr 7 m)	NI	N	–	N
34.Yambuk (Vic) *Pacific Hydro*	192 (128) 1.5	Jan 2007 (5 y 11 m)	88	N	–	N
Sub-total: 34 farms	3130.3 MW (1567 turbines)		12334	16 farms with 119 complainants		14
B: Farms with <10 MW capacity						
Blayney (NSW) *Eraring Energy*	9.9 (15) 0.66	Oct 2000 (12 y 2 m)	37	N	–	N
Bremer Bay (WA) *Verve*	0.6 (1) 0.6	Jun 2005 (7 y 6 m)	250	N	–	N
Coober Pedy (SA) *Energy Generation*	0.15 (1) 0.15	1999 (13 y)	3500	N	–	N
Coral Bay (WA) *Verve*	0.825 (3) 0.275	Oct 2006 (6 y 2 m)	200	N	–	N
Crookwell (NSW) *Union Fenosa/Eraring*	4.8 (8) 0.6	Jul 1998 (14 y 5 m)	200	Y:4	Jan 2012 (13 y 6 m)	Y
Denham (WA) *Verve*	1.6 (4) 0.4	Jun 1998 (14 y 6 m)	600	N	–	N
Esperance, 9 Mile Beach (WA) *Verve*	3.6 (6) 0.6	2003 (8 y)	50	N	–	N
Esperance, 10 Mile Lagoon (WA) *Verve*	2.025 (9) 0.225	1993 (19 y)	50	N	–	N
Hampton Park (NSW) *Wind Corp*	1.32 (2) 0.66	Sep 2001 (11 y 3 m)	150	N	–	N
Huxley Hill, King Island (Tas) *Hydro Tas*	2.458 (5) 0.49	Feb 1998 (14 y 1 m)	10 houses (26)	N	–	N
Hopetoun (WA) *Verve*	1.2 (2) 0.6	Mar 2004 (8 y 9 m)	600	N	–	N
Kalbarri (WA) *Verve*	1.6 (2) 0.8	Jul 2008 (4 y 5 m)	10	N	–	N
Kooragang, Newcastle (NSW) Energy Australia	0.6 (1) 0.6	1997 (15 y)	3–4 km from Mayfield 9000	N	–	N
Leonards Hill (Vic) *Community owned*	4.1 (2) 2.05	Jun 2011 (1 y 6 m)	232	Y:6	On-going from earlier	Y
Mt Barker (WA) *Mt Barker Power*	2.4 (3) 0.8	Mar 2011 (1 y 9 m)	2000	N	–	N
Rottnest Island (WA) *Rottnest Island*	0.6 (1) 0.6	Sep 2006 (6 y 3 m)	150	N	–	N
Thursday Island (Qld) *Egon Energy*	0.225 (2) 0.113	Aug 1997 (15 y 5 m)	2500	N	–	N

Table 2. Cont.

Wind farm name (state) *owner*	Installed Capacity (MW)+(number of turbines)+average turbine size MW	Date commenced operation & total years (to Dec 2012)	Approx. population within 5 km	Health or noise complainants (Y/N) & number (persons unless specified)	Date of first complaint (months since opened)	Local or visiting opposition group activity?
Sub-total:17 farms	38 MW 67 turbines		20405	2 farms with 10 complainants		2
Total:51 farms	3168.3 MW 1634 turbines		32739	18 farms with 129 complainants		16

NI = no information.

*13 residents submitted affidavits in a court case but only 2 complained to the company (*AGL*), and none to the local Council or Environmental Protection Agency. Average residents per house in 2011:2.6 http://www.censusdata.abs.gov.au/census_services/getproduct/census/2011/quickstat/0.

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provided estimates of the number of individuals, while others provided data on the number of houses. In Table 2, we have multiplied cells showing the number of *houses* by 2.6, this being the average number of residents per household in Australia today, to give a total estimate of surrounding residents.

Results

Table 2 shows the history and distribution of complaints from all 51 Australian wind farms. Complaints came either from individuals or from households with several occupants each or collectively complaining. Some wind companies initially reported the number of complainants as *households*, while others reported individual complainant numbers. In these cases we sought clarification from companies about whether complaints came from single individuals, couples or more than two members of a family so as to report total the estimated total number of individual complainants.

Hypothesis 1: Many Wind Farms would have no History of Complaints

Of all 51 wind farms, 33 (64.7%) had never been subject to health or noise complaints, with 18 (35.3%) receiving at least one complaint since operations commenced. The 33 farms with no histories of complaints, and which today have an estimated 21,633 residents living within 5 km of their turbines, have operated for a cumulative total of 267 years.

Of the 18 wind farms which had received complaints, 16 were larger wind farms ($\geq$10 MW capacity). In summary, 18/34 (52.9%) of larger wind farms, and 15/17 (88.2%) of small farms have never experienced complaints. Wind farm opponents sometimes argue that it is mainly very large, "industrial" wind turbines which generate sufficient audible noise and infrasound to cause annoyance and health problems. If 1 MW is taken to define a "large" turbine, 18/34 (52.9%) of farms using large turbines had never attracted complaints while 15/17 (88%) of farms using smaller turbines had no histories of complaints. Both the total energy generating capacity of farms and whether the turbines used were over 1 MW were thus significant predictors of residents having ever complained, with small total capacity farms being far less likely to have complainants (88% vs 53%; $\chi^2 = 6.18$, 1 df, $p = 0.013$).

The distribution of farms which have ever received complaints is highly variable across Australia. Figure 1 shows no consistency between the percentages of farms receiving complaints in different states, whether they have many or few wind farms. Western Australia has 13 wind farms (3 with large turbines), including some of the longest running in Australia (Esperance 10 Mile Lagoon 1993, Denham 1998). No complaints have been received at any of these wind farms. Verve, which operates 8 farms in the state replied "we have never received any form of notification of health complaints in the vicinity of our wind farms." The three farms in Tasmania have also never received complaints.

Our hypothesis about many wind farms – including those with large turbines – having no history of complaints, with strong spatial (geographical) factors being associated with farms receiving complaints was thus strongly confirmed.

Hypothesis 2: There would be a Small Proportion of Complaining Residents

Nationally, a total of 129 individuals in Australia appear to have ever formally or publicly complained about wind farm noise or health problems affecting them. Of these, well over half (94 or 73%) came from residents living near just six wind farms (Waubra = 29, McArthur = 21, Hallett 2 = 13, Waterloo = 11, Capital = 10 and Wonthaggi ~10). Of the remaining farms which have experienced complaints, 9 had between 2 and 6 complainants, and 4 had only single complainants. Of 18 wind farms which had attracted complaints, 11 (72%) have had 6 or less complainants.

There are an estimated 32,789 people living within 5 km of the 50 wind farms for which we obtained residential estimates. Most (20,455 or 62%) live near the 17 smaller wind farms, while 12,334 live within 5 km of the 32 larger farms. In summary, nationally, an estimated 129 individuals have complained out of an estimated 32,789 nearby residents: a rate of about 0.4% or 1 in 254. Of the 34 wind farms with larger (>1 MW) turbines, their 124 complainants represented some 1 in 100 of the surrounding 12,366 residents. Large wind farms with relatively large surrounding rural populations and no histories of complaint include Wattle Point (560), Albany, Starfish Hill (each 200) and Challicum Hills (143).

Again, our hypothesis that the number of complainants living near those wind farms with any history of complaints would be a small proportion of the exposed population, was strongly confirmed.

Hypothesis 3: Few Wind Farms would have any History of Complaints Consistent with Claims that Turbines cause Acute Effects

Wind farm complainants describe both acute and chronic adverse effects. Acute effects are of particular interest to the psychogenic hypothesis because it is often claimed that even brief exposure to wind turbines can cause almost immediate onset of

symptoms. For example, a recent report describes a visit to turbine-exposed houses where people become immediately affected: "The onset of adverse health effects was swift, within twenty minutes, and persisted for some time after leaving the study area" [45]. Symptoms are said to disappear when those affected move away temporarily, only to return as soon as they come back. A highly publicised Lake Bonney complainant who had hosted turbines on his previous property without complaint for six years today claims he and his wife are affected at their new address, further away, but that symptoms disappear as soon as they leave their new home for one or two days [46].

If wind turbine exposure can cause such "instant" problems, any history of delayed or non-reporting of such complaints and the absence of any reports about such complaints in the news media, months or sometimes years after various wind farms began operating creates serious coherency problems for such claims. Such delays would be incompatible with there being widespread or important "acute" effects from exposure.

Table 2 shows that first complaint timing ranged from immediately after turbines commenced operation (sometimes at only a fraction of full capacity) to many months and even many years later (eg: Crookwell, 13.5 years, Lake Bonney, over 7 years later. In five cases (Clements Gap, Hallet 2 & 4, Leonards Hill, Waubra), wind companies advised that complaints anticipating health problems were received before the farms commenced operation. Of the 51 wind farms, 33 (64.7%) have seen no complaints; 6 (11.8%) saw complaints commence at times ranging from 2 months to 13.5 years after turbine operation; and 12 (23.5%) saw either on-going complaints continue from before the wind farms commenced operation or within the first month.

Early complaints from some wind farms could be consistent with acute effects caused directly by turbine exposure but also with nocebo effects caused by anticipation of adverse effects [32]. However, gaps of months or sometimes years between the commencement of turbine operation and complaints are inconsistent with turbines causing acute effects. Moreover, if such effects were serious or common, clinical case reports would have almost certainly appeared in peer reviewed journals, given the many years that wind farms have operated in Australia. No such reports have been published.

Hypothesis 4: Most Complaints would Date from 2009 or Later, when Anti Wind Farm Groups began to Publicise Alleged Health Effects

The nocebo hypothesis would predict that the spread of negative, often emotive information would be followed by increases in complaints and that without such suggestions being spread, complaints would be less. Australia's first still operational wind farm commenced operation in 1993 at 10 Mile Lagoon near Esperance, Western Australia. However, objections to wind farms in Australia appear to date from the early years of the 2000 s when press reports mentioned negative reactions of some in rural communities to their intrusiveness in bucolic country landscapes ("behemoths" [47]), bird and bat strikes, the divisiveness engendered in communities by the perceived unfairness of some landowners being paid hosting fees of up to $15,000 per year per turbine while neighbours received none, and debates about the economics of green energy. Unguarded, frank NIMBYism "I'm quite happy to admit that this is a not-in-my-backyard thing, because my backyard is very special" was also evident in 2002 [47].

Groups explicitly opposing wind farms ostensibly because of agendas about preserving pristine bush and rural environments were active from these early years and included many branches of the Australian Landscape Guardians (for example Prom Coast (2002), Spa Country [48], Grampians-GlenThompson [49], Western Plains, Daylesford and District). Key figures in the Landscape Guardians have links with mining and fossil fuel industries [50]. Interests with overt climate change denial agendas also actively opposed wind farm developments, particularly in Victoria. Chief among these were the Australian Environment Foundation, registered in February 2005.

However, health concerns were marginal in these early oppositional years, with one early press report from September 2004 [48] noting "some objectors have done themselves few favours by playing up dubious claims about reflecting sunlight, mental health effects and stress to cattle".

An unpublished British report said to refer to data gathered in 2003 on symptoms in 36 residents near unnamed English wind farms is frequently noted by global wind turbine opponents as the first known report of health effects from wind turbines, although curiously, it does not appear to have been produced until 2007 [51]. The Daylesford and Districts Landscape Guardians referred to Harry's work in a 2007 submission opposing a wind farm at Leonards Hill [52].

In Australia, a rural doctor from Toora, Victoria, David Iser, produced another unpublished report [53] in April 2004 following his distribution of 25 questionnaires to households within 2 km of the local 12 turbine, 21 MW wind farm, which had commenced operation in October 2002. Twenty questionnaires were returned, with 12 reporting no health problems. Three reported what Iser classified as "major health problems, including sleep disturbances, stress and dizziness". Like that of Harry, Iser's report provides no details of sample selection; whether written or verbal information accompanying the delivery of the questionnaire may have primed respondents to make a connection between the wind turbines and health issues; whether those reporting effects had previous histories of the reported problems; nor whether the self-reported prevalence of these common problems were different to those which would be found in any age-matched population.

In the 10 years between the commencement of operation of the first Esperance wind farm and the end of 2003 when the Harry and Iser health impact reports [51,53] began being highlighted by turbine opposition groups, 12 more wind farms commenced operation in Australia. In that decade, besides two complainants from Toora, we aware of only one other person living near the north Queensland Windy Hill wind farm who complained of noise and later health soon after operation commenced in 2000. Importantly in that decade, five large turbined wind farms at Albany, Challicum Hills, Codrington, Starfish Hill and Woolnorth Bluff Point commenced operation but never received complaints.

With the exception of those just mentioned and Wonthaggi (~10 complainants in 2006, but none today) all other health and noise complainants (n = 116) first complained after March 2009–six years after Iser's Toora small, unpublished survey of health complaints [53] - and particularly from the most recent years when anti wind farm publicity from opposition groups focused on health has grown. Again, the nocebo and the 'communicated disease' hypotheses would predict this changed pattern and contagion of complaints, driven by increasing community concern. Sixty nine percent of wind farms began operating prior to 2009 while the majority of complaints (90%) were recorded after this date.

Responding to the nocebo hypothesis and the view that opposition groups were fomenting a 'communicated disease', the Waubra Foundation's Sarah Laurie stated: "There is also plenty of evidence that the reporting of symptoms for many residents at

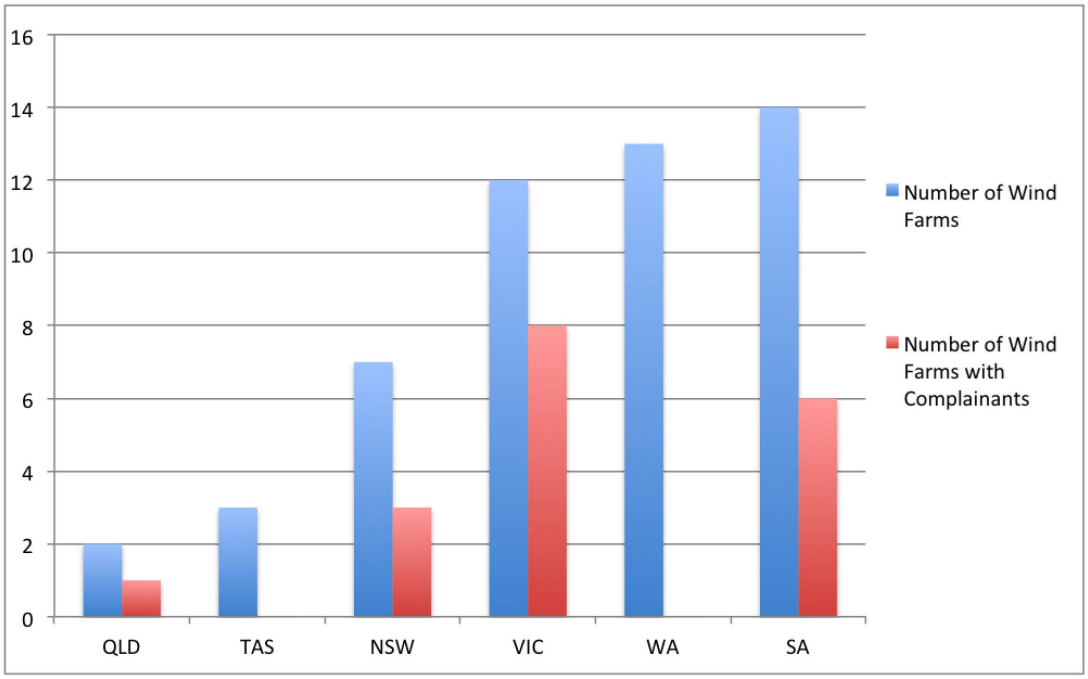

Figure 1. Farms with wind turbine complainants by state, Australia 1993–2012.
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wind developments in Victoria such as Toora, Waubra and Cape Bridgewater *preceded the establishment of the Waubra Foundation* (emphasis in original). In the case of Dr David Iser's patients at Toora the time elapsed is some 6 years." [54].

This statement neglects to note that the Waubra Foundation's registration in July 2010 was preceded by several years of virulent wind turbine opposition – which included health claims – by the Landscape Guardians and the Australian Environment Foundation. For example, in November 2009, 8 months before the formation of the Waubra Foundation the Western Plains Landscape Guardians published a full-page advertisement in the local Pyrenees Advocate newspaper headed "Coming to a house, farm or school near you? Wind Turbine Syndrome also known as Waubra Disease". It listed 12 common symptoms (e.g. sleeping problems, headaches, dizziness, concentration problems). Peter Mitchell is the founding chairman of the Waubra Foundation and in 2009 and at least until February 2011, was also actively advocating for the Landscape Guardians [55].

Table 2 shows that of the 18 wind farms which have seen complainants, 15 (83%) have experienced local opposition from anti wind farm groups. No wind farm with any history of wind turbine opposition avoided at least one health or noise complaint. We conclude that health and noise complaints were rare prior to the decision of anti wind farm groups to focus on these issues and that anti wind farm activists are likely to have played an important role in spreading concern and anxiety in all wind farms areas in which they have been active.

Discussion

This study shows there are large historical and geographical differences in the distribution of complainants to wind farms in Australia. There are many wind farms, large and small, with no histories of complaints and a small number where the large bulk of complaints have occurred. Just over half of wind farms with larger turbines have seen complaints, but nearly just as many have not. These differences invite explanations that lie beyond the turbines themselves.

Our historical audit of complaints complements recent experimental evidence [32], that is strongly consistent with the view that "wind turbine syndrome" and the seemingly boundless and sometimes bizarre range of symptoms associated with it has important psychogenic nocebo dimensions [2]. While wind turbines have operated in Australia since 1993, including farms with >1 MW turbines from 2001 (Albany and Codrington), health and noise complaints were very rare until after 2009, with the exception of Wonthaggi which saw about 10 complainants in 2006.

Several wind farm operators reported that many former complainants had now desisted. For example, Waubra management advised that not all complainants identified by our public searches had complained to them, and that more than half of the 17 complainant households who had complained to them, had had their complaints resolved. Similarly, Wonthaggi management said that none of some 10 complainants from 2006/2007 were still complaining today. Some of these former complainants from different farms had had their houses noise tested with the results showing they conformed to the relevant noise standard, some received noise mitigation (e.g. double glazing), while others simply stopped complaining.

Opponents sometimes claim that only "susceptible" individuals are adversely affected by wind turbines, using the analogy of motion sickness. Our data produce problems for that explanation: it is implausible that no susceptible people would live around any wind farm in Western Australia or Tasmania, around almost all older farms, nor around nearly half of the more recent farms. No credible hypotheses other than those implicating psycho-social factors have been advanced to explain this variability.

As anti wind farm interest groups began to stress health problems in their advocacy, and to target new wind farm developments, complaints grew. Significantly though, no older

farms with non-complaining residents appear to have been targeted by opponents. The dominant opposition model appears to be to foment health anxiety among residents in the planning and construction phases. Health complaints can then appear soon after power generation commences. Residents are encouraged to interpret common health problems like high blood pressure and sleeping difficulties as being caused by turbines.

For example, sleeping problems are very common, with recent Australian and New Zealand estimates ranging from 34% [56], to moderately poor (26.4%) and very poor sleep quality (8.5%) [57]. A German study undertaken to obtain benchmark reference data on common symptoms and illnesses experienced in the past 7 days in the general population for comparison with those experienced by clinical trial enrollees presents data on several problems most often attributed to wind turbines. These include headache (45.3%), insomnia (25.6%), fatigue and loss of energy (19.1%), agitation (18.4%), dizziness (17%) and palpitations (8.6%) [58].

A case brought before The Ontario Environmental Review Tribunal by residents claiming to be affected by a wind farm, collapsed when the Tribunal requested that complaints supply their medical records to determine whether their complaints pre-dated the operation of the wind farm [59].

Wind farm opponents frequently argue complainants are legally "gagged" from speaking publicly about health problems, thus underestimating the true prevalence of those affected. This is said to apply to turbine hosts who are contractually gagged or to non-hosts who have reached compensation settlements with wind companies after claiming harm. The first claim is difficult to reconcile with the example provided by a high profile Lake Bonney wind farm host who continues to complain publicly without attracting any legal consequences [27]. Confidentiality clauses are routinely invoked in any legal settlement to protect parties' future negotiating positions with future complainants. They usually refer to the settlement figure rather than to the reasons for it.

We purposefully took a liberal view of what a "complainant" was, by including those who had voiced their displeasure about noise, sleep or health in news media or submissions even if they had never lodged a formal complaint with the relevant wind farm company. Despite this, the numbers complaining in Australia were very low and largely concentrated in a small number of "hotbeds" of anti wind farm activism.

A 2012 CSIRO report on nine wind farm developments in three Australian states found widespread acceptance among local residents of both operating and planned farms, and noted that: "The vocal minority are more often prominent in the media … These groups often contact local residents early in the project and share concerns about wind farms." And that "The reasons for opposition by some participants suggest that wind farms proposals are triggering a range of underlying cultural or ideological concerns which are unlikely to be addressed or resolved for a specific wind farm development. These underlying issues include pre-existing concerns that rural communities are politically neglected by urban centres, commitment to an anti-development stance, and opposition to a 'green' or 'climate action' political agenda." [60].

Limitations

The data we obtained on the number of individuals or occupied houses near the farms were current estimates. These numbers may have varied in different directions for different farms over the 20 year period that wind farms have operated in Australia. But no data are available on that variation. Our estimates of the ratios of complaints to population are therefore unavoidably fixed around the most current population estimates. They would include children who do not lodge complaints, but who are often mentioned by wind farm opponents as subject to health effects [2].

It is possible that there were other complainants who complained earlier than in the periods covered by our corroborative checks. However, this seems highly unlikely: Australian anti wind farm groups would have strong interests in widely publicising such complainants, had they existed. The Waubra Foundation for example, repeatedly refers to the 2004 Iser report [53], in its efforts to emphasise that health concerns had been raised before the Waubra Foundation became established [54] As wind farm opponents have not highlighted more complainants than we have identified, this strongly suggests there were no earlier health or noise complainants.

It is also possible that some of the health complainants are disingenuous, thereby inflating the true number of people actually claiming to experience turbine-related health problems when their objections may be only aesthetic. Controversy arose when an anti wind farm activist who lives 17 km from the Waterloo wind farm was recently accused of "coaching" residents who disliked the local wind farm to explicitly mention health issues [61].

We selected the 5 km distance from turbines as a compromise between the 2 km minimum setback distance designated by the Victorian government for future wind farm approvals, and the 10 km often named by the Waubra Foundation as the advisable minimum distance. We also note here, that one prominent critic of wind farms claims to to be able to personally sense low frequency noise up to 100 km away from wind turbines under certain conditions [62]. Had we chosen the 10 km distance counseled by the Waubra Foundation, this would have significantly increased the numbers of people exposed but not complaining.

The estimates provided by the wind companies of the number of residents within 5 km of wind farms need to be seen as approximations. Census data is available by local government areas and by the Australian Bureau of Statistics statistical regions. However, these do not correspond with the 5 km zone of residence of interest here. The wind companies which provided this data obtained it from their own knowledge of the number of residences near their wind farms and we checked local township sizes from Australian census data. This information is typically obtained during the planning stages of wind farm development when development applications often require such estimations to be provided. At least one company used Google Earth photography to calculate their estimate of the number if dwellings. However, such estimates will always be imprecise and approximations only. They nonetheless provide "ballpark" denominators against which the known number of complainants can be compared.

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Author Contributions

Analyzed the data: SC AStG KW VC. Wrote the paper: SC AStG KW VC. Conceived of study: SC. Collected data: SC AStG KW VC. Contributed to writing: SC AStG KW VC.

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Can road traffic mask sound from wind turbines? Response to wind turbine sound at different levels of road traffic sound

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ABSTRACT

Wind turbines are favoured in the switch-over to renewable energy. Suitable sites for further developments could be difficult to find as the sound emitted from the rotor blades calls for a sufficient distance to residents to avoid negative effects. The aim of this study was to explore if road traffic sound could mask wind turbine sound or, in contrast, increases annoyance due to wind turbine noise. Annoyance of road traffic and wind turbine noise was measured in the WINDFARMperception survey in the Netherlands in 2007 (n=725) and related to calculated levels of sound. The presence of road traffic sound did not in general decrease annoyance with wind turbine noise, except when levels of wind turbine sound were moderate (35–40 dB(A) Lden) and road traffic sound level exceeded that level with at least 20 dB(A). Annoyance with both noises was intercorrelated but this correlation was probably due to the influence of individual factors. Furthermore, visibility and attitude towards wind turbines were significantly related to noise annoyance of modern wind turbines. The results can be used for the selection of suitable sites, possibly favouring already noise exposed areas if wind turbine sound levels are sufficiently low.

1. Background

Wind power plays a small but significant role in the ongoing conversion to renewable energy sources. Installed electric wind power is increasing with an annual rate of 27% globally (IEA, 2008), meaning that the number of operational wind turbines is rapidly growing. Wind power is generally favoured by the public, though at the same time wind turbines often are opposed in the local community (Ek, 2005; Breukers and Wolsink, 2007). Wind turbines are by some viewed upon as visual and audible intruders, destroying the landscape scenery and emitting noise (Pedersen et al., 2007). Remote places with a low population density were considered suitable locations for wind farms, but long distances to the existing power grid are costly. Also, remote places often are otherwise unspoiled landscapes with high values for recreation and tourism that could decrease with the construction of a wind farm. Suitable places for wind farms are therefore more often sought after also in populated areas.

One of the parameters to assess the suitability of a location could be the existing background sound level due to natural or man-made sources. It seems plausible that high levels of background sound can reduce annoyance by masking the noise from a wind farm, either physically when the sound cannot be heard, or cognitively when the sound is perceived as attracting less attention. If this is true, a row of turbines could cause less noise annoyance when placed next to a motorway instead of a quiet agricultural area. One modern 2–3 MW turbine at high speed produces a sound power level (105–108 dB(A)) that is approximately equal to a car on a motorway (see road traffic sound power levels in Jabben et al., 2001). Siting wind turbines next to a motorway could thus be an attractive alternative, certainly if they then also would be perceived as visually less intrusive as they serve as visible 'milestones' along the motorway. However, it is not yet clear if road traffic can indeed mask wind turbine sound and to what extent. Physical masking of wind turbine sound by wind induced noise in vegetation has been investigated by Bolin (2007) and masking by sea waves by Appelqvist et al. (2007). The capacity for masking will change with time as high turbine sound levels can occur at low levels of vegetation or wave noise, either on a short time scale during wind gusts or on a longer time scale associated with changes in the vertical wind profile. Also, wind turbine sound can be audibly amplitude modulated due to differences in wind speed over the area swept by the rotor blades (van den Berg, 2005). Amplitude modulations in a sound are more easily detected by the human ear (Fastl and Zwicker, 2007) than a constant sound. Masking will

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also depend on the spectral distribution of the masking sound relative to the masked sound. Wind turbine and road traffic sound are not very different in this respect as both have high levels of sound at roughly 1–2 kHz (due to trailing edge and tyre noise respectively) at close distance and high levels at low frequencies due to inflow turbulent sound and engine sound. Here we assume that road traffic sound needs to exceed the actual level of wind turbine sound in order to be able to mask wind turbine noise.

When placing a wind farm close to another noise source, the other source could (at least for part of the time) mask the sound from the wind farm, but synergetic effects cannot be excluded: the response to exposure from one noise source could be enhanced due to exposure from another noise source. The prevalence of annoyance due to road traffic noise has been found to be significantly *higher* in areas with high exposure of both road traffic and railway noise, in comparison with areas with only high exposure of road traffic (Ahlstrom et al., 2007). On the other hand, the prevalence of annoyance due to high levels of railway noise was *lower* when high levels of road traffic sound were present compared to when they were not (Lercher et al., 2007). Vos (1992) found no synergetic effect when people were simultaneously exposed to sound from gunfire, aircraft and/or road traffic: the annoyance was shown to depend on the total sound level (logarithmic summation of sound level from each source), though sound levels were corrected with penalties to account for the difference in dose–response relations. Synergetic effects, if present, hence appear to depend on the character or origin of the sounds, or other circumstances related to the source, and can differ for each type and perhaps level of sound exposure.

Observed synergetic effects could also be due to confounders. Variables known to moderate the response to noise are noise sensitivity (Miedema and Vos, 2003) and attitude towards the noise source (Job, 1988). An association between annoyances with two noise sources could hence be due to individual factors that change the threshold for a negative appraisal and not actually to a synergetic effect. For wind turbines, the prevalence of annoyance with the noise increased if the wind turbines could be seen from the dwelling or outside the dwelling by the receiver (Pedersen and Larsman, 2008), is possibly due to a multi-sensory effect where the ability to detect and recognize external stimuli is enhanced when more than one sense is involved (Calvert, 2001). Also road traffic noise has been found to be more annoying if the road is visible than if it is not (Bangjun et al., 2003). It could be presumed that in landscapes where the noise sources are easily visible the possibility of noise annoyance increases due to the multi-modal stimuli, rather than annoyance with one noise source enhancing annoyance with a second source. Thus, situational factors also have to be taken into account when a possible synergetic effect is studied.

The objective of this paper is to explore if road traffic sound can mask wind turbine sound. To put it more precisely: Is perception and annoyance with wind turbine sound reduced when road traffic sound dominates the wind turbine sound?

2. Methods

The analyses are based on data from a large cross-sectional study that was carried out in the Netherlands (Pedersen et al., 2009). The objective was to evaluate human responses to exposure from wind turbines, especially for people living close to modern wind farms. The study included three different settings in order to vary background sound levels: built-up areas, rural areas with a main road (within 500 m from a selected wind turbine) and rural areas without a main road. Wind turbines were selected (from all wind turbines in the Netherlands) when they had a nominal power of 500 kW or more and another turbine within 500 m, and were not (re)placed in the previous year. A stratified sample of 1948 people living within different levels of wind turbine sound outside their dwellings was chosen for the study. Of those, 725 completed and returned a questionnaire (response rate 37%) measuring perception and annoyance with environmental factors, including wind turbine and road traffic sounds. The questionnaire also comprised questions about attitude towards the noise sources and individual factors such as health symptoms and perceived stress. A follow-up survey found no differences between respondents and non-respondents regarding the main annoyance question (Pedersen et al., 2009).

2.1. Assessments of sound levels

Coordinates for all respondents were available from the sampling process and used for calculating the distance to all wind turbines within 20 km of each respondent's dwelling. Emission (sound power) levels of wind turbines were obtained from technical specifications published by manufacturers and consultancies. Equivalent immission levels in dB(A) of wind turbine sound outside the dwelling of each respondent were calculated in accordance with ISO-9613 (1993) for a wind speed of 8 m/s at 10 m height and a wind profile in a neutral atmosphere. The sound levels at each respondent's dwelling due to all wind turbines in the area were summarized logarithmically.

In the European Union, two time averaged sound levels are now recommended: Lden and Lnight. Lden is the average sound pressure level (A-weighted) over a longer period of time, including a penalty of 5 dB(A) in the evening and 10 dB(A) at night; Lnight is the average sound pressure level (A-weighted) over the night time period only (EU, 2003). We will use the difference between Lden from wind turbines and Lden from road traffic, as Lden is the usual metric related to annoyance. Lnight would be a more proper choice when investigating sleep disturbance. The calculated immission levels (at 8 m/s wind speed) were transformed into levels of day–evening–night values (Lden) by adding 4.7 dB as proposed by van den Berg (2008). In this article all sound levels are expressed in dB(A) Lden.

The Dutch National Institute for Public Health and the Environment (RIVM) supplied calculated day–evening–night sound immission levels (Lden) due to road, air and rail traffic in 5 dB intervals and for a 25 m by 25 m grid over the entire country. The levels are based on traffic volumes in 2002. Mopeds, motor bicycles, and local traffic on minor roads are not included in the road traffic sound level, and overflying (i.e. not taking of or landing) aircraft are not included in the aircraft sound level. For (nearly) all respondents there is no railroad or airport nearby, so road traffic will dominate the Lden value. The Lden values of background (=not wind turbine) sound ,thus, are an approximation of the road traffic sound level. For each respondent the value at the nearest grid point has been used. To obtain a best approximation for the road traffic sound level, the midpoint value of each interval (2.5 dB below the maximum value of the interval) is used.

2.2. Statistical analyses

In the questionnaire annoyance was measured with several questions. It was therefore possible to derive factor scores for annoyance with turbine sound (5 items, Cronbach's alpha=0.892) and for annoyance with road traffic sound (6 items, Cronbach's alpha=0.863). Such factors scores are a more reliable measurement of annoyance than if only the response to one question is used. In this case, principal component analyses were used. The

derived factors have a mean value of 0 and a standard deviation of 1. A factor score below 0 means lower than average of the total sample, a factor score above 0 higher than average.

Symptoms of stress were also measured with several items of which six were suitable for constructing a factor score as described above (Cronbach's alpha=0.840). The six items were: feeling tense or stressed, feeling irritable, having mood changes, being depressed, suffering from undue tiredness and having concentration problems.

The study sample was divided into three sub-samples corresponding to the difference between the level of wind turbine and road traffic sounds. In the 'WT dominant' sub-sample the level of wind turbine sound for each respondent was more than 5 dB higher than the level of road traffic sound. In the 'RT dominant' sub-sample the reverse is true. In the 'No dominant source' sub-sample the difference between the two sound levels was 5 dB or less. The 5 dB cut-off approach has previously been used by, for example, Cremezi et al. (2001) and Lim et al. (2008).

Differences between sub-samples were tested with ANOVA for continuous variables and Chi-square test for binary variables. Associations between two variables were tested with the Pearson's moment correlation (r) for continuous variables, the Spearman's rank correlation (r_s) for ordinal scales and with the Mann–Whitney U-test for differences between sub-samples (Z_{MWU}). The association between several independent variables and one dependent variable was tested in models using multiple linear regression. The association between several independent variables and two dependent variables was tested with multivariate general linear model. A p-value <0.05 was taken as an indication of statistical significance, though the number of tests were carried out calls for precaution. All respondents had not answered all questions in the questionnaire. Missing cases were not substituted in any way, while some analyses include a lower number of respondents than the total number in the study. The number of respondents are noted in the tables listing the results of multiple or multivariate modelling.

2.3. Overview of variables used in the analyses

The following variables were used in the analyses:

- WT sound: wind turbine sound outside the dwelling of the respondent; WT sound level is Lden in dB(A) on a continuous scale.
- RT sound: road traffic sound outside the dwelling of the respondent; RT sound level is Lden in dB(A) in 5 dB intervals, but here treated as a continuous scale.
- WT annoyance: annoyance with wind turbine sound. Factor score. continuous scale. Five items: (i) "Below are a number of items that you may notice or that could annoy you when you spend time outdoors at your dwelling. Could you indicate whether you have noticed these or whether these annoy you." (sound from wind turbines; 5-point verbal scale from "do not notice" to "very annoyed"), (ii) same question but indoors, (iii) "To what extent are you affected by wind turbines in your living environment? Please indicate for each item whether you notice or are annoyed by it in your living environment." (sound from rotor blades; 5-point scale verbal from "do not notice" to "very annoyed"), (iv) "To what extent are you annoyed by the sound of wind turbines when you are outdoors at your dwelling?" (11-point scale from 0="I am not at all annoyed" to 10="I. am extremely annoyed"), and (v) the same but for indoors.
- RT annoyance: annoyance with road traffic sound. Factor score. Continuous scale. Six items: (i) "Below are a number of items that you may notice or that could annoy you when you spend time outdoors at your dwelling. Could you indicate whether you have noticed these or whether these annoy you." (road traffic sound; 5-point verbal scale from "do not notice" to "very annoyed"), (ii) same question but sound indoors, (iii) "To what extent are you affected by busy roads in your living environment? Please indicate for each item whether you notice or are annoyed by it in your living environment." (sound indoors; 5-point scale verbal from "do not notice" to "very annoyed"), (iv) same question but sound outdoors, (v) "To what extent are you annoyed by the sound of busy roads when you are outdoors at your dwelling?" (11-point scale from 0="I am not at all annoyed" to 10="I am extremely annoyed"), and (vi) the same but for indoors.
- Hear wind turbines: no or yes as answer of the question "Can you hear a wind turbine from your dwelling or your garden/balcony?"
- Hear busy road: no or yes as answer to the question "Can you hear the sound of busy roads from your residence or garden/balcony?"
- WT visibility: no or yes as answer to the question "Can you see a wind turbine from your dwelling or your garden/balcony?"
- RT visibility: no or yes as answer of the question "Can you see a busy road from your residence or garden/balcony?"
- WT attitude: attitude towards wind turbines, measured with the question "What is your opinion on the impact of wind turbines on the landscape scenery?" on a 5-point scale from "very positive" to "very negative" and dichotomized into "not negative" (point 1, 2 or 3) and "negative" (point 4 or 5).
- RT attitude: attitude towards road traffic, measured with the question "What is your opinion on the impact of busy roads on the landscape scenery?" on a 5-point scale from "very positive" to "very negative" and dichotomized into "not negative" (point 1, 2 or 3) and "negative" (point 4 or 5).
- Noise sensitivity: noise sensitivity measured on a 5-point scale from "not at all sensitive" to very sensitive and dichotomized into "not sensitive" (scale point 1, 2 or 3) and "sensitive" (scale point 4 or 5).
- Stress: factor score constructed from six items with a 4-point scale rated from "(almost) never" to "(almost) daily". Continuous scale with zero as mean value and standard deviation 1.

3. Results

3.1. Descriptive

The mean levels of wind turbine and road traffic sound in each of the three sub-samples are shown in Table 1 together with response to the sounds and variables possibly influencing the response. The mean Lden of wind turbine sound as well as road traffic sound differed significantly among the sub-samples (all $p<0.001$) with the highest WT sound levels in the WT dominant sub-sample and the highest RT sound levels in the RT dominant sub-sample. In the WT dominant sub-sample a larger proportion of respondents could hear the wind turbine sound ($p<0.001$), was annoyed by the sound ($p<0.001$), and could see wind turbines from their dwellings ($p<0.001$), in comparison to the other two sub-samples. Also a larger proportion of respondents was negative to the impact of wind turbines on the landscape scenery in the WT dominant sub-sample than in the other sub-samples ($p<0.001$), and, vice versa, a larger proportion of respondents in the RT dominant sub-sample was negative to the visual impact of busy roads ($p<0.001$). No significant differences

Table 1
Description of sound levels, response to sound and variables possibly influencing the response in the three sub-samples.

	WT dominant (n=150)	No dominant source (n=230)	RT dominant (n=338)
WT sound Lden in dB(A), mean (SD)	46.5 (5.5)	40.7 (5.6)	36.2 (4.3)
RT sound Lden in dB(A), mean (SD)	31.6 (4.9)	40.9 (5,.5)	42.5 (5.5)
Difference between WT and RT sound Lden, mean (SD)	15.1 (4.9)	−0.2 (4.0)	−14.7 (4.9)
Age, mean (SD)	50 (13)	53 (15)	57 (15)
Gender, %male	47	56	46
Hear wind turbines, %yes	82	49	28
Hear busy road, %yes	32	50	59
WT annoyance, mean (SD)	0.29 (0.96)	0.08 (1.06)	−0.21 (0.93)
RT annoyance, mean (SD)	−0.34 (0.65)	−0.08 (0.93)	0.20 (1.12)
Noise sensitive, %sensitive	24	31	30
WT visibility, %yes	91	71	53
RT visibility, %yes	48	50	41
WT attitude, %negative	30	34	40
RT attitude, %negative	13	18	21
Economical benefits from WT, %yes	41	11	3
Stress, mean (SD)	0.01 (1.02)	−0.06 (0.89)	0.03 (1.06)

Table 2
Difference between levels of WT sound and RT sound at 5-Lden intervals of WT sound in the three sub-samples.

	WT dominant			No dominant source			RT dominant		
WT sound intervals Lden	WT sound mean Lden	RT sound mean Lden	*Diff*	WT sound mean Lden	RT sound mean Lden	*Diff*	WT sound mean Lden	RT sound mean Lden	*Diff*
30–35				33.4	35.4	*2.0*	32.9	48.7	*15.8*
35–40	37.5	27.5	*10.0*	37.2	38.6	*1.4*	37.7	50.2	*12.5*
40–45	42.0	28.8	*13.2*	42.4	41.8	*0.5*	41.9	56.7	*14.8*
45–50	47.4	32.7	*14.7*	47.4	46.1	*1.4*	47.4	59.6	*12.1*
50–55	52.3	34.2	*18.1*	51.8	50.0	*1.8*			

between the sub-samples were found for noise sensitivity and stress. More than 40% of the respondents in the WT dominant sub-sample benefited economically from the wind turbines, in comparison with 11% in the no dominant source ($p<0.001$) and 3% in the RT dominant sub-sample ($p<0.001$). Economical benefits decreased the possibility for noise annoyance, but not the possibility to hear the sound (Pedersen et al., 2009). Economical benefits are thus an important moderating factor and should therefore be considered in the analyses when annoyance is explored.

Table 2 shows the differences between levels of WT and RT sounds in relation to 5-dB(A) intervals of wind turbine sound. The WT sound levels clearly exceeded the RT sound levels at all intervals in the WT dominant sub-sample. Similar, the RT sound clearly exceeded the WT sound in the RT dominant sub-sample.

3.2. Possibility to hear wind turbine sound in different levels of background sound

The proportion of respondents that could hear a wind turbine from their dwelling or garden/balcony increased with increase in levels of wind turbine sound as expected. However, in the WT dominant sub-sample the possibility of hearing the wind turbine sound remained constant for WT sound levels up to 50 dB(A) and at levels up to 45 dB(A) the proportion of respondents that could hear the sound was larger than in the other sub-samples (Fig. 1). At levels below 45 dB(A) the difference between the WT dominant sub-sample and the others was statistically significant ($Z_{MWU}=-3.01$, $p<0.01$; $Z_{MWU}=-3.22$, $p<0.01$). Fig. 1 looks the same when respondents who benefited economically are excluded (data not shown).

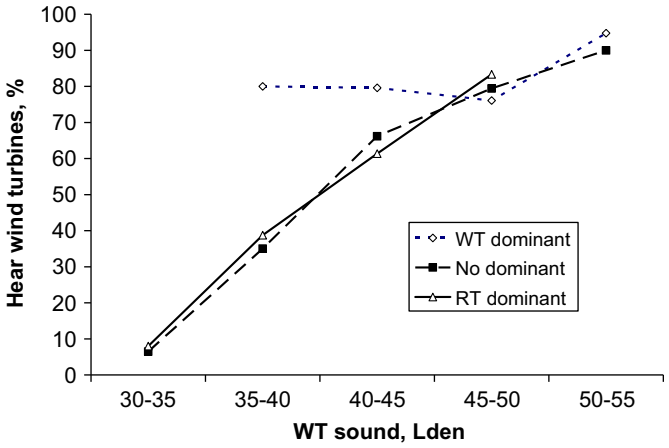

Fig. 1. Proportion of respondents that could hear wind turbine sound at their dwelling or garden/balcony (%) related to levels of wind turbine sound (Lden) for sub-samples with either WT or RT sound as the dominant sound or none of both. All respondents (n=706). Only points representing >5 respondents are depicted.

3.3. Annoyance with wind turbine noise in different levels of background sound

Annoyance with wind turbine noise increased with increase in levels of wind turbine sound (r=0.374, n=622, $p<0.001$) and was approximately the same in the three sub-samples at lower levels (<45 dB(A)) of wind turbine sound (Fig. 2). Although annoyance was highest in the sub-sample dominated by road traffic sound at 45–50 dB(A) WT sound levels, this difference was not statistically significant.

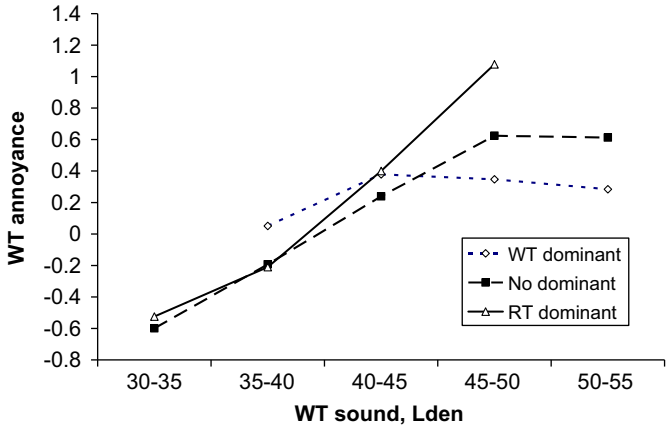

Fig. 2. Mean annoyance score for wind turbine noise in relation to sound levels of wind turbine sound (Lden) for sub-samples with either WT or RT sound as the dominant sound or none of both. All respondents (n=617). Only points representing >5 respondents are depicted.

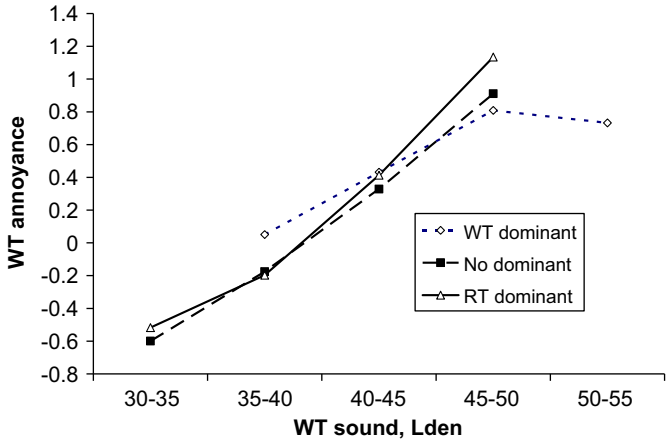

Fig. 3. Mean annoyance score for wind turbine noise in relation to levels of wind turbine sound (Lden) for sub-samples with either WT or RT sound as the dominant sound or none of both. Only respondents that did not benefit economically from wind turbines (n=511). Only points representing >5 respondents are depicted.

Of the respondents that owned wind turbines or otherwise had economical interests in wind turbines (n=100), 64% belonged to the sub-sample dominated by wind turbine sound (Table 1). These respondents showed very little or no annoyance from WT sound. When they were withdrawn from the sample no differences in annoyance scores remained between sub-samples at any level of wind turbine sound (Fig. 3); differences of mean annoyance scores were tested for each interval of sound level and found to be not statistically significant. A comparison between Figs. 2 and 3 shows that the mean value of annoyance with wind turbine sound is in both figures is the same in the RT dominant sub-sample but higher in Fig. 3 than in Fig. 2 for the two other sub-samples. This is in agreement with the fact that almost no one in the RT dominant sub-sample benefited economically from wind turbines and therefore this annoyance score was indifferent to the withdrawal of respondents with economical benefits.

The observation that annoyance with wind turbine noise was *not* lower in the sub-sample dominated by road traffic sound could be due to differences between the sound levels being too small for a masking effect to occur. Also, the average differences between the two sound levels were rather similar for all intervals of WT sound. To investigate this the no dominant sound and RT dominant sub-samples were taken together and divided into

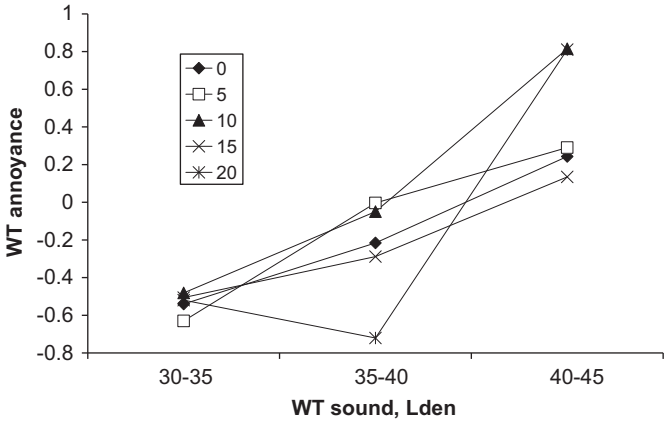

Fig. 4. Mean annoyance score for wind turbine noise in relation to levels of wind turbine sound (Lden) for five situations where RT sound level exceeds WT sound level with 0–5, 5–10, 10–15, 15–20 or >20 dB(A) Lden.

groups with levels of RT sound exceeding those of WT sound with 0–5, 5–10, 10–15, 15–20 or >20 dB(A) in order to explore a possible masking effect when the difference increased. Fig. 4 shows that WT annoyance was reduced when the RT sound level exceeded WT sound level with 20 dB(A), but only in the WT sound interval 35–40 dB(A). This reduction in WT annoyance was significantly different only with respect to the WT annoyance where RT sound exceeded WT sound with 5–10 dB(A) ($t=-0.69$, $p<0.05$); no other differences were statistically significant.

Thus, Fig. 4 indicates that there is a decrease in the WT annoyance and thus a possible masking effect from RT sound at an intermediate level of WT sound, but this masking effect vanishes at higher levels of WT sound for all levels of RT sound studied. A possible synergetic effect at these high levels is explored in the next paragraph.

3.4. Interaction effects between annoyance with wind turbine and road traffic noise

The influence of annoyance with road traffic noise on the relationship between sound levels and wind turbines was modelled with multiple linear regression within the total sample and the three sub-samples. Both respondents that benefited economically and those that did not were included, but all models were adjusted for economical benefits from wind turbines. The continuous annoyance score for wind turbine noise was assigned as dependent variable. The direct influences of the two sound levels were first explored for WT sound only, then WT sound and RT sound simultaneously. Annoyance with wind turbine noise increased with increase in levels of wind turbine sound in the total sample, and road traffic sound at higher or lower levels had no influence on this (Table 3, model 2) as already seen in Fig. 3. Annoyance with road traffic noise was in the third model entered into the regression to explore a possible enhancing effect on annoyance with wind turbine noise (Table 3, model 3). Annoyance with road traffic noise was correlated with sound levels of road traffic (r=0.387, n=587, $p<0.001$), but this correlation did not change the outcome of the regression: WT annoyance did not change substantially when RT sound level was removed (Table 3, model 4). When exploring the sub-samples, road traffic sound level was found to have a negative effect, i.e. a masking effect, on annoyance (Table 3, model 3) with wind turbine noise in the sub-sample dominated by road traffic sound, but not in the others. This reduction due to RT sound *level* was, however, balanced by an increase in WT annoyance caused by RT *annoyance*. Noise annoyance with road traffic was associated with noise

Table 3
Linear regression models exploring the influence of wind turbine sound, road traffic sound and annoyance from road traffic sound, on annoyance with wind turbine sound. Independent variables in the models are wind turbine sound level and/or road traffic sound level and/or road traffic noise annoyance.

	Total		**WT dominant**		**No dominant**		**RT dominant**	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Model 1[a], *R-square*[b]	*0.20 (n=609)*		*0.07 (n=145)*		*0.22 (n=201)*		*0.21 (n=263)*	
WT sound	**0.53**	**<0.001**	0.19	0.054	**0.152**	**<0.001**	**0.047**	**<0.001**
Model 2[a], *R-square*[b]	*0.20 (n=609)*		*0.09 (n=145)*		*0.25 (n=201)*		*0.22 (n=263)*	
WT sound	**0.53**	**<0.001**	0.13	0.220	**0.39**	**<0.001**	**0.51**	**<0.001**
RT sound	0.02	0.571	0.11	0.260	**0.18**	**<0.05**	−0.09	0.166
Model 3[a], *R-square*	*0.25 (n=525)*		*0.08 (n=122)*		*0.29 (n=159)*		*0.27 (n=244)*	
WT sound	**0.50**	**<0.001**	0.21	0.087	**0.35**	**<0.001**	**0.51**	**<0.001**
RT sound	−0.06	0.137	0.04	0.712	0.08	0.433	**−0.17**	**<0.05**
RT annoyance	**0.24**	**<0.001**	0.10	0.283	**0.30**	**<0.001**	**0.23**	**<0.001**
Model 4[a], *R-square*	*0.25 (n=525)*		*0.08 (n=122)*		*0.29 (n=159)*		*0.26 (n=244)*	
WT sound	**0.51**	**<0.001**	**0.24**	**<0.05**	**0.40**	**<0.001**	**0.43**	**<0.001**
RT annoyance	**0.22**	**<0.001**	0.10	0.102	**0.32**	**<0.001**	**0.18**	**<0.01**

[a] Adjusted for economical benefits from wind turbines.
[b] *R*-square for the model, i.e. the proportion of variation in the dependent variable explained by all the independent variables in the model.

Table 4
Associations between explorative variables (tested one by one) on the one hand and annoyance with wind turbine and road traffic noises on the other hand, respectively.

	WT annoyance		**RT annoyance**	
WT sound	r=0.374	$\mathbf{p<0.001}$	r=0.027	p=0.513
RT sound	r=−0.029	p=0.474	r=0.387	$\mathbf{p<0.001}$
Age	r=0.012	p=0.775	r=0.002	p=0.965
Gender	Z_{MWU}=−1.20	p=0.231	Z_{MWU}=−0.06	p=0.956
Noise sensitive	r_s=0.127	$\mathbf{p<0.01}$	r_s=0.343	$\mathbf{p<0.001}$
WT visibility	Z_{MWU}=−12.99	$\mathbf{p<0.001}$	Z_{MWU}=−1.51	p=0.131
RT visibility	Z_{MWU}=−5.57	$\mathbf{p<0.001}$	Z_{MWU}=−9.34	$\mathbf{p<0.001}$
WT attitude	r_s=0.289	$\mathbf{p<0.001}$	r_s=0.153	$\mathbf{p<0.001}$
RT attitude	r_s=0.118	$\mathbf{p<0.01}$	r_s=0.279	$\mathbf{p<0.001}$
Economical benefits from wind turbines	Z_{MWU}=−3.14	$\mathbf{p<0.01}$	Z_{MWU}=−2.06	$\mathbf{p<0.05}$
Stress	r=0.128	$\mathbf{p<0.01}$	r=0.177	$\mathbf{p<0.001}$

annoyance due to wind turbines in the sub-sample dominated by road traffic sound and that with no dominance, but not in the WT dominant. Also, none of the models explained more than 9% of the variance of annoyance with wind turbine noise in the WT dominant sub-sample meaning that other factors must be of importance in this sub-sample. In the total sample WT sound predicted 20–25% of the WT annoyance, but there was also a relationship between annoyances with the two sounds so that an increase in annoyance with road traffic sound increased annoyance with wind turbine sound. This could be a synergetic effect, or the effect of common confounders such as noise sensitivity leading to annoyance with both sounds. Possible confounders were therefore investigated in the next step.

3.5. Possible confounders

The association between annoyance with wind turbine noise and road traffic noise that was found in the regression models could be due to other underlying factors influencing both. Possible factors are listed in Table 4 with their relation to WT and RT annoyances, respectively. As expected, levels of wind turbine sound and visibility of wind turbines were correlated with annoyance due to wind turbine noise, but not with annoyance due to road traffic noise. Age and gender were not associated to either annoyance score. Noise sensitivity, stress and being negative to the visual impact of wind turbines and/or roads on the landscape scenery were variables that were all positively correlated with both the annoyance scores. Both annoyance scores were also higher for those who could see busy roads, in comparison with those who could not, but WT annoyance was related to the visibility of wind turbines only. Also, both annoyance scores were higher for those who did not benefit economically from wind turbines.

Variables that were found to be associated with one or both the annoyance scores in Table 4 were tested in a multivariate general linear model in which the association between explorative and two dependent variables were tested simultaneously, including all respondents. Dose–response relationships between sound levels and annoyance were found for wind turbines and road traffic, respectively, but levels of one sound did not influence annoyance with the other sound (Table 5). Visibility of a source did only influence annoyance with that source, and, similar, attitude towards a source was only related to annoyance with that specific source. Noise sensitivity and symptoms of stress were associated with *both* annoyance due to wind turbine and road traffic sounds.

4. Discussion

The expectation that the presence of road traffic sound would reduce the prevalence of annoyance due to noise from wind turbines in general was not confirmed in this systematical

Table 5
Result of multivariate general linear model where the association between possible explorative variables (column 1) and the two measurements of annoyance were tested simultaneously (n=480).

	WT annoyance		RT annoyance	
	Adj. R-sq.[a]=0.43		Adj. R-sq.[a]=0.38	
	P eta[b]	p	P eta[a]	p
WT sound	**0.12**	< **0.001**	0.01	0.140
WT visibility	**0.06**	< **0.001**	0.00	0.865
WT attitude	**0.17**	< **0.001**	0.00	0.413
RT sound	0.00	0.615	**0.13**	< **0.001**
RT visibility	0.00	0.253	**0.11**	< **0.001**
RT attitude	0.00	0.942	**0.04**	< **0.001**
Noise sensitive	**0.01**	< **0.05**	**0.06**	< **0.001**
Stress	**0.01**	< **0.05**	**0.01**	< **0.05**

[a] R-square for the dependent variable, i.e. the proportion of variation in the dependent variable explained by all the independent variables in the model.
[b] Partial eta-squared value; describes the proportion of total variability attributable to a factor; adjusted for economical benefits from wind turbines.

analysis of a large data set. The relationships between sound levels and annoyance with the noise were in most cases separate for wind turbine and road traffic, respectively, and not interacting. Several interesting findings could however guide future planning for wind farms.

Wind turbine sound is, as found in other studies (Pedersen and Persson Waye, 2004; 2007), very easily perceived and about 80% of the respondent in this study could hear the sound at levels as low as 35–40 dB(A) Lden when background sound levels were low. Wind turbines were less easily heard when road traffic sound dominated over wind turbine sound, but this did not result in a change in annoyance: the dose–response relationship between levels of wind turbine noise and annoyance were about the same despite levels of road traffic sound. The exception is that high levels of road traffic sound (>55 dB(A)) did seem to have a masking effect on wind turbine sound, but only at moderate levels of wind turbine sound (35–40 dB(A)). This statistically significant finding was confirmed in the regression models where an *increase* in road traffic noise led to a *decrease* in annoyance of wind turbine noise in the sub-sample dominated by road traffic noise. This is consistent with previous findings (for the same data set) of a reduction of annoyance with wind turbine noise in rural areas with a main road as opposed to areas without (Pedersen et al., 2009). The effect at 35–40 dB(A) vanished when the wind turbine sound level increased further. It is hence possible to reduce the prevalence of annoyance with wind turbine noise if the turbines are placed in areas with high levels of road traffic noise, but the levels of wind turbine noise need to be held back even at these sites. The reduction as yet cannot be predicted due to the low number of respondents with road traffic noise exceeding wind turbine noise with more than 20 dB(A). An explanation for the low masking potential of even relatively high levels of background sound may be that the Lden background level in fact averages over fluctuations in traffic intensity and daily patterns (rush hour) and over slower variations related to weather (down/upwind). Wind turbine sound may not be masked at times of low background sound levels (the 'troughs' in the level over time) and these times may determine annoyance, perhaps independent of the time length of the exposure. Wind turbine sound levels do not follow the same behaviour as road traffic noise levels. Road traffic usually calms at night, whereas modern, tall wind turbines may produce more sound at night than in daytime. Also, there is less difference between downwind and upwind audibility due to the fact that the source is high above ground and thus for an upwind situation the sound shadow is further away than it is for a low source (road traffic). Only at relatively very high background sound levels, the troughs are not deep enough to reach the level of the wind turbine sound.

Except for the masking at 35–40 dB(A) wind turbine sound, no other effects were found. This study shows that being exposed to road traffic noise as well, did not lead to more annoyance related to wind turbine noise. The observed relation between annoyance with road traffic and wind turbine noises could be explained by common confounders, in this case noise sensitivity and stress. Noise sensitivity is usually not seen as a result of annoyance, but as a personal trait independent of exposure (Job, 1999). It is reasonable to believe that individual factors enhance the possibility of annoyance both with wind turbine and road traffic noises, and that no other interaction between annoyances with the two noise types takes place.

5. Application to wind farm planning

In the sometimes heated local debates about wind farm proposals it is important to consider the qualities of the proposed sites if the conversion from electricity generation based on fossil fuels to that of wind is to be successful and not cause adverse effects on residents and local communities. The presence of other noise sources such as road traffic is one of these qualities.

Residents near busy roads are less likely to oppose potential wind farm developments (van den Horst, 2007). Placing wind farms in areas with low background levels is more delicate. This is not unique for wind turbines; also annoyance due to aircraft noise is higher in low background sound regions in comparison to those with high background levels (Lim et al., 2008). It is not clear if indeed the differences in background levels between areas cause the difference in noise annoyance or another, possibly related factor such as landscape type. Landscape values are strongly related to the acceptability to wind farms; industrial areas and military grounds are considered suitable, while landscapes with natural and cultural preservation values are rated as not suitable (Wolsink, 2007).

The present study shows that road traffic noise can provide a significant masking of wind farm noise, but only at intermediate levels of wind turbine sound (35–40 dB(A)), not at higher or lower levels. This only occurs if the road traffic is substantially louder (+20 dB) than the wind turbines. These intermediate levels are within the range where most countries have noise limits for wind turbines (35–45 dB(A)).Thus, one would expect less noise annoyance from a not too near wind farm if residents are already exposed to road traffic sound levels of 55–60 dB(A).

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BEFORE THE PUBLIC UTILITIES COMMISSION
OF THE STATE OF SOUTH DAKOTA

IN THE MATTER OF THE APPLICATION BY CROWNED RIDGE WIND, LLC FOR A PERMIT OF A WIND ENERGY FACILITY IN GRANT AND CODINGTON COUNTIES	)))))	EL19-003 **CERTIFICATE OF SERVICE**

I hereby certify that true and correct copies of Robert McCunney's Rebuttal testimony and attachments in this matter were served electronically to the parties listed below on the 24th day of May, 2019, addressed to:

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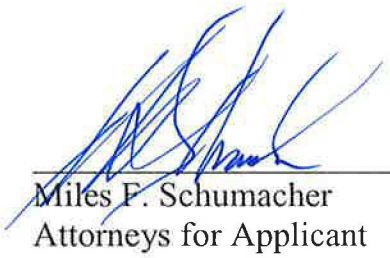

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