When Are Medication Side Effects Due to the Nocebo Phenomenon?

To the Editor: In their discussion of the nocebo phenomenon, Dr Barsky and colleagues[1] do not adequately address the issue of causality. Like the distinction between "adverse events" (which occur while receiving a drug, irrespective of causality) and "adverse drug reactions" (which have a plausible causal relationship to the drug), any discussion of the nocebo phenomenon should distinguish between adverse events occurring while receiving placebo vs those directly attributable to it. In the studies that Barsky et al cite as offering quantitative support for their position, it is not clear that this distinction has been made, since most clinical trials elicit adverse events by asking questions such as "Have you felt differently in any way since your last visit?" Because it is even more difficult to determine causality for placebos than for active drugs, it will be challenging to obtain accurate information on the magnitude of this important problem.

Robert H. Palmer, MD
Forest Laboratories, Inc
New York, NY

1. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA.* 2002;287:622-627.

To the Editor: I would like to add 3 clarifications to the article by Dr Barsky and colleagues on nonspecific medication side effects and the nocebo phenomenon.[1] First, following the model suggested by Hahn,[2] a distinction must be made between the nocebo phenomenon and placebo side effects. According to Hahn, the nocebo hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause such symptoms in patients who expect them. Placebo side effects, on the other hand, occur when expectations of healing produce sickness; that is, when a positive expectation has a negative outcome. Likewise, nocebos may also have side effects; that is, when negative expectations produce positive outcomes or outcomes other than those expected. This distinction is not just a matter of semantics. I suspect that much of what is labeled as the "nocebo phenomenon" represents, in fact, placebo side effects. In patients who somaticize and in those who are diffusely pessimistic, distinguishing between the 2 concepts admittedly may be difficult. The key is that expectations play a causal role in health and healing as well as in sickness.[3]

Second, the assertion that in clinical trials placebo side effects " . . . could reduce the treatment effect"[1] needs more elucidation. Not all placebos are alike. Whereas the most common form of placebo is inactive, other placebos are active, that is, they produce detectable side effects without any therapeutic effects. For example, in the double-blind evaluation of tricyclic antidepressants, atropine can be used in the control group to mimic side effects, thus decreasing the likelihood that either investigators or subjects would infer the correct treatment assignment. Indeed, there are indications that the difference in effectiveness between active drug and placebo is markedly less when an active drug is compared with an active placebo.[4] Thus, recent reviews have emphasized the importance of an active placebo control group in drug efficacy trials, due to their superior capacity to maintain blinding.[4]

Finally, direct evaluation of drug effects, expectancy effects, and their interactions can best be obtained by the balanced placebo design, which yields a 2×2 matrix comprising 4 conditions in which subjects are (1) told they will get a drug and receive the drug, (2) told they will get a drug but receive placebo, (3) told they will not get a drug but receive the drug in disguised form, and (4) told they will not get a drug and receive no drug.[5] I recommend that this design be used more often in clinical trials of efficacy evaluation.

Opher Caspi, MD, MA
Program in Integrative Medicine
University of Arizona
Tucson

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To the Editor: Dr Barsky and colleagues[1] discuss mechanisms by which patients who receive placebos may report adverse effects (the "nocebo phenomenon"). While they identify several important factors, such as misattribution of temporally coincident symptoms and perhaps conditioning, they do not consider that placebo ingredients may produce symp-

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toms. There are no regulations dictating what constitutes a placebo; placebo constituents are seldom reported, precluding accountability and input regarding effects of these constituents, and there is no foundation for the assumption that any placebo constituent is truly physiologically inert.[2-4]

Even substances that are not absorbed can have effects. Sugar pills may affect blood insulin levels with their cascade of physiological effects, and a lactose "placebo" reportedly led to increased dropout rates in the control group in a study of patients with the human immunodeficiency virus, who have high rates of lactose (and sucrose) intolerance[5]; similarly, lactose placebos were a possible source of markedly increased gastrointestinal side effects in the placebo group in a study of patients with cancer.[6] Subjects may react to excipients, stabilizers, dyes, or other elements, and I have cared for one patient whose painful unilateral neuropathy symptoms were ultimately traced—in repeated n-of-1 blinded comparison—to magnesium stearate, a common lubricant in pill formulation.

Apparent positive, negative, or neutral effects of an active drug could be spurious consequences of a negative, positive, or same direction results of a placebo, and there are cases in which such effects appear to have occurred.[2] Inconsistent findings across studies could result, in some instances, from differences in the agent to which the active drug is compared. But even if placebo constituents have no impact on the primary outcome being studied, the assumption that they can have no effect on adverse symptoms is unsupportable.

Thus, physiological effects of the placebo ingredients—in addition to factors like misattribution or perhaps suggestibility—may influence nocebo effects. Because the manufacture of placebos and designation of their composition are often determined by the companies that manufacture the drug under study, and because the composition is typically unreported, there is potential for conflict of interest in selection of ingredients. For many reasons, then, the full disclosure of both placebo and active drug preparations should be reported.

Beatrice Golomb, MD, PhD
Department of Medicine
University of California, San Diego, School of Medicine
La Jolla

1. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA.* 2002;287:622-627.
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To the Editor: Dr Barsky and colleagues[1] observe that patients who somatize or who are anxious or depressed have better recollection of side effects to antidepressant therapy. While I agree with this observation, there is little support for their suggestion of a collaborative strategy to treat anxious, depressed, or somatizing patients. Depressed patients with elevated anxiety and somatic symptoms receiving usual care for depression have been found to adhere well to antidepressant therapy, and their anxiety and somatization improve with treatment of depression.[2,3]

In their list of psychological characteristics associated with side effects, I believe that Barsky et al missed 2 characteristics—health concerns and conversion—that have been shown to also predict the important clinical outcome of nonadherence in depressed primary care patients.[3] Depressed patients with elevated levels of health concerns and conversion appear to interpret side effects as worsening overall health status and are less likely to adhere to antidepressant therapy. The collaborative strategy and reattribution process outlined by Barsky et al may be more appropriately applied to this subgroup of depressed patients. Researchers investigating nonadherence, side effects, and the nocebo effect may want to incorporate psychometric instruments measuring health concerns and conversion along with the more common measures for somatization, anxiety, and depression.

Robert Keeley, MD
Department of Family Medicine
University of Colorado Health Sciences Center
Denver

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In Reply: These letters underscore how complex and complicated a topic the nocebo phenomenon is and how important precise terminology becomes. We agree with Dr Palmer that "adverse events" are distinct from "side effects" and not all adverse events are attributable to the placebo or to the drug. In clinical practice, however, this distinction may be all but impossible to make. This is why we defined "side effects" as any unintended adverse symptom that the patient attributed to the drug. Several of these letters refer to the role of expectancy in the occurrence of side effects, and Dr Caspi accurately points out that the term "nocebo" most properly refers to symptoms that occur when the suggestions, instructions, and/or expectations accompanying the placebo are negative, as exemplified by hexing and voodoo curses. This has been distinguished from "placebo side effects," which occur when the explicit intent and expectations accompanying the placebo are positive and beneficial. In clinical practice, obviously, physicians do not prescribe medication with harmful intent and therefore it is only the patient's negative expectations that are relevant.

These letters also point out the complexities inherent in the placebo notion itself. Thus, Caspi notes that several types of placebo may be used in controlled trials. Although most pla-

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cebos are devoid of all pharmacological activity, a more sophisticated variant is a placebo that produces symptoms resembling the side effect profile of the active drug it is being compared with. Dr Golomb points out that even placebos assumed to be chemically inert may actually have physiological actions that produce symptoms. We agree with her suggestion that the composition of the placebo used in each study should be reported explicitly.

Finally, as Dr Keeley notes, side effect reporting is related to the problem of nonadherence. We agree that the combination of depression and elevated health concerns may be particularly likely to result in nonadherence to the therapeutic regimen.

Arthur J. Barsky, MD
Malcolm P. Rogers, MD
Jonathan F. Borus, MD
Brigham and Women's Hospital and Harvard Medical School
Boston, Mass

Should Physicians Address Patients' Spiritual Needs?

To the Editor: The article by Dr Lo and colleagues[1] recommends practical approaches for clinicians exploring the spiritual crises of gravely ill patients. We agree with Lo et al that the roles of physician and pastoral counselor should be separate in the early stages of the relationship because patients and their families may not be prepared initially to trust or understand the role of such a fused figure. However, as the patient-physician relationship develops, we believe that it may be of value to both the patient and the caregivers for the physician to explore the patient's existential and spiritual concerns. For physicians to attain the self-confidence to perform this function, however, requires a deeper understanding of the issues than can be provided by reading an article on practical guidelines. Our experience in a clinical pastoral education program modified for clinicians[2] provided us with the skills, language, and experience to carry out the valuable recommendations of Lo et al.

Spiritual distress is also experienced by caregivers of critically ill patients. For example, in our neonatal intensive care unit, only 4% of staff surveyed denied experiencing suffering in their work and 83% reported privately praying for their infant patients.[3] Many patients have expressed a wish to have their spiritual and religious concerns addressed by the physician. It behooves the medical profession to respond in a constructive way, recognizing both patients' and physicians' spiritual and religious needs.

Elizabeth A. Catlin, MD
I. David Todres, MD
Ethics and Spiritual Support Unit
MassGeneral Hospital for Children
Boston, Mass

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This letter was shown to Dr Lo, who declined to reply.—ED.

RESEARCH LETTERS

Frequency of Inappropriate Metformin Prescriptions

To the Editor: Metformin is commonly used in the management of type 2 diabetes. More than 25 million prescriptions for metformin were written in 2000, making it the most commonly prescribed branded diabetes medication in the United States.[1] Metformin has been associated with the development of lactic acidosis, and since its initial marketing in 1995 the US Food and Drug Administration (FDA) has required a "black box" warning in the package insert.[2,3] Labeled contraindications include renal dysfunction and congestive heart failure (CHF) requiring pharmacologic treatment.[4] We sought to determine the frequency of metformin use in a sample of patients with these 2 primary contraindications to therapy.

Methods. We performed a retrospective chart review of patients receiving metformin through our outpatient pharmacy at an academic medical center. Institutional review board approval was obtained, and all patients with 2 or more prescriptions for metformin processed between January 1, 2000, and September 30, 2000, were identified. These patient records were randomized using a random number generator (SAS v6.12, SAS Institute Inc, Cary, NC).

The prevalence of inappropriate prescriptions for metformin was defined as the percent of patients receiving metformin who had documented CHF or renal dysfunction. Patients were considered to have CHF if the diagnosis was included in the medical problem list or clinic notes, and if they were taking medications for CHF (diuretics, angiotensin-converting enzyme inhibitors, digoxin). Renal dysfunction was defined as a serum creatinine greater than 1.5 mg/dL (132.6 μmol/L) for men and greater than 1.4 mg/dL (123.8 μmol/L) for women. Patient records were also reviewed for documentation of functional cardiac status or evidence that contraindications were considered.

Results. Pharmacy records identified 241 patients with 2 or more prescriptions for metformin; 100 of these were randomly selected for chart review. Twenty-two patients (22%; 95% confidence interval, 14%-30%) were found to have either CHF requiring medications or renal insufficiency. Of these 22 patients, 14 had CHF only, 5 had renal insufficiency only, and 3 had both. For patients with contraindications to metformin, the mean age was 60 years, 50% were women, and 50% were African American. These characteristics were similar for patients without contraindications. Patients with contraindica-

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tions did have a significantly longer duration of diabetes (14.2 vs 6.4 years; $P<.001$).

Of the 17 patients with CHF, 4 patients had a documented New York Heart Association functional classification (class II: n=2; class III: n=2). Of the 8 patients with renal dysfunction, the mean serum creatinine was 1.8 mg/dL (159.1 µmol/L) and mean blood urea nitrogen was 27 mg/dL (9.639 mmol/L). Only 2 patients had documentation in the medical record that providers considered metformin contraindications.

Comment. In our review, almost one quarter of patients with a prescription for metformin had 1 or more absolute contraindications. Several recent studies in Europe have documented similar rates of inappropriate metformin prescribing.[2,5,6]

Adverse event reports suggest the incidence of metformin-associated lactic acidosis is between 1 in 10 000 to 1 in 100 000 patient-years.[7] In the first 14 months after its release in the United States, the FDA received 47 confirmed cases of lactic acidosis associated with metformin, with a 42% mortality rate. More than 90% of patients had relative or absolute contraindications to metformin.[3]

Because our assessment of the prevalence of contraindications to metformin use relies on a chart review, it may underestimate the frequency of contraindications and it is difficult to determine whether clinicians are aware they are prescribing metformin against a black-box warning. Nonetheless, our results suggest that metformin frequently may be inappropriately prescribed despite black-box contraindications. Documentation of this potential risk in the medical record is limited and health care providers should consider improving the documentation of the risk of lactic acidosis and provide appropriate counseling for patients who receive the drug.

Cheryl Horlen, PharmD
School of Pharmacy
Campbell University
Buies Creek, NC

Robb Malone, PharmD, CDE
Betsy Bryant, PharmD, CDE
Department of Medicine
University of North Carolina
Chapel Hill

Betty Dennis, PharmD, MS, CDE
University of North Carolina Hospital Pharmacy
Chapel Hill

Tim Carey, MD, MPH
Mike Pignone, MD, MPH
Russell Rothman, MD, MPP
Department of Medicine
University of North Carolina
Chapel Hill

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Skeletal Muscle Glucocorticoid Receptor Density and Insulin Resistance

To the Editor: In Cushing syndrome, elevated plasma cortisol levels cause insulin resistance, hyperglycemia, hypertension, and dyslipidemia. In patients without Cushing syndrome, these cardiovascular risk factors are associated with more subtle elevations in plasma cortisol concentrations[1] and enhanced tissue responsiveness to glucocorticoids.[2] We explored the possibility that insulin resistance in patients without Cushing syndrome involves dysregulation of glucocorticoid receptor (GR) expression in muscle.

Methods. We obtained biopsies of vastus lateralis skeletal muscle under local anesthesia from 23 men without fasting hyperglycemia participating in the the Uppsala Longitudinal Study of Adult Men.[3] As previously described, participants underwent a 75-g oral glucose tolerance test, euglycemic hyperinsulinemic clamp, and ambulatory blood pressure recording. Height, weight, and waist and hip circumferences were measured. Glucocorticoid receptor messenger RNA (mRNA) levels were measured in muscle total RNA using a quantitative reverse transcriptase (RT) polymerase chain reaction (PCR) assay with synthetic RNA competitors for GR mRNA and 18S mRNA as internal control. Both competitors contained 83 base pair deletions to distinguish PCR products derived from endogenous and synthetic RNAs.[4] The interassay coefficient of variation was 12%. Stata v5.0 (Stata Corp, College Station, Tex) was used for all analyses.

Results. Results are shown in the TABLE. After adjusting for body mass index (BMI), higher levels of skeletal muscle GR mRNA were associated with hypertension, higher insulin levels after a glucose load, and insulin resistance in a euglycemic hyperinsulinemic clamp. Muscle GR mRNA was not associated with plasma lipids, glucose, or BMI alone.

Comment. These data show that men with insulin resistance and hypertension have increased GR mRNA levels and, by inference, increased numbers of GRs in skeletal muscle. Glucocorticoid receptors mediate diverse effects on insulin sensitivity (in liver, adipose tissue, and skeletal muscle) and blood pressure (in kidney, blood vessels, and brain). Increased numbers of receptors in these sites could contribute to the association between features of the insulin resistance syndrome, and explain enhanced responsiveness to glucocorticoids.[2] Glucocorticoid receptors also contribute to negative feedback regulation of the hypothalamic-pituitary-adrenal axis. If receptor expression were similarly increased in central feedback sites, it might be expected that lower circulating cortisol levels would compensate for peripheral hypersensitivity.

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Table. Associations of GR mRNA Levels With Cardiovascular Risk Factors*

Risk Factor	Mean (SD)	Partial Correlation Coefficient†	*P* Value	*P* Value Adjusted for BMI
Fasting plasma glucose, mg/dL‡§	99.1 (16.2)	–.05	.80	.58
Fasting plasma insulin, μIU/mL‡§	1.5 (1.2)	0.41	.06	.09
Insulin 1 h postglucose, μIU/mL‡§	10.7 (6.8)	.53	.01	.02
Insulin sensitivity as M/I ($mg \cdot min^{-1} \cdot kg^{-1}[mU/1]^{-1}$)‖	5.2 (2.0)	–.36	.10	.05
24-Hour systolic blood pressure, mm Hg¶	142	NA	.05	.05
Triglycerides, mg/dL‡§	106.2 (79.6)	0.26	.24	.30
BMI, kg/m^2	26.3 (3.3)	0.16	.46	Reference
Waist-hip ratio	0.95 (0.05)	0.14	.53	.91

*GR indicates glucocorticoid receptor; mRNA, messenger RNA; BMI, body mass index; and NA, not applicable.
†All associations with GRs are adjusted for 18s mRNA.
‡Median and interquartile range are presented, but variables were $\log_e$ transformed for statistical comparisons.
§To convert mean (SD) glucose values to mM, multiply by 0.0555; to convert insulin values to pM, multiply by 6.945; to convert triglyceride values to mM, multiply by 0.0113.
‖M/I = glucose infusion rate ($g \cdot min^{-1}$) between 60 and 120 minutes of the euglycemic clamp divided by body weight (kg) and mean insulin level ($mU \cdot 1^{-1}$).
¶Associations with 24-hour mean ambulatory blood pressure were examined by censored normal regression to discount the effect of antihypertensive therapy. The 6 men receiving antihypertensive therapy and the 3 with untreated values above 150 mm Hg were allocated to the top tertile; median is presented and no partial correlation coefficient can be calculated.

However, dysregulation of GR expression appears to be tissue-specific. In an animal model of insulin resistance, dysregulation of GR expression was associated with increased GR mRNA in the liver but decreased GR mRNA in central negative feedback sites.[5] Further understanding of tissue-specific variations in GR expression and function may offer fundamental insights into the pathophysiology of insulin resistance and its association with hypertension.

Rebecca M. Reynolds, MRCP
Karen E. Chapman, PhD
Jonathan R. Seckl, PhD
Brian R. Walker, MD
Molecular Medicine Centre
University of Edinburgh
Western General Hospital
Edinburgh, Scotland

Paul M. McKeigue, PhD
London School of Hygiene and Tropical Medicine
London, England

Hans O. Lithell, PhD
Department of Geriatrics
Uppsala University
Uppsala, Sweden

Acknowledgment: Dr Reynolds is a Wellcome Trust Cardiovascular Research Initiative Clinical Training Fellow. Dr Walker is a British Heart Foundation Senior Research Fellow.

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