Nonspecific Medication Side Effects and the Nocebo Phenomenon

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Patients taking active medications frequently experience adverse, nonspecific side effects that are not a direct result of the specific pharmacological action of the drug. Although this phenomenon is common, distressing, and costly, it is rarely studied and poorly understood. The nocebo phenomenon, in which placebos produce adverse side effects, offers some insight into nonspecific side effect reporting. We performed a focused review of the literature, which identified several factors that appear to be associated with the nocebo phenomenon and/or reporting of nonspecific side effects while taking active medication: the patient's expectations of adverse effects at the outset of treatment; a process of conditioning in which the patient learns from prior experiences to associate medication-taking with somatic symptoms; certain psychological characteristics such as anxiety, depression, and the tendency to somatize; and situational and contextual factors. Physicians and other health care personnel can attempt to ameliorate nonspecific side effects to active medications by identifying in advance those patients most at risk for developing them and by using a collaborative relationship with the patient to explain and help the patient to understand and tolerate these bothersome but nonharmful symptoms.

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ALMOST 3 BILLION PRESCRIPTIONS are filled each year in outpatient settings in the United States, an increase of 50% since 1992.[1] Although many side effects (generally defined as an action of a drug other than the one for which it is being used) result directly from these drugs' pharmacological activity, many others cannot be attributed to their specific pharmacological actions. These nonspecific side effects distress patients, add to the burden of their illness, and increase the costs of their care. They may lead to nonadherence, cause physicians to discontinue what is otherwise an appropriate therapy, or prompt attempts to treat these side effects with additional drugs.

In this article, we use the nocebo phenomenon to explore the occurrence of adverse, nonspecific side effects in patients taking active medication and suggest ways in which clinicians can deal more effectively with them. Side effects occurring in patients taking active medication may be divided into 2 types. "Specific side effects" are symptoms or physiological changes that result directly from the specific biological and pharmacological activity of the drug and tend to be dose-dependent and predictable. "Nonspecific side effects" are symptoms or physiological changes that cannot be explained on the basis of the known pharmacology of the drug and are idiosyncratic and not dose-dependent. In theory, nonspecific side effects may be positive and beneficial or negative and adverse. In this article, we are concerned only with the latter, and in the interests of brevity will use the general term "nonspecific side effects" to refer only to negative or adverse symptoms or physical changes. Similarly, the term "side effects" will be used to refer to unintended adverse effects.

The nocebo phenomenon may help us understand (adverse) nonspecific side effects. The nocebo (meaning in Latin "I will harm") phenomenon refers to symptoms and/or physiological changes that follow the administration of an inert, chemically inactive substance that the patient believes to be an active drug. The term nocebo was originally coined to distinguish the noxious or distressing effects of a placebo (meaning in Latin "I will please") from its beneficial, therapeutic effects,[2-4] and in this article it will be used broadly to refer to all distressing symptoms that accompany placebo administration.

Methods

We conducted a focused review of articles relevant to the nature, incidence, magnitude, and medical management of nonspecific medication side effects. The MEDLINE database was searched for English-language articles from 1966 through the present, using the following Medical Subject Headings (MeSH) terms: *adverse effects, side effects, symptoms, nocebo, placebo, drug*

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reaction, and *ambulatory care*. The search was extended using the bibliographies of pertinent recent articles and reviews. Articles were screened for relevance based on the title, key words, and abstracts. Articles were reviewed, analyzed, and synthesized, but no formal meta-analysis was conducted for 2 reasons: first, this article is not intended to be a systematic or comprehensive summary of the literature, but rather a focused review. Second, the research is too variable in methods and quality for any standardized comparison. More weight, however, was given to empirical studies using more rigorous sample selection, comparison groups, more sophisticated analytic methods, and standardized assessment tools.

The Incidence and Nature of Nonspecific Side Effects

In 1995, drug-related adverse effects and illnesses were estimated to account for $76.6 billion in hospital costs and 17 million emergency department visits in the United States.[5] Most studies have focused on the incidence of serious side effects among hospitalized patients and little attention has been devoted to nonspecific side effects in ambulatory settings.[6-9] In general, only a small fraction of such side effects are reported,[10,11] due in part to uncertainty as to whether the symptoms were definitely caused by the medication. In one study of drugs commonly prescribed in primary care practice, 10.9% of reported adverse effects were clearly attributable to the medication, 68.7% were judged to be probably related, and 20.3% were thought possibly related.[12]

These nonspecific symptoms may arise from a variety of sources, since a large reservoir of preexisting, ambiguous somatic symptoms are available for attribution to a newly instituted medication. First, the symptoms of the underlying disease for which the patient is being treated may be mistakenly ascribed to the medication.[13] For example, in a randomized controlled trial of an analgesic device, 12% of the patients receiving a placebo device reported intensification of their preexisting pain.[14] Second, the symptoms may be the somatic concomitants of emotion (such as anxiety or depression) or of psychosocial stress. Third, patients may mistakenly ascribe the symptoms of mild infirmities or benign, self-limited ailments (such as headaches, cramps, and extrasystoles) or of normal physiological functioning (eg, orthostatic dizziness) to the medication. To explore the similarity between reported side effects and such endemic symptoms, Reidenberg and Lowenthal[15] ascertained the incidence of 25 commonly reported symptoms in healthy persons who were not taking any medicines. Thirty-nine percent reported fatigue, 26% difficulty concentrating, 23% drowsiness, 14% headache, and 5% dizziness[15]; only 19% of the respondents reported experiencing no symptoms in the previous 3 days. In a more recent study, Khosla et al[16] found that 73% of 236 healthy volunteers who were not taking any medications reported symptoms in the preceding 3 days. The most common were fatigue, headache, difficulty concentrating, and somnolence.

Thus, when a patient starts taking a new medication, there is already a large reservoir of bodily symptoms available for misattribution by the patient to the medication. This misattribution is more likely to occur in: (1) patients who expect to experience side effects; (2) patients who have been previously conditioned to experience side effects; (3) patients who have particular psychological characteristics; and (4) certain circumstances and conditions. Before discussing each of these 4 risk factors, however, it is necessary to review the nocebo phenomenon.

The Nocebo Phenomenon

The placebo effect is assumed to occur in patients taking active drugs and therefore to account for some fraction of that drug's total therapeutic effect. A placebo control group[17] is important in drug trials because it allows researchers to determine that fraction of the overall treatment effect that is attributable to the drug's specific, pharmacological activity. By analogy, we suggest here that some fraction of the side effects experienced by the patients taking an active drug can be attributed to the nocebo effect.[18]

Approximately one quarter of patients taking placebo report adverse side effects.[19,20] (In one striking example, hypervagotonia manifested by an idioventricular rhythm occurred with placebo administration in a double-blind study of a calcium channel blocker.[21]) Rosenzweig et al[22] found that 19% of healthy volunteers taking placebos in 109 double-blind, placebo-controlled trials spontaneously reported adverse side effects. In an earlier survey of 67 placebo-controlled trials, an average of 23% of patients taking placebo spontaneously reported at least 1 bothersome side effect.[23] When subjects are actively queried about side effects, a substantially higher incidence (between 27% and 71%) is found.[24-27]

In placebo-controlled trials for diseases that are largely asymptomatic, the incidence of nocebo side effects may equal or even exceed the incidence of side effects reported by patients taking the active drug. Thus, in trials of antihypertensive medications and agents to treat cerebrovascular insufficiency, side-effect rates among those taking placebo are comparable to those reported taking an active drug,[17,28-30] and headache in particular is more common among those taking placebo.[17,28] Many commonly reported nocebo symptoms are generalized and diffuse such as drowsiness, nausea, fatigue, and insomnia.[13] In summarizing a large number of studies, headache occurred in 7% of those taking placebo, drowsiness in 5%, weakness in 4%, dizziness in 1%, and nausea in 1%.[22] In another study, somnolence was found in 25% of those taking placebo, fatigue in 17%, gastrointestinal complaints in 16%, difficulty concentrating in 13%, and headache in 12%.[31]

The mechanisms underlying the nocebo phenomenon remain unclear. Conditioned learning and expectancy effects (discussed in the following section) have been implicated.[32-34] A pos-

sible biological basis is suggested by the recent finding that cholecystokinin mediates the hyperalgesia that can result from the administration of a placebo and that proglumide (a cholecystokinin antagonist) blocks this nocebo effect.[35] Nocebo symptoms occur significantly more often in women than in men.[30,36-38] Although cultural and ethnic factors are thought to be important, little empirical evidence exists.[39]

In controlled clinical trials, these nocebo effects can be severe enough to lead to discontinuation and dropout from the trial,[17] yet three quarters of patients and a like number of health care professionals (nurses) are not aware of the nocebo phenomenon.[40] One practical implication of this ignorance is that patients receiving placebo in a clinical trial who experience side effects may conclude that they are taking an active drug, which could in turn reduce the treatment effect.[40] The nocebo effect furnishes a justification for including placebos in clinical trials since it permits a more accurate appraisal of the side-effect profile of the active medication. Without such a placebo comparison, the active medication may be associated with side effects that are not in fact specifically attributable to it, but rather are the nonspecific consequences of taking any medication and due to interindividual differences.

Factors Associated With Nonspecific Side Effects

Expectation and Suggestion. Patients who expect distressing side effects before taking a medication are more likely to develop them. Such negative expectations make the individual more likely to notice and attend to new or unwelcome sensations; interpret preexisting, ambiguous, and vague sensations unfavorably and attribute them to the medication; and overlook positive changes and evidence of symptom remission.[24,41,42]

Several studies illustrate the role of negative expectations and suggestion. In a multicenter, placebo-controlled trial of aspirin treatment for unstable angina, the informed consent form at 2 of the participating centers specifically listed "gastrointestinal irritation" as a possible side effect, while the consent form at the third center did not.[43] Patients at the former institutions reported a significantly higher incidence of gastrointestinal symptoms, but did not have a higher incidence of confirmed gastrointestinal disease than the patients whose consent forms did not mention these side effects and 6 times as many patients in the former group withdrew from the study because of gastrointestinal distress.[43] The information given a patient about a drug modifies his/her expectations of it and therefore his/her response to it.[33] Thus, among patients given a muscle relaxant, those who were told it was a stimulant reported greater muscle tension than those who were told it was a relaxant.[33] Similarly, when an aerosolized, active bronchoconstrictor (carbachol) was administered to asthmatic subjects, it produced more airway resistance and dyspnea in patients who were told it was a bronchoconstrictor than in those who were told it was a brochodilator.[44] Approximately one half of asthmatic patients inhaling nebulized saline who were informed that it was an allergen developed dyspnea, increased airway resistance, and decreased vital capacity,[45,46] and when patients with food allergies are injected with saline that is described as an allergen, one quarter develop allergic symptoms.[47] In another study, pain patients' initial expectations of discomfort associated with the placement of a sham analgesic device were associated with increased pain reports.[14] The ethical issues (eg, deception of subjects) inherent in such studies are generally not addressed in these reports, perhaps indicating that our current heightened sensitivity to such considerations is relatively recent.

Expectations also induce symptoms in healthy nonpatients. More than two thirds of healthy volunteers experienced a headache after being told that a mild electric current that induces headache would be passed through their heads, although no electricity was administered.[48] Instructing volunteers to pay attention to any evidence of "nasal obstruction" while they breathe induces more upper airway symptoms than instructing them to attend to the "free passage of air."[41] Community residents who mistakenly believe they have been exposed to a toxic substance or hazardous waste have an increased incidence of symptoms that they ascribe to the supposed exposure.[49,50]

Prior Conditioning. Patients may manifest side effects to a prescribed medication not because of its specific pharmacological actions, but rather because they have experienced side effects to other drugs in the past. This occurs as a result of classical conditioning in which a neutral, inert, or inactive stimulus (such as a substance, person, or procedure) acquires the capacity to elicit a physiological change (for example, in blood pressure, immune response, or airway resistance) if it has previously been repeatedly paired with a provocative stimulus.[51] In this way, patients can become conditioned to develop medication side effects. Conditioned nausea is seen in as many as 33% of chemotherapy patients[52-54] who become profoundly nauseated when encountering a previously neutral stimulus that has now become associated with the chemotherapy, such as meeting the infusion nurse outside the hospital or entering a room painted the same color as the infusion room.

Conditioned responses have been observed in patients with asthma and other allergies. Asthmatic attacks can be precipitated by presenting patients with a sealed glass jar filled with dust or with a plastic rose to smell.[46,55] Residents of communities close to hazardous waste sites display a similar response. Thus, the occurrence of malodorous air and unpleasant-tasting water (widely associated with contamination, pollution, or poisoning) in a community was followed by an increased incidence of distressing somatic symptoms; however, air sampling and water quality evaluations disclosed no evidence of toxic contaminants.[56]

Psychological Characteristics. Several psychological characteristics, including anxiety, depression, and soma-

tization, have been associated with side effects to active drugs and with nocebo symptoms.[57,58] Clinicians have noted that the side effects reported by highly anxious patients are often the somatic concomitants of anxiety itself (eg, tachycardia, dyspnea, or sweating).[59] Although empirical evidence is lacking, depressed patients also seem particularly prone to medication side effects. Bodily distress is often an integral feature of depression: depressed patients are somatically preoccupied, expect to suffer and experience discomfort, and don't feel they deserve to get better. Symptoms experienced as medication side effects also serve as the rationale for nonadherence to the medication regimen, and approximately one third of depressed patients in primary care practice stop taking antidepressants within the first month of treatment.[60,61] Finally, higher levels of generalized psychological distress predispose people to reporting nonspecific side effects. Thus, neuroticism (a generalized and enduring tendency to experience a wide range of psychological symptoms and emotional distress) appears to be associated with the nocebo effect.[29]

A tendency toward somatization, symptom amplification, and a heightened awareness of bodily sensation have also been associated with nonspecific side effects. Measures of somatization are associated with an increased likelihood of developing pain at the site of a placebo injection in patients with chronic temporomandibular joint pain,[62] and a measure of hypochondriasis predicted side-effect reporting in healthy, nondepressed volunteers taking an antidepressant.[29] In a study of patients switching from a standard anxiolytic to an extended-release form, baseline measures of somatization significantly predicted the subsequent incidence of adverse side effects.[63] In patients with rheumatoid arthritis, self-report measures of somatization and of the tendency to amplify benign bodily sensations were significant predictors of medication side effects over the ensuing 3 months, even after controlling for arthritis severity.[64] A heightened awareness of autonomic sensation has also been associated with increased symptom reporting following placebo administration.[65,66]

Situational and Contextual Influences. Nonspecific side effect reporting is influenced by the context and environment in which the medication is given, and by the physical and symbolic characteristics of the medication itself. Although clinical experience supports this widespread conviction that situational characteristics (eg, the setting and environment in which medication is prescribed) and interpersonal factors (such as the nature of the patient-physician relationship) influence the incidence and nature of side effects,[67,68] there is little rigorous, empirical evidence about this.

The characteristics of the medication itself, both physical and symbolic, can also influence side effects. The symbolic properties that the patient attributes to the medication reflect the information, opinions, and beliefs he/she has about it. These may be powerfully shaped by the mass media and other sources of information such as the Internet and the direct advertising and marketing of pharmaceuticals to the general public. Erroneous information and misunderstandings may foster anxiety, suspicions, and a sense of vulnerability, all of which can amplify benign bodily sensations and cause them to be misattributed to the medication. Because of their historical reputation, some medications may be more likely to have adverse effects ascribed to them. For example, penicillin allergy is widely recognized by the public, and up to 10% of hospitalized patients report being allergic to it.[69] However, on careful investigation, 97% of adults[70] and 94% of children[71] labeled as "penicillin allergic" were found to tolerate oral penicillin. It was suggested that these patients had misinterpreted coincidental symptoms as allergic in origin, or labeled as allergic some symptoms that were actually due to the underlying illness (eg, sore throat).[72] Thus, the fear of a penicillin reaction may deprive many patients of an effective treatment.[73]

Some attributes of pills (eg, size, color, shape, and even the name) may influence the likelihood or nature of nonspecific side effects. Red, orange, and yellow tablets are associated with stimulant effects, and blue and green suggest sedative effects.[74] Thus, volunteers taking blue placebos report more drowsiness then those taking pink placebos.[75] Color is also associated with specific sites of action: red is associated with cardiac activity, and tan and beige with dermatological activity.[76]

Clinical Implications

Maintain a High Index of Suspicion for Side Effects That Are More Properly Ascribed to the Patient Than to the Drug. When a patient reports troublesome side effects, the clinician should not automatically assume they result from the pharmacological action of the medication and therefore necessitate a dosage adjustment, discontinuation, or the addition of another medication to treat them. A heightened index of suspicion is called for when the patient's symptoms are vague, ambiguous, or prevalent in daily life; when the patient has a history of negative side effects to many different classes of drug; and when the patient is exceptionally anxious about, or even seems to expect, difficulties with the medication. In such cases, a change in the regimen may not be necessary and may even be counterproductive.

Identify at the Outset Those Patients Most at Risk for Nonspecific Side Effects. Patients who somatize or who are anxious or depressed are at greater risk of nonspecific side effects. Ask patients about prior "bad experiences" with drugs, whether they consider themselves "especially sensitive" to drugs, and inquire about a history of medically unexplained complaints. Pointing out that the anticipation or fear of an adverse reaction can become a self-fulfilling prophecy (by causing the misattribution of unrelated, preexisting symptoms to the newly instituted drug) may in itself help to obviate some nonspecific side effects. It may also be helpful to discuss the nocebo phenom-

enon explicitly with such patients. It may help to explain how somatic symptoms caused by preexisting medical illnesses or by anxiety and depression, and those that are simply endemic to daily life, can be misattributed to a newly instituted medication.

Use a 2-Step, Collaborative Strategy for Prescribing. For patients at risk of nonspecific side effects, pharmacotherapy may be undertaken in collaboration with the patient in 2 discrete phases with distinctly different goals. The goal of the first phase is simply to help the patient tolerate a very low dose of medication; therapy is initiated at doses that may be subtherapeutic, with the objective of allowing the patient to get used to the idea of taking a medication. Because the symptoms of the underlying medical condition are likely to persist during this first phase of pharmacotherapy, the patient may conclude prematurely that the medication is ineffective, so it is important to explain that such a gradual titration may mean that the symptoms of his/her illness will persist a while longer. In the second phase of therapy, the dose is gradually increased into the therapeutic range, acknowledging whatever side effects develop, and coupling this with support and encouragement. Patients should be reassured that although the nonspecific side effects may be bothersome, they are not medically dangerous. Patients may be encouraged to research a drug (eg, on the Internet), as long as the results of this search are then discussed with their physician. Timing can be crucial: some patients simply need more time to initiate treatment. It is usually unwise to pressure apprehensive and ambivalent patients into premature acquiescence, as this insistence can exacerbate side effects.

If Nonspecific Side Effects Occur, Provide an Explanation and Help the Patient Reattribute Them. If nonspecific side effects occur, it is helpful to discuss the process of symptom misattribution described earlier and to explore whether the patient may have relabeled or misattributed the symptoms of his/her disease, or the somatic concomitants of emotion or of normal physiology, to the new medication. The goal here is not to eliminate the side effects, but rather to help the patient tolerate them; patients who understand the basis of their somatic distress are less frightened by it and find it more bearable. It can be useful to clarify that although the patient's symptoms are distressing, they are not medically dangerous and do not indicate bodily harm. A study of patients with functional gastrointestinal disorders treated with atropine provides empirical evidence that the way in which side effects are framed affects overall outcome.[67] The physical well-being ratings of these patients differed significantly depending on whether the specific medication side effect of dry mouth was presented favorably (as a sign the medicine was taking effect and should be ignored) or unfavorably (as a possible toxic effect that might require discontinuation of the medication).[67]

If Side Effects Occur, Find Out if the Patient Is Dissatisfied With His/Her Care. If bothersome side effects occur, it can be useful to ask patients about any dissatisfactions they may have with their medical care in general. Patients may harbor misgivings, uneasiness, or suspicions about their treatment, but may feel uneasy about voicing these concerns openly. Reporting troublesome side effects may be a less confrontational way of expressing such disaffection. Nonspecific side effects may then be a nonverbal statement of patients' misgivings about treatment; such side effects provide an acceptable excuse for not taking the medication, without having to openly refuse it or directly confront the clinician with reservations about their care. The clinician should ask patients if they suspect that the wrong diagnosis has been made or the wrong medication prescribed. Would they prefer some other treatment? Do they believe they are receiving too many pills? Though it may not be possible to accommodate the patient's concerns, elucidating and discussing them may help to reestablish a collaborative alliance. Again, the goal is not the elimination of all bothersome symptoms, but rather to help patients tolerate them.

Physicians also help patients tolerate side effects by remaining available to discuss them and to provide reassurance and encouragement. Keeping the patient's expectations of pharmacotherapy modest and realistic is also wise; overselling the virtues of a medication and downplaying its side effects may lead to eventual dismay when they do occur. Conversely, physician frustration, irritation, or dissatisfaction with the patient may exacerbate the patient's discomfort and ultimately, his/her side effects.

Include Other Health Care Personnel in the Process. Outpatients often discuss their side effects with nurses, pharmacists, physician assistants, and other health care personnel. It is important that these professionals understand the issues and know about the possible sources of nonspecific side effects, so that they can provide the information, explanation, reassurance, and encouragement needed.

Conclusions

Nonspecific medication side effects are distressing and frightening to patients. They result in wasted medication and nonadherence, physician visits that are not medically necessary, and unnecessarily complicated regimens when additional drugs are added to treat these side effects. Because this phenomenon is common, distressing, and costly, it deserves greater clinical scrutiny and more empirical investigation. Future research should focus on identifying the personal characteristics and situational influences that make nonspecific side effects more likely to occur, and on developing effective clinical strategies to ameliorate them.

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