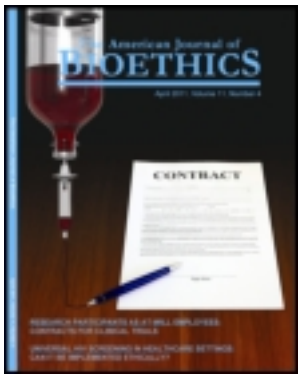

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To Tell the Truth, the Whole Truth, May Do Patients Harm: The Problem of the Nocebo Effect for Informed Consent

Rebecca Erwin Wells [a] & Ted J. Kaptchuk [b]
[a] Brigham and Women's/Faulkner Hospitals, Harvard Medical School
[b] Beth Israel Deaoness Medical Center, Harvard Medical School

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Target Article

To Tell the Truth, the Whole Truth, May Do Patients Harm: The Problem of the Nocebo Effect for Informed Consent

Rebecca Erwin Wells, Brigham and Women's/Faulkner Hospitals, Harvard Medical School

Ted J. Kaptchuk, Beth Israel Deaoness Medical Center, Harvard Medical School

The principle of informed consent obligates physicians to explain possible side effects when prescribing medications. This disclosure may itself induce adverse effects through expectancy mechanisms known as nocebo effects, contradicting the principle of nonmaleficence. Rigorous research suggests that providing patients with a detailed enumeration of every possible adverse event—especially subjective self-appraised symptoms—can actually increase side effects. Describing one version of what might happen (clinical "facts") may actually create outcomes that are different from what would have happened without this information (another version of "facts"). This essay argues 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." This essay suggests a pragmatic approach for providers to minimize nocebo responses while still maintaining patient autonomy through "contextualized informed consent," which takes into account possible side effects, the patient being treated, and the particular diagnosis involved.

Keywords: decision making, informed consent, professional ethics, professional–patient relationship

The ultimate goal of physicians is to help the healing process of their patients. In treating patients, physicians often recommend pharmaceutical agents and explain the medicines' benefits and risks, typically describing the possible side effects that could occur. However, in the very process of describing side effects, physicians may induce nocebo (negative placebo) responses and cause harm, rather than relieve suffering. Such a nocebo response is thought to occur because of patients' negative expectations, anticipations, and anxiety (Benedetti et al. 2007). Evidence suggests that the nocebo effect can significantly increase various nonspecific symptoms and complaints, resulting in psychological distress, significant excess costs because of increased medication nonadherence, extra treatment visits, and additional medicines prescribed to treat the nocebo effects (Barsky et al. 2002). Thus, the question arises: How much information should doctors provide to their patients about medication side effects? This question raises an ethical conundrum: On the one hand, full disclosure of possible side effects is required by the ethical norms of respect for persons and informed consent, yet detailed disclosure may produce harm. However, an examination of the extensive experimental research in nocebo effects may help attenuate this dilemma. This literature demonstrates that the information provided to a patient regarding medication side effects is not an abstract neutral fact: The development of many medication side effects depends on what information is provided to the patient about side effects. For some patients, detailed information of every possible subjectively-assessed side effect (one version of fact) will create those very same side effects, many of which would not have occurred without the information (another version of fact). Adverse effects are ambiguous and chameleon-like, and information about adverse effects is itself an "active" component of the patient–physician encounter. There is no simple "truth" about adverse effects. 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. We propose what we call *contextualized informed consent* as an ethical procedure in clinical medicine whereby a provider considers the possible side effects, the patient being treated, and the particular diagnosis involved, to provide information tailored in a way that reduces expectancy-induced side effects while still respecting patient autonomy and truth-telling. We believe that such a strategy engages the physician's need to balance informed consent and nonmaleficence while upholding respect for person.

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Address correspondence to Rebecca Erwin Wells, MD, MPH, Brigham and Women's/Faulkner Hospitals, Harvard Medical School, John R. Graham Medical Center, 1153 Centre St., Suite 4970, Boston, MA 02130, USA. E-mail: rwells3@partners.org

EVIDENCE OF NOCEBO EFFECTS

Research demonstrates that detailed disclosures of possible adverse effects, compared to minimal descriptions, can lead to more adverse events through what is usually called the nocebo (negative placebo) response. In a trial of aspirin for the treatment of unstable angina ($n = 555$), inclusion of a statement in the informed consent outlining possible gastrointestinal (GI) side effects, compared to no inclusion of the GI side effects, resulted in a sixfold increase in the number of subjects withdrawing from the study due to minor, subjective GI symptoms (Myers et al. 1987). Major and objectively documented GI side effects were the same whether the information was in the informed consent or not. A study that examined the presence of erectile dysfunction in adults using beta-blockers ($n = 96$) found that the group that was not told their assignment had the least incidence of the side effect of erectile dysfunction after 3 months (3.1%), the group told the name of the medicine but not informed of the side effect of erectile dysfunction had a 15.6% incidence of erectile dysfunction, and the group told the name of the medicine and informed of the side effect of erectile dysfunction had the highest incidence of erectile dysfunction (31.2%) ($p < 0.01$) (Silvestri et al. 2003). In a trial of adults being treated for benign prostatic hypertrophy with finasteride ($n = 120$), those told of the sexual side effects reported three times more sexual side effects than those not told (44% vs. 15%, $p < 0.05$) (Mondaini et al. 2007). Other studies have shown that pain increases when harsher words are used to describe an upcoming experience. For example, one study showed that the use of the word "pain" resulted in subjects reporting more pain than use of the phrase "cool sensation" (Lang et al. 2005), while another study found that saying "you will feel a bee sting" prior to 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" (Varelmann et al. 2010). In all these examples, information changed the adverse effect profile. Furthermore, some have speculated that the rates of the nocebo effect seen in clinical trials may be an underestimate of the true prevalence, as patients who are reluctant to receive novel medical treatments due to anxiety or mistrust (and may be more susceptible to the nocebo response) might avoid participation in a clinical trial (Mitsikostas et al. 2011).

In addition, the specific information told to patients directly shapes the specific side effects experienced. Information can be self-fulfilling. A trial comparing two placebo groups, placebo acupuncture versus a placebo pill, revealed that the types of side effects patients experienced were completely different in the two study groups and entirely mirrored the information provided to participants (Kaptchuk et al. 2006). Patients who received placebo acupuncture and were told they had a 50–50 chance of receiving genuine or placebo acupuncture experienced side effects typical of acupuncture (pain during treatment, increased pain after "removing" the needle, and local redness or swelling), while those who were administered placebo pills and were told they could be receiving either placebo pill or amitriptyline complained of the usual side effects of this medication (drowsiness, dry mouth, restlessness, dizziness, and headache). A systematic review of adverse events in placebo groups of anti-migraine clinical trials showed that the adverse events in the placebo arms corresponded to those of the antimigraine medication against which the placebo was compared (Amanzio et al. 2009). For example, typical adverse effects of certain anticonvulsants (memory problems and anorexia) were present only in the placebo arm of trials with those anticonvulsants. A systematic review from 143 placebo controlled trials of antidepressant medications (with data from over 12,000 subjects) also showed that the adverse effects reported in those receiving placebo closely related to the corresponding drug in the trial (Rief et al. 2009). Again, the information provided to subjects in trials produced the side effects that mimicked the information given. Such nocebo effects can be severe enough to have patients withdraw from treatment: Between 4 and 26% of patients in trials randomized to the placebo group discontinue the placebo because of perceived adverse events (Amanzio et al. 2009; Rief et al. 2006; Rief et al. 2009).

When it comes to subjective self-appraisal, it seems that humans have a tendency to perceive what they expect to perceive (Barsky and Borus 1999; Geers et al. 2010; Pennebaker and Skelton 1981). This was demonstrated clearly in a recent study that examined the determinants of patients' side effects from arthritis medication. The study showed that patients with more concerns about their medicines at baseline reported more side effects in follow-up, even after adjusting for disease activity, the type of medication being used, and levels of prior experience with side effects (Nestoriuc et al. 2010). Those who expected more side effects were the ones who were most likely to develop them.

At this point, the psychological mechanism of nocebo is thought to involve negative expectations and anxiety (Barsky et al. 2002). Basic science research also has begun to reveal the objective neurophysiological correlates of the nocebo phenomenon. For example, a functional magnetic resonance imaging study of the nocebo hyperalgesia response revealed the involvement of the affective–cognitive pain pathway (Kong et al. 2008). Verbally induced nocebo hyperalgesia has been shown to be associated with hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, and both the hyperalgesia and the HPA hyperactivity were antagonized by a benzodiazepine, suggesting that anxiety plays a role (Benedetti et al. 2006). Cholecystokinin (CCK) has also been shown to be involved in the hyperalgesic nocebo response (Benedetti et al. 1995). In addition, Scott and colleagues showed that while 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 (Scott et al. 2008).

PUBLIC HEALTH IMPLICATIONS OF THE NOCEBO RESPONSE

In addition to the burden to individual patients, the nocebo response has significant public health ramifications and other less direct negative consequences. Drug-related adverse effects contribute to patient nonadherence, illness burden, and psychological distress. Many of these adverse effects may actually be due to nocebo effects related to negative expectancy or anxiety. The adverse effects experienced and the resulting altered treatment regimen can result in significant psychological distress, "wasted medication and non-adherence, physician visits that are not medically necessary, and unnecessarily complicated regimens when additional drugs are added to treat these side effects" (Barsky et al. 2002, 626).

Frequent medication changes can result in suboptimal care and complications from the underlying disease process. For example, adverse effects that result in stopping or changing antihypertensive medications have been shown to be associated with worse blood pressure control (Davies et al. 2003) and an increased incidence of cardiovascular disease (Psaty et al. 1990). This leads to more physician visits and a total increase in the cost of medical care. In 1995, drug-related adverse effects were associated with $76.6 billion in hospital costs and 17 million emergency-department visits (Johnson and Bootman 1995). While it is difficult to estimate how much of this problem is a nocebo response, as opposed to the direct consequence of a medication, some amount of those adverse effects and their costs is likely attributable to the nocebo reaction, given the clear presence of adverse effects in the placebo arm of most randomized controlled trials and the research described above.

The recent formulation change of thyroxine replacement therapy in New Zealand and the resulting dramatic increase in adverse reaction reports graphically demonstrates the impact that the nocebo response can have on public health (Faasse et al. 2009). In 2007, the manufacturing of the thyroid replacement drug approved and funded by New Zealand's government, Eltroxin, moved from Canada to Germany, resulting in a change in the tablets' inert ingredients, although the active ingredient (thyroxine) remained unchanged and continued to be made in Austria. Many patients inaccurately perceived the change to be the result of a cost-cutting measure for New Zealand's pharmaceutical budget (even though the new formulation was more expensive than the old one), and adverse effects of the new chemically identical formulation were reported in the media. The initial media reports led to a cascade of additional incidents in adverse effects until the rate of adverse event reporting rose nearly 2000-fold. The areas with the most intense media coverage of the adverse events had the highest rates of adverse events. The number of adverse events dramatically decreased once an announcement was made that an alternative brand was being approved. Generic substitutions are increasingly being used to help control skyrocketing health care costs, but as the situation in New Zealand demonstrates, the nocebo response may limit their use, resulting in broad public health ramifications. This kind of adverse effect is probably related to mass psychogenic illness attributed to supposed poison exposures (Jones et al. 2000).

COMMON NOCEBO SYMPTOMS

There are certain reactions more susceptible to the nocebo response than others. Evidence has shown that vague nonspecific medication side effects are more likely due to nocebo responses than drug-specific side effects (Davies et al. 2003). Nonspecific side effects are nonserious symptoms that are idiosyncratic, not clearly attributable to the pharmacological action of the drug involved, and not dose dependent (Barsky et al. 2002). These types of symptoms include difficulty concentrating, drowsiness, nausea, dizziness, fatigue, headache, insomnia, and vague ill health. In contrast, specific side effects are physiological changes genuinely related to the pharmacological action and biological activity of the drug involved and tend to be dose dependent. The majority of side effects are likely nonspecific (Gurwitz et al. 2003; Rief et al. 2011) and are often attributable to their background prevalence in the population (Grimes and Schulz 2011), as many vague and nonspecific symptoms are often present at baseline or as part of the natural course of a disease and are inappropriately attributed to medication side effects (Barsky et al. 2002). Furthermore, nonspecific symptoms are commonly reported in healthy patients not taking any medicines (Reidenberg and Lowenthal 1968).

WHAT IS AN ACCURATE DESCRIPTION OF ADVERSE EFFECTS?

The research just described raises a critical question: What is a truthful description of possible adverse effects? The nexus of the complexity is that a medication's side-effect profile may be dependent on the presence or absence of a detailed description to the patient about the medication's potential side effects. The reality of potential adverse events can be significantly modified by what the physician says. There is no absolute "truth" about a medication's side-effect profile independent of what the physician says or does not say. The "facts on the ground" that are created upon describing vague nonspecific side effects are different from the reality of not describing such side effects. If an informed consent involves describing every possible side effect, more symptoms are more likely to occur. But if an informed consent provides limited information about vague, nonspecific side effects, such symptoms happen less frequently. For example, for patient A, a physician recommends a drug and describes all the potential side effects, specific and nonspecific. For patient B, the physician tailors the information provided to only describe the drug-specific side effects of the same medication. Patient B rarely develops any side effects, while patient A develops a multitude of nondescript symptoms. While patient A was told the truth about the medication, the knowledge that was given actually created that truth. Patient B was also told the truth—what was expected to happen when more limited information was given. Since the truth was revealed in both scenarios, but one scenario

results in more harm to the patient, the best option is the one that involves the least harm to the patient. It seems that there is no straightforward accurate description of potential side effects that exists independent of the patient–physician interaction. The information provided to a patient regarding potential side effects affects the presence/absence of those very side effects. Telling every possible subjective adverse symptom is not a declaration of objective and hard data. The development of nonspecific side effects represents, to a significant degree, the particular consequences of the interaction between the patient–physician interaction and the art of medicine.

CONTEXTUALIZED INFORMED CONSENT

One of the primary aims 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 (Gillon 2003). We believe that the data from the nocebo literature allow us to propose a method to balance these two imperatives. Instead of considering the full detailed disclosure of all medication side effects an absolute rule, one can abide by both principles through what we call *contextualized informed consent*. This involves taking into account the possible side effects, the person being treated, and the disease involved, to tailor the information provided about medication side effects to provide the most transparency with the least potential harm. Since the chief motivation behind informed consent is the protection of patients, then through the principle of beneficence, withholding self-fulfilling nocebogenic information may be appropriate through contextualized informed consent.

The first important factor involved in contextualized informed consent is the potential side effect involved: The type of side effect should help a physician determine how much information to reveal. As described earlier, nonspecific symptoms, such as difficulty concentrating, drowsiness, nausea, dizziness, fatigue, headache, insomnia, and vague ill health, are most susceptible to the nocebo response. Almost any medicine is susceptible to vague, nonspecific side effects. A physician may consider not labeling these nonspecific effects when dispensing a new medication, but rather explaining to the patient that he/she should contact the physician with "any new or unusual symptoms." If the patient does call back with a vague, nonspecific symptom, the physician can then evaluate the patient to see whether the reaction is due to the medication or due to an unrelated process independent of the new medicine.

On the other hand, drug-specific side effects are less likely to contribute to the nocebo response. These types of side effects are critical to reveal because they may result in more debilitating symptoms/conditions and thus may be more important for the patient's full informed consent. For example, the reported side effect of lymphoma with the use of cyclosporine, and that of nephrolithiasis with topiramate use, are serious, life-threatening conditions that may alter a patient's decision to take the medication. In addition, before starting prednisone, a patient with a history of borderline diabetes or psychiatric illness would want to know about the possible worsening of these conditions by prednisone. Informing the patient of these potential reactions is important to provide accurate and detailed information on the medication. Additionally, if they do occur, the patient needs to know to consider the medication as the underlying etiology in order to notify the physician immediately to discuss discontinuation of the offending agent. Further, there often are many medications that can be used to treat the same condition, and patients may choose which medication to take based on the drug-specific side effects. For example, in the treatment of musculoskeletal pain, patients with jobs that require the use of motor vehicles may opt to defer the use of cyclobenzaprine, which is frequently associated with the dose-dependent effect of central nervous system (CNS) sedation, and opt for ibuprofen, recognizing but accepting the risk of peptic ulcer disease with frequent nonsteroidal anti-inflammatory use. Finally, telling patients about drug-specific side effects allows patients to be fully involved in the decisions about their health care, without exposing them to the risk of the nocebo response with nonspecific drug side effects. This allows patients to feel empowered in terms of taking control of their health, which improves adherence and overall patient outcomes (Epstein et al. 2004).

A second major factor for a provider to consider in balancing informed consent with nonmaleficence is the patient being prescribed the medication. Some patients may be more susceptible than others to the nocebo response. There is a wide range of suggestibility among different individuals (Spiegel 1997). Individuals who have experienced prior adverse reactions are also more likely to experience future ones, theorized to be due to the effects of prior conditioning (Barsky et al. 2002). Furthermore, adults who have previously experienced side effects are more likely to attribute symptoms to medication side effects when they may, in reality, be benign, self-limited ailments that are commonly present in healthy adults not taking medications (Barsky et al. 2002). The knowledge of taking a medication may cause certain patients to monitor symptoms in more detail, resulting in an amplified negative perception of benign sensations and normal physical symptoms (Barsky and Borus 1999). Patients experiencing nonspecific symptoms at baseline are more likely to report them as side effects of a new medication: An analysis of the nocebo response to placebo agents in cancer patients showed that those with worse baseline symptoms of sleep, appetite, and nausea were associated with increased reporting of those exact symptoms as side effects (de la Cruz et al. 2010). Further, individuals with psychological symptoms (such as anxiety and depression) (Davies et al. 2003), and those with a tendency toward somatization have been found to be more likely to develop the nocebo response (Barsky et al. 2002). Thus, to help prevent the induction of the nocebo response, a physician should identify high-risk patients (those with a prior history of adverse events, those who have nonspecific symptoms at baseline, and those with a tendency toward somatization or with a history of anxiety/depression) and tailor the amount

of information about medication side effects to these patients such that only the drug-specific side effects are described.

A third key element to consider in contextualized informed consent is the diagnosis being treated. If a patient's underlying condition that is being treated is mild or if there are other treatment options (e.g., nonpharmacological approaches), then any side effect might not be worth the patient starting a medicine and an expanded full disclosure is important. For example, benzodiazepines can be used to treat anxiety. However, they can be habit-forming. Because of this, an individual with mild anxiety may defer the use of benzodiazepines and opt to treat the anxiety with non-pharmacological options. However, in critical, life-threatening conditions, minor side effects of a medication may be of less concern and less important to provide. The drug tissue plasminogen activator (tPA) can be given in the setting of an acute stroke and potentially dramatically decrease the consequences of the stroke; the tPA side effect of mild transient dizziness arguably is of little consequence in this setting.

Another possible option to dealing with how much information to provide a patient would be to abide by the "Golden Rule," in which the doctor would inform the patient in the same manner as she would wish to be informed herself if she were the patient. One study suggests that patients often want to know more information than their physicians actually provide (Faden et al. 1981). Perhaps physicians could ask their patients whether they want to know about the possible side effects of a medicine. However, how would patients be able to weigh the benefit of gained information with the self-fulfilling risk of those side effects without knowing the adverse events in question? In addition, humans often temporarily prefer processes that pay off quickly (e.g., immediate information) over richer, but slower paying processes (e.g., no information, but fewer side effects) (Ainslie 2001).

Furthermore, patients are often unaware of influences that impact their decision making. Patients may think they are making autonomous decisions, when in reality, unknown biases may be affecting their decisions (Schwab 2006). McNeil and colleagues showed that patients perceived treatments as more/less attractive based on whether the same outcomes were framed in terms of the probability of living or the probability of dying (McNeil et al. 1982). A similar study of influenza vaccine compared the effect of positive framing (revealing the percent that remain free of influenza and have no side effects) versus negative framing (describing the percent who acquire influenza and experience side effects) (O'Connor et al. 1996). While the framing did not influence patients' decisions about vaccination, the positive framing group had fewer side effects and less work absenteeism. Contextualized informed consent may best serve patients: As Miller and Collaca point out, side-effect information framed to minimize nocebo effects is ideal provided that relevant side-effect information is explained (Miller and Colloca 2011).

ARGUMENT AGAINST CONTEXTUALIZED INFORMED CONSENT

The major ethical objection to the idea of contextualized informed consent is that it is paternalistic and does not uphold the principles of respect for patient autonomy and truth-telling. Withholding information under the guise of therapeutic privilege assumes that the doctor can determine what is best for the patient and is paternalistic. The nocebo response usually involves the development of minor side effects, but not informing patients about major side effects such as cytopenia or GI bleeding could be devastating. Furthermore, if respect for autonomy is the priority, then the harm done from informing patients about potential side effects (especially if it results in only minor symptoms) should be done. Finally, truthful and meaningful communication is paramount in patient care as it affects "not only patient satisfaction with care, but also patient knowledge and behavior" (Rastam et al. 1992, 123). However, we argue that since the way information is disseminated to patients about medication side effects actually changes the reality of those side effects as the information provided can be self-fulfilling, tailoring information about side effects then creates at least one accurate description of the likely clinical outcome.

INNOVATIVE THINKING ON INFORMED CONSENT

Our contextualized informed consent argument is consistent with the important bioethical analysis by Manson and O'Neill (2007). They propose a new way of thinking about informed consent that is consistent with our contextualized informed consent and is both feasible and justifiable without returning to paternalistic or pre-Nuremberg ways. They recognize that the information conveyed in an informed consent does not exist independently of the process of conveyance and that it is both context dependent and audience sensitive. They view the "old" model of informed consent as focused on the disclosure of information such that a "conduit" transfers information (viewed as "stuff" that can be acquired and stored) to a "container" and the content is the focus of the interaction, but the act of communication is hidden. They propose a new model of informed consent in which the focus is not only on the content, but also on the complex social transaction that occurs during informed consent between "agents." This new model recognizes the interactive character of successful communication to satisfy epistemic and ethical norms.

They further add that all informed consents cannot be and need not be fully explicit or fully specific, as long as the treatment does not deceive, manipulate, or coerce the patient. Rather, for the communicative transaction to uphold epistemic and ethical norms, contextual relevance and "adequately accurate" information is more important than "illusory completeness."

Barilan interprets their new process of informed consent as one focused on the interaction between the responsible doctor and patient (Barilan 2010). He proposes that an enhanced therapeutic alliance results from the physician's attempt to both respect each patient's needs as an

individual and follow "evidence-based medicine" guidelines. The focus on the doctor–patient relationship is important for many reasons, including that "a successful doctor–patient relationship can . . . mitigate any nocebo response" (Olshansky 2007, 415).

OTHER PRACTICES CONSISTENT WITH CONTEXTUALIZED INFORMED CONSENT

There are many situations that are routinely considered ethical that are consistent with our contextualized informed consent. For example, novice doctors often perform procedures on patients without readily explaining their inexperience. In addition, often physicians will investigate the possibility of a patient having a life-threatening or incurable illness (such as cancer, Huntington's disease, amyotrophic lateral sclerosis, or dementia), but not disclose the details of this investigation to the patient until the results return. When asked why tests are being run, often physicians will respond by saying "to rule out other conditions" without specifically describing what is being ruled out, in order to protect patients from unnecessary worry.

Another clear example of how physicians make clinical judgments about what is best to tell patients is in the diagnosis of conversion disorder. Kanaan and colleagues describe this in their qualitatively analyzed interviews with neurologists who have diagnosed conversion disorder (Kanaan et al. 2009). They showed that neurologists rarely disclose the possibility of the symptoms being caused by a psychiatric disorder until all tests have been run to rule out an organic cause. Those interviewed felt that if a patient is told too early about the possibility of conversion disorder, they will "lose [the patient's] trust and then find it more difficult to manage that problem." Their interviews revealed that often physicians decide how much they will reveal about the condition based upon the receptivity of the patient to the possibility of a psychiatric condition. Further, even when the neurologists feel confident in the diagnosis of conversion disorder, they often don't fully disclose this diagnosis; most have come up with their own way of saying "we don't know what is causing this" or "the symptoms might have a psychological cause" without fully disclosing the truth of the conversion disorder diagnosis. Finally, when the neurologists were concerned the patient was feigning or malingering the illness, they almost never discussed this possibility with the patient. Physicians routinely make decisions about what "truth" to tell a patient and alter their discussion based on the patient involved (Kanaan et al. 2009).

A final example of how physicians do not always tell the "truth" to their patients, and perhaps the strongest example, is in regard to the concept of "number needed to treat." When rigorous clinical trials are done to show the benefits of a medication in the treatment or prevention of disease, the results reveal the total number of patients that need to receive the drug in order to see a benefit in one person (e.g., "number needed to treat [NNT]"). When a doctor then prescribes a drug "to prevent stroke" or "treat hypertension," she does not reveal the "scientific truth" that 10 (or even 100 or more!) patients need to take the drug in order for only one to receive this benefit. If such a truth of the therapeutic expectations were revealed, patient nonadherence probably would skyrocket and patient willingness to tolerate side effects likely would diminish.

Finally, if the ultimate goal of the physician is to help the healing of the patient, once one fully discloses all possible medication side effects, there is no way to go back and reverse the knowledge given if a patient experiences the nocebo effect. The decision to describe side effects is bounded by time. Once a patient experiences the nocebo response, resulting in adverse reactions, trying to convince the patient of the nocebo origin is often unsuccessful (Stern 2008).

LIMITATIONS

This article considers the ethical issues of contextualized informed consent but does not explore practical issues of legal liability or the possibility of patients learning of potential side effects from other sources. That discussion will await a future paper.

CONCLUSION

In conclusion, research on the nocebo response provides data and an important perspective on informing patients of potential adverse effects. Side effects, especially nonspecific vague ones, are not objective phenomena, but are influenced by the patient–physician interaction. Truth in clinical medicine, especially for vague, nonspecific symptoms, is complex and seldom absolute. We proposed what we call *contextualized informed consent* as a more accurate and beneficial method to address how to provide information to patients regarding potential medication side effects. Physicians cannot avoid framing information they provide, and truthful information can be given in different ways (Miller and Colloca 2011). Since information framing is unavoidable, clinicians should become more aware of the impact of their conversations on patients' experiences and endeavor to shape their discussions with patients to optimize outcomes while maintaining patient autonomy. Tailoring a discussion to each specific patient is not only good communication, but it is also good medical practice (General Medical Council [Great Britain] 2008). In the case of adverse effects, the decision on how to craft this consent—and deciding what is the boundary between nonspecific and specific adverse effects—is a judgment call related to the art of medicine. As Kathryn Montgomery writes, "Medicine's success relies on the physician's capacity for clinical judgment" (Montgomery 2006, 5). There is not one formula for obtaining informed consent in clinical practice, but it is contextually dependent and may change with time (Barilan 2010; Manson and O'Neill 2007). We propose the process of contextualized informed consent as a way for physicians to take into account the many variables that affect informed consent and as a way to reduce the development of nonspecific side effects while still maintaining patient autonomy and truth-telling. Contextualized informed consent provides a framework by which physicians can critically

think about the information they provide to patients regarding medication side effects to best serve their patients. This approach is theoretical, and we recognize the need for it to be empirically tested. But for now, the power of nocebo suggests that it may be "healthier to err on the side of optimism than on the side of pessimism" (Hahn 1997, 610). ■

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