The Potential of a Placebo/Nocebo Effect in Pharmacogenetics

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Key Words

Adverse outcome • Nocebo effect • Pharmacogenetic testing • Placebo effect

Abstract

Pharmacogenetic testing holds great promise to improve health outcomes and reduce adverse drug responses through enhanced selection of therapeutic agents. Since drug responses can be manipulated by verbal suggestions, it is of particular interest to understand the potential impact of pharmacogenetic test results on drug response. Placebo and nocebo-like effects may be possible due to the suggestive nature of pharmacogenetic information that a drug will or will not likely lead to improved health outcomes. For example, pharmacogenetic testing could provide further reassurance to patients that a given drug will be effective and/or cause minimal side effects. However, pharmacogenetic information could adversely affect drug response through negative expectations that a drug will be less than optimally effective or cause an adverse response, known as a nocebo-like effect. Therefore, a patient's perceived value of testing, their understanding of the test results, and the manner in which they are communicated may influence therapeutic outcome. As such, physicians should consider the potential effect of pharmacogenetic test results on therapeutic outcome when communicating results to patients. Studies are needed to investigate the impact of pharmacogenetic information on therapeutic outcome.

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Physicians have long been aware of some patients' improved outcomes following administration of a substance with no known pharmacological properties (i.e., an inert treatment or placebo). Known as the placebo effect, several variables have been found to modulate the degree of this effect including environmental, psychosocial, cognitive, and emotional factors as well as the behavior of healthcare providers [1, 2]. Equally important to the well-known placebo effect is the nocebo effect, whereby negative suggestions following administration of an inert substance result in an adverse outcome [3]. Psychological manipulation of information communicated by a doctor, friend, or family member has been shown to influence outcome [4, 5]. With the advent of pharmacogenetic (PGx) testing, we speculate that patient perceptions and understanding of test results as well as the manner in which they are communicated can influence therapeutic outcome, regardless of the result. While studies are needed to test this hypothesis, physicians should begin to consider the potential power of PGx testing when delivering test results and monitoring therapeutic outcome.

Placebo/Nocebo Effect and the Power of Words

The gold standard of clinical trials research is the double-blind, placebo-controlled, randomized clinical study. The rationale behind this study design is to separate non-specific from specific effects [6]. The existence of a placebo and/or non-specific effects can confound interpre-

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tation of clinical trials outcomes. Although some have argued that the placebo effect is part of the expected range of outcomes from the natural course of disease [7, 8] or that it is indistinguishable from patients enrolled in no-treatment arms of a clinical study [9], others have provided support for a psychobiological basis [10]. Evidence of a physiological effect of placebo analgesia was 1st shown in 1978 from stimulation of endogenous opioids [11]. More recently, neurochemical studies have shown that response to placebo analgesics can involve either opioid or non-opioid channels [12–14]. Imaging analysis has also demonstrated that neurobiological responses in patients treated with a placebo are similar to that seen in patients treated with an active agent [15].

The lesser-known nocebo effect or response has the opposite outcome of the placebo effect, whereby verbal or other suggestions of a negative outcome with administration of an inert substance result in a poor response. In cases where no inert substance is administered, nocebo-related effects can still result due to expectations of poor outcome based on suggestions [16–18], personal beliefs, environmental factors, or emotional states [19]. In addition, knowledge of sickness in other individuals can establish expectations of sickness [20]. It is important to distinguish the nocebo response from non-specific side effects to a placebo, whereby the effect is not attributable to pharmacological actions or to the expectation of a negative outcome [21]. Physiological responses have also been documented in response to negative expectations [22–24].

Two general theories have been put forth to account for the placebo/nocebo effect [4]. The conditioning theory, based on the classic Pavlovian conditioning theory, contends that certain things such as places, people, and even pill color linked with an unconditioned stimulus (an effective drug) can elicit a ‘conditioned’ response [25–28]. The expectation theory postulates that suggestive actions such as encouraging words in conjunction with the administration of a placebo can trigger a physiological response [29–31]. Participants’ presumption that they have been randomized to the treatment arm in a clinical study has been associated with increased expectations of benefit [32, 33]. Both the conditioning response and expectations can result in the stimulation of measurable physiological responses [4, 31, 34].

Of particular relevance to pharmacogenetics, the context of patient care has also been shown to be associated with placebo effects, including physicians’ attitudes, actions, and words [5]. For example, patients who have undergone a complete clinical work-up are more likely to

experience a placebo effect since they perceive the physician to be taking control of the illness [1, 35]. Referred to as the ‘placebogenic power’ of the physician, words of encouragement and confidence from a physician can also influence outcome [4, 36]. Differences in response have been noted between the simple phrases ‘it may work’ and ‘it does work’ delivered by a medical professional [37, 38].

Potential Impact and Value of PGx Testing on Outcome

While the purpose of PGx testing is to guide drug selection and dosage, PGx testing could provide further reassurance to patients that a given drug will be effective and/or cause minimal side effects which could lead to increased compliance. The encouraging words of a physician may be reinforced by the test result which could serve as an independent validation. Although a PGx test result can increase a patient’s likelihood of responding favorably to a drug, the potential for a nocebo-like effect is equally possible. The latter scenario in which PGx information may adversely affect drug response through negative expectations is of particular concern. For example, PGx testing that reveals that a patient’s condition is caused by a mechanism for which there is no target-specific drug available may reduce a patient’s confidence in a non-targeted drug. Or a patient found to be a poor metabolizer and thereby requiring a lower dose to avoid drug-induced toxicity may have less confidence in the drug’s effectiveness and/or a heightened sensitivity and anxiety about possible adverse effects.

A patient’s overall perception of the meaning of their PGx test result and its subsequent potential impact will likely pivot on 2 major factors: (a) the manner in which the physician communicates information about the test and test result, and (b) the degree to which the patient values, perceives, and understands the limitations of the test and the probabilistic implications of the test result. The patient’s relationship with their physician is a 3rd factor to consider in their understanding and perception of PGx testing and its impact on outcome [39].

Various interpretations will be applied to the PGx test result, 1st by the testing laboratory, next by the physician, and finally by the patient. Which interpretation is communicated to the patient relies upon the physician’s understanding of the test itself as well as its significance for the patient on both clinical and personal levels [40]. Physician preference and comprehension may lead to positive

or negative message framing when discussing the implications of a test and/or test result with their patient [41]. Variance in framing has been linked to differences in health/risk perception and health behaviors [42]. In addition, the certainty with which the test is framed in regard to the current state of the science has also been shown to influence patient choice [43]. Others have shown that the influence of message framing is limited to verbal versus written content [44].

The use of clinical tests for patient evaluation can influence non-specific drug responses as it impacts patients' perceived level of care [45]. For instance, patients who underwent diagnostic testing felt that they received 'better than usual' care and had a lower incidence of short-term disability [46, 47]. If an informed consent is required for PGx testing, this may signal to the patient an increased importance of this type of test compared to other types of clinical tests. Although testing can increase both physician's and patient's confidence in an initial diagnosis, it can also raise patient anxiety levels despite a normal test result [48, 49]. However, patients who are more aware of their treatment options and potential outcomes tend to feel more empowered about their decision [50].

Communication and understanding of genetic risk information is challenging for the physician and the patient, respectively. Numerous studies have compared patient preferences and understandability of various approaches of risk communication of genetic risks (e.g., numerical, graphical, absolute vs. relative risk) [51–54]. PGx test results may represent a greater communication challenge if the result is based on a compilation of multiple genetic and non-genetic factors. Prior studies have found that the lack of reassurance following mutation-negative clinical testing is most likely due to failure of providers to clearly communicate the test results to patients [55, 56]. This may be influenced by both the complexity of the test and the patient's innate perceptions.

Patient understanding is influenced on many levels including prior life/health experience, current emotionality of health treatment, and the implied clinical significance of the given test [40]. Both patient anxiety and desire for information have been positively correlated with information recall after a genetic counseling session [57]. Accurate recall, however, may not correspond with correct perceptions of the implications of that information [58]. Even if the results are 'normal' or encouraging, additional explanation may be required to provide patients a basis to understand the results and to strengthen the patient-physician relationship [55, 59]. If a PGx test result indicates a high risk of non-response or side effects, ad-

Fig. 1. Schematic of study design to ascertain impact of placebo effect of pharmacogenetic information.

ressing patients' concerns directly instead of dismissing them or referring them to other specialists may provide the needed reassurance sought by patients [49]. The potential biasing effects stemming from these factors must be considered in advance with respect to how best to communicate PGx test results.

Testing the Effect of PGx Information

Research is needed to explore the potential impact of PGx information on patients' psychobiological response to the resulting drug prescribed. Such research will be essential to guiding the appropriate communication of test results to reduce harm due to placebo/nocebo effects.

To study the impact of PGx information on either safety or efficacy, a traditional randomized study design could be used to measure the existence of a placebo effect attributed to PGx information. In this scenario, participants are enrolled in a clinical study for a new drug under investigation. To assess the impact of PGx information on efficacy, participants in the placebo arm of the study are randomized into 2 groups – the 1st group receives PGx information indicating the drug is genetically targeted and the 2nd group receives no PGx information (fig. 1). Similarly, to assess the impact of PGx information on safety, participants would instead receive PGx information indicating that the drug should not cause any adverse side effects or no PGx information.

A more straightforward observational study design could also be used where a placebo is administered to all participants, although they would be led to believe that they were receiving a test drug. Although both study designs require deception, exposing all participants to placebo only while manipulating the information would al-

low researchers to isolate the situation/context to determine the impact of words (or test results) on response with no specific effect attributable to an active drug [5]. It would further determine whether genetic information provides additional value to standard clinical information. If PGx information can influence placebo/nocebo effects, we would anticipate the informed subjects to have a potentially exaggerated response compared to those who did not receive PGx information.

Several personal factors can contribute to the development of a placebo/nocebo-like effect. One important factor to consider is the special significance often associated with genetic information. Whether culturally constructed or mediated, if an individual considers genetic information to be more significant or predictive of outcome, these preconceptions can contribute to potential placebo/nocebo effects. Therefore, it would be important to assess participants' feelings regarding the significance of genetic information compared to other types of clinical information to determine whether their *a priori* belief about genetic information is a strong predictor of placebo/nocebo-like effects. Other personal factors that may be predictive of placebo/nocebo-like effects include health and genetic literacy and risk comprehension and, as such, these should be measured in the proposed studies. Lastly, patients' perception of the severity of their illness requiring treatment as well as of the severity of treatment-associated side effects and the impact of non-response to the treatment must be considered particularly within the burgeoning field of PGx-guided cancer treatment.

Another set of studies is needed to investigate health professionals' understanding and delivery of PGx-related

messages and how this affects patient response. In particular, qualitative data collected from controlled studies are needed to investigate professionals' interpretation of the test result, the perceived predictive value of the result, the amount of information communicated to the patient, message framing, and method of communication on patients' response. These studies will provide useful data that will enhance delivery of pharmacogenetic information and highlight areas for additional professional education.

Conclusion

The impact of words on drug response and outcome cannot be overlooked with respect to PGx testing. While the overall benefits of PGx testing may far outweigh the risks with respect to improved drug selection and dosage, research is needed to understand how patients will respond to this information and how that response may in turn affect clinical studies of drug efficacy. In the interim, physicians should be sensitive to the potential impact of PGx results, regardless of whether they are considered as positive or negative on their patients' drug response and give special consideration to how best to deliver these test results to minimize adverse responses.

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