“Is it me, or does this actually work?”

The promises and perils of genetic screening for the placebo response to maximize approval of effective treatments

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Abstract

Genetics is emerging as a stable predictor of the placebo response. The potential to screen for or against the placebo response promises to increase the likelihood of effective drugs gaining approval to serve the public. Here, some criteria for the implementation of screening are suggested as well as a concrete example. Such screening presents its own pitfalls such as confounding gene-drug-placebo interactions. Specific recommendations for future pharmacological research are outlined in order to bring the promises of placebo response screening closer to reality.

Sugar pills work. Patients receiving treatment without any active therapeutic effects often still perceive improvements in their health: an effect known as the placebo response. This phenomenon cannot simply be attributed to bias on part of the patient or the researcher to report positive treatment effects: The placebo effect can trigger the body's pain suppression systems just like ten milligrams of morphine would, and furthermore, the suppression can be blocked by by certain compounds like opioid-receptor antagonists (Levine, 1984; Levine, 1981; Levine, 1978). Thus, the placebo response must necessarily involve real categories of biological processes with a basis in psychological physiology.

The magnitude of the response varies from person to person. The ability to characterize this variation and identify persons with a greater placebo response promises immense benefits to medical researchers. This is because treatments must perform substantially better than a placebo to gain approval for mass marketing. The accuracy of drug trials, then, depends on approximately equal distribution of volunteers highly susceptible to the placebo response among the active/drug group and the placebo/control group. If by chance, more placebo responders were placed in the active group, then the active group would not perform better enough compared to the control group for the experiment's results to prove conclusive. The trial would be biased towards the null hypothesis, and a truly effective treatment might not get approval to serve the public. Likewise, a relatively higher concentration of placebo responders in the control group might enable an ineffective drug to gain approval when it should not have been able to. The improved accuracy of drug trials upon controlled randomization of volunteers across control and active groups most applies to trials involving pathologies or procedures where the placebo effect is strong like irritable bowel syndrome (Patel, 2005). That said, all trials will observe benefits from placebo response screening as the improved accuracy of trial design will lower requirements on the number of volunteers.[1]

Recently, genetics have been linked to the placebo response, providing a plausible stable predictor for screening for placebo responders. In order of evidence, the four main physiological pathways affecting the magnitude of the placebo response that have been linked to particular alleles are the dopamine, opioid, serotonin, and endocannabinoid systems. As a specific example, the single nucleotide polymorphism (SNP[2]) rs4680 occurs in the gene encoding the enzyme catechol-O-methyltransferase (COMT), which metabolizes dopamine and other catecholamines (Lachman, 1996). By coding for methionine instead of valine in codon 158 (val158met), rs4680 reduces enzyme activity by a factor of three to four, resulting in higher levels of dopamine in the prefrontal cortex and thus contributing to the placebo response (Yavich, 2007).[3] Homozygous occurrence of rs4680 exhibits a greater placebo response compared to heterozygous occurrence (val/met).

Each polymorphism only has a small, individual effect on the placebo response, which itself, it should be remembered, serves as an umbrella term for what is really a multifaceted response (Benedetti, 2013). Such a result should not come as a surprise given the context of most genome-wide association studies, which usually find that a large number of variants with small, individual effects are required to explain a given trait (Gibson, 2012). However, as a workaround, a combination of multiple biological markers may be used to greatly improve accuracy. For example, in a different context, two distinct characteristics pertaining to brain structure and activity offered significantly greater predictive power on

[1] Besides researchers, medical care providers would benefit from knowledge of patients' responsiveness to the placebo effect as well: They may, for example, adjust dosage of morphine and other pain-killers to account for patients' responsiveness to the placebo effect (Rakvag, 2005; Rakvag, 2008).

[2] i.e., the DNA sequence variation of a single nucleotide.

[3] Due the complexity of the interactions between neurotransmitter signalling, the pathology being studied, and expectations informed by treatment, a deeper understanding of the molecular mechanism remains an ongoing project.

when considered together (Hashmi, 2014). Likewise, information from multiple genetic markers can be combined in screening to maximize predictive power. As a cautionary example, however, comes in the form of a study linking a common SNP in the gene monoamine oxidase A to placebo-related reduction of depressive symptoms. The study observed COMT SNPs to have the opposite effect on such symptoms compared to what might be expected, with met alleles correlated with lesser placebo-induced depressive symptoms (Wendt, 2014). Thus, given the complex, non-additive, and sometimes antagonistic interplay between genetic predictors, they must be studied in tandem to ascertain the possibility of and method of effectively integrating their predictive power.

To develop effective genetic screening for the placebo response, the following criteria are hereby suggested:

1. The linkage to the placebo response must be well-evidenced.
2. The polymorphisms must be common. If they are extremely uncommon, then their applicability is severely reduced, especially in the context of combination of multiple genetic markers.
3. Multiple genetic markers, if used, should be studied in tandem to ensure effective integration of their predictive power.

rs4680 and rs6280 serve as promising co-candidates for predicting the placebo response per the above criteria. rs4680 is not only the most studied polymorphism in dopamine metabolism but also one of the most well-supported gene variants linked with the placebo response (Colagiuri, 2015). Furthermore, rs4680 occurs in a significant portion of the population, with approximately 20–25% minor allele individuals in Caucasians. As for rs6280, the common serine-to-glycine polymorphism in the DRD3 dopamine receptor increases affinity for dopamine and has been implicated in the modulation of the placebo response in a double-blind placebo-controlled randomly controlled trial (RCT) for schizophrenia (Bhathena, 2013). As for the third criterion, the same study also found a correlation between homozygosity for rs4680 and a greater placebo response, thus implying the ability to integrate rs4680 and rs6280's predictive power.

As with any other form of screening, screening against the placebo response introduces a confounding variable in the volunteer pool due to placebo-drug interactions. Some 2x2 studies crossing the factors of instruction about drug (patient is told they are receiving a drug vs. receiving a placebo) and actual drug administrated (patient is administered the drug vs. administered the placebo) point to the placebo effect and drug effects being additive, while other demonstrate the placebo and drug effects to be interactive (Kong, 2009; Schenk, 2014). In particular, COMT has been correlated with varied clinical outcomes in both placebo and drug treatment groups, indicating a gene-drug interaction and implicating a gene-placebo-drug interaction. For example, in a study of a tolcapone, a COMT inhibitor used in treating Parkinson's disease, met/met individuals performed better in the control group compared to the active group and vice versa for val/val individuals, suggesting a gene-placebo-drug interaction (Bitsios, 2011). In a different study of female cardiovascular disease, the COMT genotype correlated not only with treatment results in both the placebo and drug groups but also with baseline cardiovascular disease, once again pointing to a gene-placebo-drug hypothesis (Hall, 2014). Thus, to not introduce confounding variables into drug trials, potential gene-placebo-drug interactions must be well characterized or an NTC (no treatment control) group must be included for placebo screening.

Gene-placebo-drug interactions need not always be a nuisance: Theoretically, they can be actively leveraged as well. Drugs may be used to increase the placebo response following treatment or to decrease the nocebo response, wherein negative expectations result in worsened perceived outcomes (e.g., for surgeries). It may also be possible to inhibit the placebo response in trials to increase trial accuracy. In any case, gene-drug interactions must be well-characterized to introduce such measures.

To develop the requisite understanding of gene-placebo-drug interactions, whether to screen for the placebo response in trials or to actively modify the placebo response, more studies are required that include NTC groups. NTC groups illuminate the real psychological-physiological processes of the

placebo effect as distinct from reporting bias and other biases. While there have been many RCTs with placebo control groups, not many include NTC groups, and further studies would help better characterize the placebo response (Colagiuri, 2015). Moreover, further studies with NTC groups would supply more comprehensive knowledge of candidates for genetic markers of the placebo response. In particular, COMT correlates with a multitude of diseases, disorders, and deficiencies, serving as an excellent focus for future studies on gene-placebo and gene-drug-placebo effects (Hall, 2015). Ultimately, it is clear that the potential accuracy and efficiency improvements in clinical trial design justifies further research into the genetic prediction of the placebo response.

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