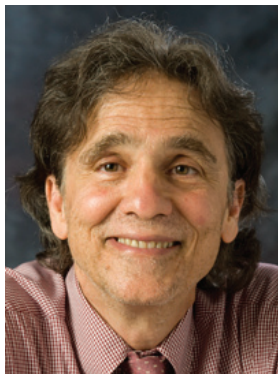


EDITORIAL

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Genetic biomarkers of placebo response: what could it mean for future trial design?

Kathryn T Hall^{1,2} & Ted J Kaptchuk^{*1,2}



“...identifying placebo-response biomarkers to guide enrichment could prove to be a valuable strategy.”

For many classes of medications, such as analgesics, antidepressants, angina treatments, antihistamines and nonsteroidal asthma prophylaxis, well-designed, randomized, placebo-controlled trials (RCTs) often show no difference between drug and placebo [1]. As a consequence, RCTs commonly use various ‘enrichment’ strategies that can selectively exclude participants based on pretreatment response to placebo (placebo run-in) or include them if they respond to drug (predictive enrichment) [2,3]. The enriched subset of patients is then randomized to drug or placebo. By presumably depleting placebo responders – or enriching for drug responders – it is expected that the trial will show a larger drug–placebo difference, thus increasing power while decreasing sample size. Many potential threats to the validity of enrichment strategies have been proposed. For example, placebo run-in subjects may experience unblinding side effects once shifted to active drug [4] and, conversely, patients pre-treated with drug then randomized to placebo can experience withdrawal relapse creating a bias against placebo [3]. Probably the most severe criticism is that empirical studies of placebo run-in methodologies generally fail to show any improved ability to detect drug–placebo differences [5].

Given the limitations of current enrichment strategies, coupled with the recent increases in clinical trial costs and placebo-response rates [6,7], identifying placebo-response biomarkers to guide enrichment could prove to be a valuable strategy. Research into the neurological basis of the placebo response was launched by the discovery that placebo-induced analgesia could be blocked by the opioid antagonist naloxone [8]. Today there is converging evidence that opioid receptors and dopamine-reward circuitry form part of the neurological placebo-response pathway [9,10]. With potential mechanisms in sight, the search for genetic biomarkers of placebo response is now a feasible proposition. We recently provided evidence that COMT, an enzyme that plays a key role in prefrontal and mid-brain dopamine tuning, may be a biomarker of placebo response in irritable bowel syndrome [11]. The COMT Val18Met single nucleotide polymorphism is a G-to-A transition that results in a valine-to-methionine substitution [12]. The methionine form of the enzyme is three to four-times less efficient at catabolizing dopamine than the valine form. Consequently Met/Met homozygotes have higher levels of prefrontal dopamine relative to Val/Met and Val/Val. Met/Met individuals have a greater tendency to seek and appreciate rewards [13] as well as to confirm new information based on their prior beliefs (confirmation bias) [14]. We recently demonstrated that Met/Met individuals have significantly greater placebo responses than Val/Met and Val/Val and that the response is highest when treated by a warm, caring practitioner.

¹Program in Placebo Studies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

²Division of General Medicine & Primary Care, Beth Israel Deaconess Medical Center, Boston, MA, USA

*Author for correspondence:

Tel.: +1 617 354 1744

E-mail: ted_kaptchuk@hms.harvard.edu

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Although genetic association does not confirm causality, our findings are consistent with a previous study that found the low activity form of monoamine oxidase A, another enzyme that modulates dopaminergic tone, to be related to increased placebo responses in depression [15]. The fact that dopamine is a key neurological substrate of placebo responses does not preclude the possibility that other mechanisms and biomarkers may be involved. Indeed, the serotonin-related polymorphisms, serotonin transporter-linked polymorphic region (5-HTTLPR) and G703T in tryptophan hydroxylase-2 have also been identified as possible biomarkers of placebo response in severe anxiety disorder [16]. Although COMT's utility and scope as a biomarker will need further research and validation, it is worthwhile to consider the impact of this or other potential genetic placebo-response biomarkers on clinical trials and medical treatment.

COMT Val158Met is a common genetic variant with a minor or Met allele frequency of 0.38 in the Caucasian population. This high frequency makes COMT Val158Met genotyping an efficient and inexpensive way of potentially identifying a significant proportion of placebo responders, thus potentially greatly reducing the clinical time and resources involved in treatment-based enrichment strategies. Whereas the exclusion of genetically designated placebo responders – that is, Met/Met – and the inclusion of non-placebo responders – that is, Val/Val – seems straightforward, the issue of whether or not to include the heterozygotes with the intermediate placebo response phenotype – that is, Val/Met – raises several issues. Based on the natural distribution of the COMT Val158Met genotypes in the majority North American population, Val/Met represents the largest group; and, according to our results, appears to have an intermediate level of placebo response. Although the inclusion of this group would be expected to decrease effect sizes, including the Val/Met would increase the pool of available subjects and broaden the subsequent generalizability of the drug treatment. If RCT were conducted only on subjects with the placebo low-response Val alleles, the safety and efficacy of the pharmaceutical agent would not be generalizable to Met/Met and approved drugs would reach the market with a label limited to people with Val alleles. RCT for Met/Met subjects, the likely placebo responders, would possibly be biased towards the null and, therefore, a costly and inefficient proposition. In addition, Met/Met participation in the treatment arm of a study for a condition that has high placebo responses could present the challenge of unnecessary risks by exposing these subjects to possible adverse effects with minimal incremental therapeutic benefit beyond a placebo response. Such methodological and ethical issues will have to be carefully considered.

In the case of the COMT-associated placebo response, which is thought to function via

dopaminergic signaling, the possibility exists that drugs acting directly or indirectly through dopamine signaling could also affect this placebo response. Such drug–placebo interactions are not unprecedented. Beyond the early placebo-blocking naloxone experiments [8], the cholecystokinin receptor agonist proglumide and benzodiazepine diazepam were also found to disrupt hyperalgesia-induced from negative (nocebo) placebo expectations [17]. Also in Parkinson's disease, placebo responses were found to increase as the drug effect decreased [18]. Furthermore, a differential effect of drugs and placebo, based on COMT Val158Met genotype, was observed in a series of studies that examined treatment outcomes relative to placebo and the COMT inhibitor Tolcapone [19,20]. These studies found that, whereas Val/Val subjects had a marginal placebo response relative to their strong drug response, Met/Met subjects had the opposite outcomes with a robust placebo response that was abrogated by the drug. Further research is warranted to examine whether the worsening of outcomes for Met/Met subjects is generalizable to other drug treatments, the mechanism of action of which interacts with the dopamine-mediated placebo pathway. Likewise, as other placebo genetic biomarkers become available, evaluating them for potential drug–placebo interactions will be important.

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Environmental factors might also interact with the placebo-biomarker genotype to shift the placebo treatment experience. In our study, we observed that placebo responses in Met/Met subjects were strongest when the patient–practitioner relationship was the most positive [11]. This finding might not only inform clinical practice but also highlights another important potential modifier of treatment outcomes in RCT. As clinical trials are often conducted at multiple sites and involve multiple clinicians at each site, it is important to monitor and, if possible, control the nature of the patient–doctor relationship as it may have a positive or, in some cases, negative effect on outcomes. It remains to be seen if this variable will be less important if studies are limited to people with placebo-nonresponder Val alleles who were less affected by the patient–practitioner interaction [11].

Finally, given that the power of placebo has always captured the public imagination, should there come

a time when people know their COMT Val158Met or other placebo biomarker genotype, it will be interesting to see how the knowledge that you are likely a placebo responder or non-responder, might affect expectation of outcome and, in turn, clinical response to placebo or drug treatment.

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With the growing size and cost of clinical trials, more than ever, clinical researchers are seeking stratification strategies that work and are not straddled with the biases and limitations of common enrichment approaches. Here, the benefit of hindsight can be leveraged to test the utility of COMT Val158Met as a biomarker of placebo response by reanalyzing previously conducted

clinical trials, especially those that already have genome-wide association data. Although it is too early to know if we are entering a new era, rigorous research to replicate and address the utility and generalizability of the COMT Val158Met placebo biomarker to other diseases, conditions or drug-treatment paradigms could be critical to fulfill the promise and address the complications of using placebo genetic markers to enrich RCTs.

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