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Genetics and the Placebo Effect: the Placebome

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Abstract

Placebos are indispensable controls in randomized clinical trials (RCTs), and placebo responses significantly contribute to routine clinical outcomes. Recent neurophysiological studies reveal neurotransmitter pathways that mediate placebo effects. Evidence that genetic variations in these pathways can modify placebo effects raises the possibility of using genetic screening to identify placebo responders and thereby increase RCT efficacy and improve therapeutic care. Furthermore, the possibility of interaction between placebo and drug molecular pathways warrants consideration in RCT design. The study of genomic effects on placebo response, "the placebome", is in its infancy. Here, we review evidence from placebo studies and RCTs to identify putative genes in the placebome, examine evidence for placebo-drug interactions, and discuss implications for RCTs and clinical care.

Keywords

placebo; RCT; COMT; no treatment control; pharmacogenomics

Biomarkers of the placebo response: a historical perspective

From the early use of bread pills as patient appeasement [1] to clinical trial nuisance variables, placebos and placebo effects (see Glossary) have a troubled history [2, 3]. Recent innovative neuroimaging [4] and physiological experiments [5] have fostered the current viewpoint that placebo effects are biological responses to psychosocial environmental cues surrounding the administration of inactive (or active) treatments. Such placebo research has established that the placebo response is more than patient report bias, regression to the mean, or spontaneous remission [6–8]. As a result of these developments, placebo responses

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are emerging as a legitimate series of biological reactions that must be rigorously characterized to facilitate efficient pharmaceutical development and optimal clinical care.

Predicting who will be a placebo responder could be of great value to researchers and patients. In drug development, detecting a difference between active intervention and the placebo control is an underlying goal of randomized controlled trials (RCTs). Being able to identify and exclude individuals who are more likely to respond to placebos could enhance trial designs seeking to find such a difference. Potential cost savings due to reduction of sample size could be of enormous benefit for drug development [9]. From a clinical perspective, knowing likely responders could modify treatment approaches (including patient-provider interactions) and allow for more careful titrations of medication dosages. Precise knowledge of the contribution of genetic variation to placebo effects, therefore, promises to guide the development of more efficient controls in experiments and refinements of clinical practice.

In the past scientists used behavioral instruments like personality measures to predict placebo responders [10, 11]. This approach has had limited success as these blunt instruments proved no match for the complex interplay of shifting states that may modify an individual's placebo response. Not only do clinical trial researchers have to contend with the type, duration, and severity of the condition, but the practitioner's "bedside manner," the patients beliefs, hopes and expectations and patient's previous experiences [12] make predicting the placebo response an ongoing challenge.

There is growing evidence that the individual's genetic makeup (a stable trait) influences clinical outcomes and potentially may allow for identification of placebo responders. Individual variations in the genome can give rise to differences in the functioning of myriad interacting gene, microRNA, and protein molecular networks. The recent availability of large-scale genomic, RNA, and protein measurements (-omics) offers a potential new approach by which to understand, control, and harness the placebo response. However, despite the promise of this technology to guide the development of safer and more effective pharmaceuticals and personalized medicine, no comprehensive studies (for e.g. genome-wide association studies; GWAS) to identify genomic correlates (or other biomarkers) of the placebo response, "the placebome", have, to our knowledge, been performed.

The search for genomic biomarkers of the placebo response is in its infancy and, thus, we initiate the discussion of placebo genomics with the search for placebo response genes. Indeed, there have been many placebo-controlled RCTs with GWAS data, but they all lack a key dimension: a no-treatment control (NTC). A NTC is one of the few methodologies that can disentangle genuine psychosocial and physiological placebo responses to the symbols, rituals, and behaviors of the clinical encounter ("placebo effects") from spontaneous remission, regression to the mean, and the natural waxing and waning of illness. The main reason for this gap is simple: trials are interested in testing drug efficacy and randomization to active treatment or placebo is thought to be a sufficient measure by which to allow clinical trial researchers to discern specific drug responses. Any improvement in subjects in the placebo arm has generally been ignored and viewed as an intrusive but necessary hurdle to overcome. However, without studies that have NTCs, a control for the placebo arm, an

accurate and comprehensive view of the set of potential placebo genetic biomarkers (the placebome) may not easily become available.

Despite this limitation, we can cull information about the genes involved in the placebome from three types of available studies in the literature: (i) a small RCT investigating placebo responses that included a NTC and conducted a candidate gene analysis; (ii) placebo-controlled RCTs in patients that included an analysis of candidate genes that coincide with genes implicated in the placebo response mechanism; and (iii) experimental studies in healthy subjects that examined candidate placebo genes. Although the generalizability of placebo response mechanisms from healthy volunteers to patients is not understood, the results of these studies can yield some insight into potential genes constituting the placebome.

The importance of identifying genes involved in the placebo response is not, however, limited to outcomes in the placebo arm of RCTs. An important underlying assumption in RCTs is that, in aggregate, the main difference between the drug treatment and placebo arms is solely the effect of the active drug. However, a not uncommon and striking observation in RCTs that include genotyping of putative placebo pathway genes, is effect modification of the outcomes by placebo genotype in both the placebo arm and the drug treatment arm; in other words, there is evidence of gene-placebo-drug interactions. The possibility that, in some drug treatment paradigms, there is placebo-drug interaction as a result of genetic variation in placebo pathway genes suggests that we may need, in some cases, to refine and re-calibrate the assumptions of placebo controls in RCTs.

Towards a physiology of the placebo response

The first solid evidence that there is an underlying biological process that gives rise to the placebo response; that the placebo effect is more than “report bias” patients pleasing the experimenter, or overenthusiastic researchers, was first published in 1978 followed by a series of studies on placebo effects in molar extraction [13]. In this and subsequent studies, Levine *et al*., demonstrated that the body’s pain suppression system could be induced by placebo and was, in turn, blocked by naloxone, an opioid receptor antagonist. Further studies by this group hypothesized that morphine and placebo might share a common opioidergic mechanism and estimated the placebo analgesic effect to be equivalent to approximately 4–6 mg of morphine [14, 15]. As the opioid system emerged as a major underlying biochemical mechanism involved in placebo analgesia, the role of m-opioid receptors in placebo analgesia was further confirmed in neuroimaging studies [16–19]. These studies used pain models to demonstrate that expectation of analgesia induced activity in key areas in the brain involved in endogenous opioid transmission and analgesia. Since these early studies, placebo researchers also raised the possibility that the opiodergic system is not exclusively responsible for placebo analgesia [12]. Further work dissected the role of endogenous opioids in placebo analgesia showing naloxone only partially blocks placebo analgesia in subjects conditioned with the nonsteroidal anti-inflammatory drug ketorolac [20], while the cholecystokinin antagonist proglumide potentiates placebo pain relief [21–23]. More recently, the endocannabinoid system has also been implicated in placebo analgesia in physiological experiments [24].

Although the analgesic effects of opioid receptor signaling explained how placebo treatment might mitigate pain in many situations, it did not address how placebos mediated clinical benefit in other treatment paradigms. Subsequently, researchers postulated that expectancy of benefit or reward might be a key general mediating process in the placebo response [25]. To test whether neural correlates of reward were also associated with anticipation of placebo responses, in 2008 Scott *et al.* used a pain model that looked at both opioid and dopamine receptor activation in brain regions associated with reward [26]. They showed that both pathways were activated in anticipation of the placebo response and that higher levels of dopamine receptor activation were seen in individuals with higher placebo responses. Conversely, they found that in individuals who reported an increase in pain (i.e. placebo non-responders or, more accurately, negative placebo or nocebo responders), dopaminergic and opioid signaling was reduced. Positron emission studies on the placebo response in Parkinson's disease also showed that striatal dopaminergic neurons were activated in anticipation of benefit or reward when a placebo was administered [27, 28]. Neuroimaging studies of subjects with major depression suggest that placebo treatment causes changes in brain function [29, 30]. Given the especially high rate of placebo responses in depression RCTs [31, 32], the serotonin pathway has also been discussed in relationship for placebo responses.

This growing list of neurotransmitters and neurological pathways mediating the placebo response provide a framework for candidate gene analyses. Indeed, treatment outcomes in the placebo arms of trials that have assessed genetic variation in the dopaminergic, opioid, cannabinoid, and serotonergic pathways suggest that genetic variation in the synthesis, signaling, and metabolism of these neurotransmitters may contribute to variation in the placebo response (Table 1).

Genetic variation in the dopamine pathway

The emergence of the dopamine-mediated reward centers as central to the underlying physiology of the placebo response make genetic variation in dopamine metabolism and signaling pathway genes prime candidates for placebo response biomarkers. Rs4680, the most studied polymorphism in dopamine metabolism, is in the gene for catechol-O-methyltransferase (COMT), an enzyme that metabolizes dopamine and other catecholamines [33]. The rs4680 single nucleotide polymorphism (SNP) has been implicated in modifying clinical outcomes in both the placebo and drug treatment arms of numerous diverse trials [34–44]. Rs4680 encodes a valine (val)-to-methionine (met) change at codon 158 (val158met) resulting in a three-to four fold reduction in enzymatic activity. Homozygotes of the less-active met allele have been associated with higher levels of dopamine in the pre-frontal cortex, a region implicated in the placebo response pathway [45, 46]. Rs4680 is a common polymorphism, and the prevalence of the less frequent met allele or minor allele (MAF) is reported as 0.37 in Caucasians [47], but varies by race/ethnicity [48, 49]. The high MAF of rs4680 translates to an estimated 20–25% of met/met individuals in Caucasian populations. Finding common SNPs is an important criterion when considering the feasibility of using genotype as a predictive placebo-response marker.

To our knowledge, the only candidate genetic association study that included a no treatment control (NTC) and examined the effect of genetic variation in *COMT* on the placebo response [38] used an RCT designed to test whether placebo treatment could incrementally combine three components related to placebos: diagnosis and observation (NTC arm), therapeutic apparatus (placebo acupuncture), and apparatus plus a supportive patient-practitioner relationship (placebo acupuncture plus a warm-caring provider) [50]. The RCT was a three-week trial in patients with irritable bowel syndrome (IBS), and the main outcome was reduction in IBS symptom severity. Patients in the arm that combined all the components, the strongest placebo treatment, reported the greatest symptom relief. The candidate genetic analysis performed on a subset of these patients, who gave genetic informed consent, looked at the association of rs4680 with IBS symptom severity, adequate relief, and quality of life in each of the treatment arms. Patients homozygous for the rs4680 low-activity met allele (met/met), known to have the high levels of dopamine, had the greatest placebo response. The high-activity val allele homozygous (val/val) patients had the lowest placebo response. The val/met heterozygotes had an intermediate response. Similar results were reported for another *COMT* SNP, rs4633, which is closely linked to rs4680.

A subsequent small acute-pain model placebo neuroimaging study in healthy volunteers looked at genetic variation in *COMT* in relation to brain activity in the reward system using resting-state functional magnetic resonance imaging [51]. These researchers showed that placebo response to pain in healthy volunteers supported the IBS results such that the number of rs4680 met alleles was linearly correlated with suppression of pain in the placebo expectation laboratory paradigm. While not having a NTC, the pain stimulation in this experiment was momentary, precise, and calibrated, so we can assume that spontaneous remission and waxing and waning of illness are not potential confounders.

Interestingly, a recent laboratory study found that the rs4680 high-activity val allele was associated with a higher frequency of nocebo effects (negative placebo side-effect) using a model of learned immunosuppression [52]. Similarly, in the IBS placebo study discussed previously, the rs4680 high-activity val allele was associated with a higher frequency of complaint reporting [40]. This association of nocebo effect with the high-activity rs4680 val allele is not necessarily unexpected given that in the absence of any significant improvements in symptoms derived from a placebo response, val/val individuals may have more complaints or experience more side-effects.

In addition to *COMT* there are several other polymorphisms in the dopamine pathway that are potential placebome candidates. Monoamine oxidase A (MAO-A) has been implicated in reward pathways through its role in catalyzing the oxidation of monoamines including dopamine. MAO-A also metabolizes serotonin and has been shown to affect serotonergic availability and signaling [53]. The MAO-A gene is X-linked, and a common rs6323 (G to T) SNP results in a 75% reduction in enzymatic activity in females homozygous for the T allele, and males hemizygous with one T allele [54]. The association of *MAO-A* with treatment response to placebo was examined in a candidate gene analysis of patients with clinical depression from four combined small placebo-controlled RCT's of three selective serotonin reuptake inhibitor antidepressants (SSRIs), venlaxafine, sertraline, or fluoxetine [55]. The primary outcome was determined by the 17-item Hamilton Depression Rating

Scale (HAM-D_{17}). Consistent with the findings described above for *COMT*, individuals with the low-activity MAO-A genotypes and, therefore, higher basal dopamine tone had a higher placebo response than those with the high-activity MAO-A genotypes. The *COMT* rs4680 association with placebo response was also examined in this study, but the results were not significant. It is unclear whether the non-significant results with *COMT* were due to lack of power, a basic difference in the subject population, or other factors.

To our knowledge, the largest study of genetic variation in RCT patients randomized to placebo treatment examined 34 candidate genes (500 polymorphisms) in four trials of bupropion for major depressive disorder [43]. Although results for rs4680 were not reported in this trial, several other *COMT* SNPs were associated with placebo response and placebo remission (although these associations did not survive correction for multiple comparisons). The placebo response association with *MAO-A* rs6609257, a SNP associated with dopamine basal tone, was one of the associations with treatment response in the placebo arm that was significant after correction, supporting the candidacy of *MAO-A* in the placebome.

Genetic variations in dopamine receptor genes which modify dopaminergic signaling also modify the function of the brain reward circuit [56, 57]. Rs6280 is a common serine-to-glycine coding polymorphism in dopamine receptor 3 *(DRD3)* that results in the *DRD3* glycine form having a higher affinity for dopamine than the serine form [58]. A recent placebo-controlled RCT of a novel drug for treating symptoms of schizophrenia (ABT-925) examined the effects of genetic variation in *DRD3* on the Positive and Negative Syndrome Scale (PANSS) [59]. Subjects homozygous for rs6280 serine allele (S/S) had significantly better outcomes in the placebo arm than when they were treated with increasing doses of ABT-95. Consistent with other studies, this study also showed that the *COMT* rs4680 met/met subjects had a higher placebo response.

Genetic variation in dopamine beta-hydroxylase (*DBH*), an enzyme that converts dopamine to norepinephrine, like *COMT*, has been associated with variation in blood pressure [39] and psychiatric disease. In studies of alcohol dependence, individuals homozygous for the CC genotype of the rs1611115 *DBH* polymorphism appeared to do better on placebo and worse on naltrexone [60]. *DBH* was also one of the genes examined in the largest 54-candidate gene analysis of the placebo arm of the bupropion trial discussed above [43]. The *DBH* SNP rs2873804 survived the correction for multiple comparisons reinforcing *DBH* as a potential candidate for a placebo response gene.

Brain-derived neurotrophic factor (BDNF) plays an important role in learning and memory, mediating and maintaining turnover of dopamine [61, 62]. BDNF's functions in neuroadaptive change and response to reward stimuli [63, 64] make it another plausible candidate for the placebome. The rs6265 SNP in BDNF encodes a valine-to-methionine substitution at codon 66 [47]. This functional polymorphism is hypothesized to reduce activity-dependent BDNF release due to inefficient BDNF trafficking to secretory granules [65]. Genetic variation at rs6265 was associated with greater placebo-induced dopamine D2 and D3 activation in rs6265 val allele homozygotes compared to met allele carriers; however, these differences in neuronal activation did not translate into differences in placebo analgesia as assessed by the pain ratings reported [66].

These data show a consistent association of outcomes in patients and healthy volunteers treated with placebo with genes involved in dopamine metabolism and signaling such that individuals with higher levels of dopamine or higher dopaminergic activity tended to be more likely to respond to placebo in the studies examined. Taken together, these associations provide support for dopamine pathway SNPs as placebo response genetic markers. More research in other conditions, dopamine pathway SNPs, and with larger samples with NTCs would help to make these associations more definitive.

Genetic variation in the opioid signaling pathway

Endogenous opioids signal through opioid receptors, and genetic variation in the μ-opioid receptor gene (*OPRM1*) has been shown to modify treatment outcomes in pain studies. The analgesic effects of placebo have been shown to be mediated through activation of endogenous opioid as well dopaminergic mechanisms. In a small experimental placebo study performed on healthy volunteers, signaling in the dopamine pathway was linked to opioid receptor signaling in anti-nociceptive responses to placebo [26]. Rs1799971 is a functional polymorphism in the *OPRM1* gene that results in an asparagine-to-aspartic acid change at codon 40. The aspartic acid variant of the receptor was found to reduce receptor function across several studies [67, 68]. The association of rs1799971 with placebo response in healthy volunteers was studied in an experimental model of placebo-induced analgesia [69]. In this study, placebo-induced activation of dopamine neurotransmission in the nucleus accumbens was greater in asparagine homozygotes compared to aspartic acid-allele carriers, suggesting that genetic variation in *OPRM1* could also contribute to variability in the placebo response.

Whether or not the association of *OPRM1* with placebo-induced analgesia is generalizable to other non-pain paradigms of placebo response remains to be determined. Indeed, work on genetic variation in *OPRM1* has examined associations with the reward-based addictive effects of psychostimulants (e.g. amphetamine) and opioid drugs (e.g. morphine). Several of these studies have shown differential outcomes in the placebo and drug treatment arms as a function of genetic variation in *OPRM1* [60, 70]; but, again, it is impossible to determine if the effect modification of treatment outcomes in the placebo arm is a function of placebo response or genetic variation effects at baseline in the absence of a NTC.

Genetic variation in endocannabinoids and serotonin signaling pathways

The two other neurological pathways implicated in the placebo response involve endocannabinoid and serotonergic signaling. Endocannabinoids are neurotransmitters that signal through the cannabinoid receptors, CB1 and CB2, and have been implicated in analgesia [71]. Placebo laboratory studies have further implicated endocannabinoids in placebo analgesia, providing a rational for considering genetic variation in the endocannabinoid pathway in the placebome [72]. The effects of genetic variation in fatty acid amide hydrolase (FAAH), the major degradative enzyme of endocannabinoids, was examined in a small study [73] that used some of the same subjects as the *OPRM1* placebo experiment described above [69]. This study found that homozygotes for the *FAAH* Pro129 allele (known to increase chronically endocannabinoid levels in the brain in response to

pain) reported more placebo-induced analgesia, supporting the endocannabinoid pathway genes as loci worth exploring further for candidacy in the placebome.

Serotonin is a neurotransmitter that is important in regulating mood, appetite, and sleep. Given the high rates of placebo responses in RCTs of treatments for mood disorders [31], the serotonin pathway is important to examine for possible placebo response-related genes. SSRIs are antidepressants thought to block the uptake of serotonin. There is some evidence from candidate gene studies that serotonin pathway genes are associated with placebo responses of depression and anxiety. The previously mentioned study that examined 34 candidate genes for placebo response in depression included several genes in the serotonergic pathway and reported significant association between placebo remission with 5-hydroxytryptamine (serotonin) transporter *SLC6A4* rs4251417, *HTR2A* rs2296972, and rs622337 [43]. Unfortunately, of the largest GWAS conducted to determine the effectiveness of different treatments for people with major depression, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, did not include a placebo control [74].

Serotonin-mediated placebo response genes have also been examined in a small RCT of social anxiety disorder (SAD). In this small candidate gene PET study of SAD, reduction in anxiety symptoms in response to placebo was accompanied by a reduction in stress-related amygdala activity [75]. This reduction was limited to subjects homozygous at two serotonin pathway-related polymorphisms, rs4570625 in the tryptophan hydroxylase-2 (*TPH2*) gene promoter and the long allele of the serotonin transporter-linked polymorphic region (*5-HTTLPR*). Although this study was limited by its small size and by not having an NCT, these findings, absent other evidence, suggest that genetic variation in serotonin pathway polymorphisms *TPH2* and *5-HTTLPR* might be potential biomarkers of placebo response in SAD.

Given the complex interplay of behavior, expectation, neurotransmitter signaling, disease, and the context of the medical treatment ritual, the molecular pathways and genes involved in contributing to placebo responses is unfolding as a potentially complex network.

The placebome: main and interaction effects in RCT design

Although we do not yet have a comprehensive understanding of the placebome, it is prudent to consider issues that might arise and the potential impact on RCT design. In general, the placebo arm is considered to be an adequate control for outcomes in the active treatment arm of RCTs. However, if the placebo response does, indeed, vary by genotype, we might expect challenges with confounding, potential gene-drug-placebo effect modification and disease specific effects.

The efficacy of a drug is determined by the difference between the aggregate outcomes of individuals randomized to drug versus placebo treatment. The accuracy of the estimate of drug efficacy, especially in smaller trials, therefore depends on the randomization balancing the numbers of placebo responders by genotype across treatment arms. If by chance, in trials where the placebo response is known to be high (such as IBS [76]), there are more genetically predisposed placebo responders in the placebo arm than in the drug arm, the

estimate of drug efficacy will be confounded by genotype and the results biased towards the null. If this imbalance is not accounted for, it would be expected to be more of a problem in smaller trials than larger trials. Ideally RCTs would be designed such that the randomization balanced genetically predisposed placebo responders across all arms of a trial.

To date pharmacogenomic research has concentrated on gene-drug interactions in the context of the drug treatment. However, since many of the putative placebo genes or pathways are also drug targets, there is the possibility that these drugs could interact with the placebo response and thus compromise the assumption drug and placebo responses are additive. Furthermore, the effect of genetic variation on placebo and/or drug response, a combined gene-drug-placebo interaction, could result in differential outcomes in the placebo and drug treatment arms as a function of genotype. Although three-way interactions are considered extremely unlikely, there are several reports in the *COMT* literature that provide reasonable supporting evidence [34, 35, 39, 41, 44, 59]. For example, in a small RCT of tolcapone (a *COMT* inhibitor used to treat Parkinson's Disease), individuals homozygous for the low-activity *COMT* rs4680 met allele performed better when treated with placebo than when treated with drug [34]. Conversely, high-activity val allele homozygotes improved with tolcapone treatment compared to placebo. These findings were interpreted as the drug "not working" for met allele homozygotes, but a gene-placebo-drug interaction hypothesis could also be applied to these differential outcomes. Although most of these studies are small and focused on mental performance outcomes, a *COMT*-drug-placebo effect modification was also observed in the Women's Genome Health Study, a large placebo controlled RCT of aspirin and vitamin E for the primary prevention of cardiovascular disease [39]. In this study, not only did clinical outcomes in both the placebo and drug treatment arms vary as a function of *COMT* genotype, an association with baseline cardiovascular disease was also reported. Of course, without a NTC interpretation of results from the placebo arm should be approached with an abundance of caution.

The diversity of diseases associated with *COMT* is striking, and ranges from dopamine-associated disorders such as Parkinson's [77] and schizophrenia [78], to epinephrine and norepinephrine-related disorders hypertension [79], pre-eclampsia [80], and major cardiovascular disease [39]. COMT enzymatic activity has been shown to be inhibited by several drugs including tolcapone [35], quercetin [81] and vitamin E [82]. This potential intersection of disease, drug and placebo effects suggest that *COMT* is an excellent model for the sophisticated network analyses that may be necessary to fully appreciate the potential complexity of the placebome. Large-scale integration of genomic effects from proteomic, metabolomic, and small molecule-induced genome-wide transcriptional studies have greatly increased our power to identify and examine complex perturbations in these molecular networks that can compromise or enhance drug efficacy and safety [83, 84]. Despite the importance of placebo controls in drug development, these systems biology and pharmacology studies do not provide any data on the placebo condition. This is partly because these studies are derived in cellular model systems and partly because the concept of interaction effects between drug and placebo treatment is novel and remains to be proven. As large-scale placebo response -omics data become available, it may then be possible to

identify disease and or drug specific placebo modules by mapping these molecules and their relationships to systems biology frameworks such as the interactome [85, 86].

The potential complexity of this network is rapidly escalated when one considers that different diseases and different placebo pathways may produce different responses in different patients. Consider, for instance, an individual who is dopaminergic-dominant and tends to be more responsive to placebo in pain studies, their placebo response in a depression trial might differ significantly depending on whether they were serotonergic-dominant or recessive. This possibility may help explain why it has been so difficult to identify consistent and reliable placebo responders [11]. Therefore understanding the net-effect of the placebome and how this varies in the context of specific diseases and treatments may be an important consideration in personalized medicine.

While studies have not as yet been conducted to identify genes and drugs that modify placebo response, hypothetically there may even be situations in which one might opt to intentionally use a drug to modify the placebo response. For instance, purposefully using a drug to inhibit the placebo response in clinical trials could minimize the placebo response and allow for a more accurate measurement of the drug effect. In this case the placebo modifying drug would be administered to both the drug treatment and placebo arm of the trial, and any potential drug-drug or gene-drug interactions would have to be well characterized.

Given that so many future RCTs already include a placebo treatment arm and plan to collect -omics data, we propose that a cost-effective approach to elucidating the placebome would be to simply add NTCs to these studies. Of course if this type of data already exists, conducting analyses designed to identify placebo response markers would also be worthwhile. Such an approach would not be limited to disease or treatment type and would constitute a concerted and expeditious effort to populate the placebome, perhaps to great clinical and pharmaceutical drug development benefit.

Clinical considerations

Information on whether a patient is likely to be a placebo responder or non-responder is not a disease or condition that would warrant automatic consideration in routine clinical care. The placebome seems less critical than knowing whether a singular genetic variant of a cancer will respond to particular tailored pharmaceutical interventions, yet, there may be important clinical implications in routine care. For example, compelling evidence suggests that persons homozygous for the low-activity met allele at *COMT* rs4680 (met/met) are more likely to respond to morphine than those homozygous for the val allele (val/val) [87, 88]. An individual difference in morphine metabolism is the usual interpretation; however, this research is based on cohort studies of patients without placebo controls. If replication of these studies with proper placebo controls demonstrate that, in fact, this difference is due to differential placebo responses or even placebo-drug interactions, a *COMT* profile could be helpful in determining an initial dose for morphine treatment (and possibly other pain medications). This question of personalizing drug doses based on genetic placebo profiles is likely to be significant in conditions other than pain that are known to have high variability

in both drug and placebo responses, such as functional urinary and bowel conditions and symptoms of fatigue, nausea, hot flashes, depression, and anxiety. Furthermore, the usefulness of a recently proposed strategy of open-label honest placebo treatments in such conditions as irritable bowel syndrome [89], acute episodic migraine attack [90], and depression [91] could prove more feasible with knowledge of a patients' placebome.

Ethical considerations

If our interpretation of this early research on the placebome and the interaction of disease, drug, and genes has validity and stands the test of further inquiry, ethical issues will have to be examined. If a genetic profile(s) of placebo responders can be established, what are the ethical implications? Can, and should, physicians test for genetic placebo response propensities? Can patients refuse permission to be tested? Should patients be told about their propensity? Can patients refuse to know or refuse to have this designation in their medical records? Can and how should physicians ethically utilize this information if it appears incidentally in genetic testing? Resolution of these issues will depend on how the entire question of genetic information will eventually be incorporated in routine clinical care. Nonetheless, from our perspective, the ethical principles of autonomy, transparency, and respect for person should remain paramount even as genetic information becomes more easily accessible [92–95]. Furthermore, such ethical issues would have to be considered in the context of shared decision-making and patient's personal values and preferences [96]. Other issues might include: Is it feasible and ethical to modify the quality of the clinical encounter of patient's treatment because they are likely placebo responders or non-responders? And, finally, how does knowing one is a placebo responder affect one's placebo response?

Whether and how information of a placebome should be applied to RCTs could also have complex ethical implications. A key goal of the RCT is to detect a drug-placebo difference. There is a long and unsuccessful history of attempts to increase the efficiency of RCTs with placebo run-in periods that eliminate placebo responders [97–99]. Could placebome data lead to new "enrichment" strategies that could eliminate *a priori* high placebo responders in RCTs? Our discussion of placebo-drug interactions suggests that genetic profiles may have the possibility of becoming an alternative strategy to make detection of drug-placebo difference more efficient. Several questions arise from implementing such an innovation in the regulatory space. Would there be a benefit to using these enrichment strategies in trial design? How would the FDA label be affected? Obviously, regulatory agencies would need to determine the medico-legal implications of such an enrichment strategy.

Limitations

The ability to predict the placebo response assumes that it is a stable trait that is not influenced by the many individual states, for example personal and cultural beliefs, conscious and non-conscious expectations, previous experiences with health care, severity of illness, history of illness, and research design factors such as treatment duration, number of active arms in the trial, practitioner characteristics variables, and their interaction factors such as the quality of the entire therapeutic encounter. Therefore, these individual,

contextual or situational variables present an important limitation on any simplistic or reductionist genetic model developed to predict placebo response [10, 100]. Although it seems plausible that genetic factors are predictive of a relative disposition to interact with such state and environmental influences, there may be epigenetic effects that are also critical to placebo responses. Furthermore, given the potential for different placebo pathways, in different classes of diseases and disorders, consideration needs to be given to developing disease or treatment specific placebo panels from the placebome. The number of genes required to build an effective placebo response screening panel remains to be determined. With small candidate genes studies lacking NTCs, there are significant limitations to available data on the placebome. Future studies will have to be large to account for the many environmental, genetic, and drug interactions. Since in the absence of definitive studies the potential of drug treatments to interact with placebo response genes remains hypothetical, the size of these interaction effects relative to placebo effects is not known, and it remains to be seen how large a trial would have to be to measure this effect modification. In the case where interactions are significant, refinement of RCT design might be a real possibility.

Concluding remarks

The placebo response is a complex phenotype with an unfolding physiology. Based on the evidence summarized here, we can speculate that the placebome consists of multiple intersecting pathways that have upstream or downstream effects on dopamine and opioid function, depending on the disease or disorder being treated. The endocannabinoid and serotonin pathways may also be involved, but the evidence is more limited. The potential overlap between placebo, drug treatment and disease add to the complexity of the placebome and underscore the importance of understanding how it fits into larger more complex biological networks. An important next step in describing the placebome would be to include a NTC in placebo-controlled RCTs that plan to capture -omics data. This approach might be cost-effective and allow for a broad view of placebo response genes and other molecules across varying conditions and treatments. Knowledge of the placebome has the potential to guide development of novel strategies for identifying placebo responders and clinical trial design. However numerous attendant regulatory, ethical and clinical questions would need to be addressed before such innovations could be integrated into drug development and clinical care (Box 1). Given the potential benefits in terms of research design, reduction in the cost of clinical trials, and safer more effective personalized medicines, continued placebome research is justified.

Box 1

Outstanding Questions

- What proportion of the variability in placebo response can be attributed to the placebome?
- How do shifts in environment and culture interact with the placebome?
- To what extent are there disease specific sub-modules in the placebome?

- Do gene-drug-placebo interaction effects exist? How do these affect outcomes in clinical trials?
- What design and analysis issues arise from using placebo response biomarkers in RCTs?
- What are the regulatory and ethical implications of using placebo response biomarkers in clinical trials?
- How might treatment in the clinic be modified if a patient is genetically predisposed to respond to placebo? In what kinds of conditions would drug dosages be modified if a patient has a disposition to have a higher placebo response?
- Will knowing if you are genetically predisposed to be a placebo responder change your placebo response?

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Glossary

Dopamine	a catecholamine neurotransmitter or hormone that is important in signaling in the reward-motivation and motor control neural pathways. Dysfunction in the dopamine system is associated with several diseases and disorders including schizophrenia, attention deficit hyperactivity disorder, addiction and Parkinson's.
Drug efficacy	the ability of a drug to produce a clinically beneficial effect. In a RCT, drug efficacy is determined by subtracting the primary clinical outcome in the placebo arm from outcome in the drug treatment arm.
Endocannabinoids	a group of neuromodulatory lipids that play a role in modulating mood, appetite, memory and pain sensation.
Genome-wide association study (GWAS)	a study used to scan and compare variation in genes across large numbers of individuals to identify genetic associations with disease incidence, treatment and prevention.
Interactome	the term given to the entire set of molecular interactions within the cell. The interactome therefore seeks to define the physical and biochemical influences that gene, protein, small molecule drugs, microRNA and other biomolecular networks exert on each other across normal or disease states.

Minor-Allele Frequency (MAF)	used to describe how many people in a given population carry the least common allele. If in a given population, the MAF is 20%, then among population members, one in five chromosomes will carry the minor allele and four out of five chromosomes will carry the other genetic variant, or major allele.
Nocebo effects	considered the opposite of placebo effects. They are negative or adverse effects in response to an inert or placebo treatment.
Nociceptive pain	caused by stimulation of pain receptors in response to pressure, temperature or irritating substances which send pain signals to the brain in response to injury or the possibility of injury. Anti-nociceptive treatments are designed to reduce such pain.
No Treatment Control (NTC)	an arm of a RCT in which randomly allocated subjects receive no treatments or interventions. This arm is sometimes called the wait list and the subjects are observed during the time of the trial. When studying placebo effects, the NTC can be an important control for the placebo arm of a RCT because it allows for an estimate of the genuine effects of a placebo intervention by controlling for spontaneous remission, regression to the means, and normal waxing and waning of an illness in the placebo treatment arm.
Endogenous Opioids	naturally occurring peptides that relieve pain and signal reward in the brain.
-omics	an informal term referring to biological studies of molecules derived from or affecting the genome. These studies tend to be large in scale and the terms used to describe them end in –omics, i.e. genomics, transcriptomics, proteomics and metabolomics.
Pharmacogenomics	the study of how variation in the genome modifies individual response to drug treatment. The goal of pharmacogenomics is to use ‘omics data to guide the development of safer and more effective and therefore more personalized medicines.
Placebo	an inert treatment e.g. dummy pills, fake injections or sham surgery designed to simulate a biomedical intervention within a RCT. Placebo response is the positive health benefits that patients receive in response the symbols, rituals and behaviors embedded in a clinical encounter.
Placebome	the hypothesized group of genome related or derived molecules (i.e. genes, proteins, microRNAs) that affect an individual’s response to placebo treatment.

Randomized controlled clinical trial (RCT)	the gold standard for clinical studies in which participants are randomized to an active exposure or inert treatment arm of the trial. In placebo-controlled RCTs participants are blinded to their treatment allocation and the results are used to test the efficacy or effectiveness of a drug or active intervention.
Serotonin	a monoamine neurotransmitter which is important in regulating mood, appetite, and cognitive functions, including memory and learning. Selective serotonin re-uptake inhibitors (SSRIs) are antidepressants that are designed to increase serotonin levels.
Single nucleotide polymorphisms (SNPs)	sites in the genome that differ in the DNA nucleotide sequence and thus give rise to genetic variability.

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Highlights

- Predisposition to respond to placebo treatment may be in part a stable heritable trait.
- Candidate placebo response pathways may interact with drugs to modify outcomes in both the placebo and drug treatment arms of clinical trials.
- Genomic analysis of randomized placebo and no-treatment controlled trials are needed to fully realize the potential of the placebome.

Table 1

Polymorphisms in candidate genes that may be part of the placebome.

Placebo pathway	Gene name	Symbol	Chromosomal location	Placebo SNPs	Ref.
Dopamine	catechol-O-methyltransferase	*COMT*	22q11.2	rs4680	[38]
	monoamine oxidase	*MAO-A*	Xp11.3	rs6323, rs6609257	[43, 55]
	dopamine B hydroxylase	*DBH*	9q34	rs2873804	[43]
	dopamine receptor 3	*DRD3*	3q13.31	rs6280	[59]
	brain derived neurotropic factor	*BDNF*	11p14.1	rs6265	[66]
Serotonin	tryptophan hydroxylase-2	*TPH2*	12q21.1	rs4570625	[75]
	5-hydroxytryptamine transporter	*SLC6A4*	17q11.2	rs4251417	[43]
	5-hydroxytryptamine receptor 2A	*HTR2A*	13q14.2	rs2296972, rs622337	[43]
	serotonin transporter gene-linked polymorphic region	*5-HTTLPR*	17q11.2	Variable tandem nucleotide repeat	[75]
Opioid	opioid receptor	*OPRM1*	6q25.2	rs510769	[69]
Endocannabinoid	fatty acid amide hydrolase	*FAAH*	1p33	rs324420	[73]