Quantifying placebo and nocebo responses: A narrative review of implications for clinical practice and research in psychiatry

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ABSTRACT
The placebo and nocebo effects are commonly understood as the patients’ responses to treatment in accordance with their positive or negative expectations, respectively, regarding their health. Such treatments involve substances or interventions with no known inherent effects on the studied condition, but which nonetheless may have a discernible effect on the condition’s presentation and evolution. Their influence on clinical outcomes confront practitioners with often underestimated therapeutic tools and challenges whose applicability are subject to ethical debate. Furthermore, placebos play a crucial part in our current understanding of therapeutic efficacy and in the development of novel interventions. This narrative review aims to present a brief exposition of the roles that placebo and nocebo effects play in psychiatric clinical practice and research.

Keywords: placebo, nocebo, treatment, expectations, health

MECHANISMS AND MODERATORS
Neurobiological underpinning of placebo and nocebo effects involve intricate interactions between a wide range of neurotransmitters such as dopamine, endogenous opioids, cannabinoids, vasopressin and oxytocin or cholecystokinin, respectively [1,7–9]. While the exact mechanisms show considerable diversity, in accordance to specific symptoms or disorders, they all seem to converge on a common factor: the mediation of future reward outcomes, commonly known as expectancies. The concept of expectancy refers to the probabilistic model which the brain constructs by integrating prior experiences in order to formulate adequate predictions of future stimuli or events. This model engages the reward system, learning and memory pathways, attention mechanisms, cognition, and emotional processing.

Dopamine and reward
The reward prediction system is comprised by dopaminergic neurons in the ventral tegmental area (VTA, and substanta nigra pars compacta (SNc) that project to the nucleus accumbens (NAc), prefrontal cortex (PFC) and the striatum (ST). The central tenet of the reward prediction system is based on the concept of reward prediction error (RPE), which is the difference between the actual reward received and the expected reward. A positive RPE (actual reward > expected reward) leads to an increase in dopamine release, a negative RPE (actual reward < expected reward) results in a decrease, and when the actual reward matches the expectation, dopamine neuron firing remains at baseline levels [10].

In the case of placebos and nocebos, expectancies on the effects and side effects of a particular medical intervention elicit physiological responses that align with these anticipations, even when the intervention itself has no inherent therapeutic or harmful component [1]. For example, in patients with Parkinson’s disease, the release of dopamine in the ventral and dorsal striatum occurs in the anticipation of a dopamine agonist [11]. Interestingly, this effect is highly modulated by verbal instructions and proves most robust when patients are told they
have 3:1 odds of receiving an active compound [12]. As dopamine neurons firing rate is proportional to the reward prediction error [13], it would be expected that placebo response should be most pronounced when they have been informed of a 1:1 chance of receiving either active or inactive intervention (representing maximum uncertainty). This effect has been demonstrated in other disorders as well, such as schizophrenia, depression, or non-psychiatric disorders such as migraine [3].

**Endogenous opioids and pain**

Most of the research on placebo mechanisms has been done on pain and analgesia [14]. Endogenous opioids are a family of neurotransmitters which play a pivotal role in the modulation of pain. Through their interactions with mu, kappa and delta-receptors, they suppress the transmission of pain at various levels of the central nervous system. Top-down pathways from the anterior cingulate cortex (ACC), frontal cortical areas, hypothalamus (HT) and amygdala (AG) project to the periaqueductal gray (PAG), which in turn exerts both inhibitory and excitatory control of dorsal horn neurons in the spinal chord [15]. The administration of opioid antagonist naloxone disrupts placebo-dependent pain disruption, but interestingly, it does not completely block subjective ratings of decrease in pain intensity [16]. This suggests the implication of nonopioidergic pathways in pain modulation, such as cholecystokinin, which has been linked nocebo responses in post-operative pain [17].

Notably, endogenous opioids are involved in psychiatric conditions as well. A small (n=25) study looked on activation of mu-opioid receptors in depressed patients given two identical placebos described as either “active” or “inactive” [8]. Those with higher responses to the “active” intervention showed increased endogenous opioid release in the subgenual anterior circulate cortex, amygdala, nucleus accumbens and midline thalamus. Furthermore, 10 weeks after the subjects started an open-label antidepressant trial, those with the higher opioid activation during the placebo interventions were also shown to have greater symptom reduction after treatment (as measured by QIDS-16SR scores) [8].

**Learning**

The principles of classical conditioning underpin the mechanisms of placebo and nocebo effects. This phenomenon occurs when a neutral stimulus, repeatedly presented alongside an unconditioned stimulus, starts to elicit a specific response on its own, having become a “conditioned” stimulus. Illustratively, gustatory cues initially associated with morphine administration could eventually induce analgesia by themselves [18]. Conversely, as Rheker et al. demonstrated, a bitter liquid usually administered in conjunction with amitriptyline can provoke distinct side effects even when coupled solely with a placebo [19].

Curiously, there is proof for vicarious experiencing of placebo and nocebo responses. A 2015 study on 60 female participants found that both live and video-based social observation can induce a placebo analgesic effect, reducing perceived pain [20]. Empathic concern, or the ability to empathize, enhanced this effect, especially in live interactions. The researchers controlled for various factors like verbal suggestions, color cues, and response bias, concluding that these didn’t account for the observed placebo effect. The findings highlight the role of social learning and empathy in pain perception [20].

Societal and cultural factors have considerable influence on expectations of treatment efficacies. Negative media coverage can contribute to increased rates of reported side effects [21]. Generic medication is perceived by patients and doctors alike as inherently less potent, limiting their use [22]. Even apparently frivolous characteristic, such as the price or the colour of the drug can prove to have profound impact on its perceived efficacy [23,24].

**Other moderators**

Consensus regarding relevance of biological sex in placebo and nocebo responses has yet to be reached. In a review of meta-analyses Weimer et al. found that only 2 out of 17 trials noted higher placebo response in women, leading the authors to conclude that gender does not appear to play a significant role [25]. These findings suggest that gender may not significantly influence placebo response rates, underlining the necessity of considering other factors when interpreting placebo effects in clinical research. Nevertheless, other authors warn against overlooking sex differences despite conflicting results, arguing that some conditions (such as bipolar, depression, anxiety or even restless leg syndrome) show consistent proof for sex based differences in prevalence and treatment response [26].

The scarcity of associations between personality profiles and placebo response in trials for depression and other psychiatric disorders suggests either a lack of definitive association or ineffective implementation of psychometric tests [27]. Researchers have primarily explored personality profiles in experimental studies involving placebo analgesia and found only a few characteristics more common in placebo responders, such as optimism, neuroticism, and an external locus of control. A review conducted in 2014 identified various predictors of the placebo response, including psychological constructs related to actions,
expected outcomes, emotional valence, behavioral control, personality variables, suggestibility, belief in expectation biases, body consciousness, and baseline symptom severity. However, inconsistent findings and a lack of replication studies make the overall picture inconclusive [25,27].

The influence of age on the placebo response also seems inconclusive. In a review of the literature Weimer et al found conflicting evidence, with some studies reporting higher response rate with younger age and others reporting the reverse phenomenon [25]. Specifically in the case of children with anxiety or attention-deficit hyperactivity disorder, only two analyses reported a potential association between ethnic origin and placebo response. Specifically, these studies observed an increased response among non-white individuals. However, the underlying causes of this association, whether it is influenced by differences in parental care or a differential genetic contribution, remain uncertain [28,29].

EXTENT IN PSYCHIATRY

Schizophrenia

Given the high burden of schizophrenia and the considerable range of both short and long-term side effects of antipsychotics, there is a considerable amount of research that focuses on their efficacy, especially when compared to placebo responses. Notably, Leucht et al has published extensively on this topic [30–33].

One meta-analysis conducted in 2017, which included 167 studies spanning over six decades of randomized controlled trials (RCTs) on antipsychotics, demonstrated that patients were twice as likely to show improvement when administered medication as opposed to a placebo, with a mean effect size of 0.47 [30]. About 30% of patients on the placebo arm showed some improvement of symptoms, with 14% reaching a good response. While medication responses did not change, the increase in placebo responses lead to an overall decrease of effect sizes across all treatments. This finding is in agreement with older studies and has been replicated in later investigations [30,32,34,35]. Efficacy did not seem to be affected by industry sponsorship; however, publication bias did contribute to decreasing effect sizes. Finally, the authors forwarded one particularly interesting conclusion: while industry-funded studies try to employ as many participants as possible in order to reach adequate statistical power, this leads to a decrease in actual effect sizes because of recruitment variability and sample heterogeneity, therefore a smaller and more thoroughly selected sample would lead to better results [30].

This was further expanded upon in a later regressive meta-regression analysis on the same 167 studies, with the aim of better describing the factors involved in drug and placebo-responses. They found that recent studies, those with a larger number of participants, studies that employed a minimum severity baseline as an inclusion criterion, and studies that used PANS (Positive and Negative Syndrome Scale) instead of BPRS (Brief Psychiatric Rating Scale) showed increased placebo responses, but not increased drug responses, leading to lower effect sizes. Mean age and duration of illness was negatively correlated with both drug and placebo responses. Finally, the authors conclude that factors predicting drug responses do not overlap with those predicting placebo responses [31].

In the case of the negative symptoms (NS), placebo responses have been found to be surprisingly large. One meta-analysis looked a small (N=18) number of studies involving add-on therapies for negative symptoms and found that placebo interventions to have a very large effect (Cohen d = 2.909) [36]. However, Czobor et al argued against the clinical plausibility of such a large result and re-assessed placebo effects by focusing specifically on improvement in control arms and comparing add-on versus monotherapy trials [37]. Their work reached a more conservative estimated effect size of 0.644 (moderate). Given that even active interventions in NS have shown modest efficacy [38], this high rate of placebo response would put into question current therapies. Nevertheless, the authors cautioned that even their own result might be an over-estimate, with longer studies and balanced active placebo ratios showing lower effects [37].

Patients with schizophrenia spectrum disorders show impaired cognitive abilities and particular psychopathology, making them more vulnerable to nocebo-like effects [39,40]. A 2019 meta-analysis showed that almost two thirds of patients in the placebo arms of trials exhibit significant side effects, leading to a 8.5% rate of discontinuation [41]. The authors found direct correlation between the severity of the disease (as measured by PANSS scores) and nervous or gastrointestinal system side effects and suggested that hallucinatory and delusional context leads to misattribution of somatic stimuli, leading to over-inclusive reporting of adverse effects [39,41].

In recent years, several mathematical models have been proposed to more effectively differentiate between drug and placebo responses [42]. Using pharmacometric approaches, such models aim to predict outcome of trials through simulations that estimate placebo effects and dropout rates. Furthermore, they couple pharmacogenetic data with biomarker analysis and other factors in order to improve study design. One such PK/PD (pharmacokinetic/pharmacodynamic) study was used to better describe the clinical utility of antipsychotics as opposed to placebo [43].
Depression and mania

The debate regarding placebo effects has been most active around the subject of depression, with some authors going as far as arguing that antidepressants responses are clinically indistinguishable from placebos [44]. An extensive meta-analysis comprising of 522 RCTs reviewed antidepressant efficacy [33]. The study was published in The Lancet in 2018 and encompassed over 116,477 adult patients with major depressive disorder and 21 first and second-generation antidepressants. All of the studied drugs differentiated from placebo in response rates, with odds ratios between 1.37 and 2.13 in favor of active treatment. There was little difference between drugs in terms of efficacy, but considerable variability in dropout rates. Interestingly, it found that while industry funding did not seem to influence results, drugs tended to show better efficacy and acceptability while novel, with effects waning as the drugs got older and better established. Furthermore, placebo-controlled trials had lower effects sizes compared to head-to-head trials, and overall effect size was modest (0.30) [33]. Some of the conclusions of this study have been subject to criticism.

A secondary, Bayesian network meta-analysis on the Cipriani dataset found that some of the older antidepressants did not significantly differ from placebos [45]. The authors state that due to their higher rate of side-effects, trials involving such drugs are prone to unblinding and thus biased, which leads to overestimating drug-placebo differences. They argue that this effect should apply to newer drugs as well, albeit at a lower degree. Nonetheless, the use of inert placebos can mislead, especially in the case of experienced clinicians who are able to correctly guess whether a patient is in an intervention or placebo arm. The study concludes that researchers should systematically assess and report unblinding, as well as reconsider the role of active placebos [45].

Some studies claim that, since the 1980s, there seems to be an increasing trend regarding placebo responses in antidepressant drug trials. Walsh et al were among the first to report this in 2001, by analyzing studies published in the prior two decades [46]. The trend was confirmed 15 years later in a study that found an increase in magnitude of placebo symptom reduction from 29.8% to 36.2% compared to the aforementioned study [47]. Another meta-analysis, focusing on RTCs of treatments in psychotic depression, found that placebo responses were basically non-existent in the ’80, while studies after 2000 showed that a third of controls improved without an active intervention [48].

On the other hand, Furukawa et al failed to corroborate this trend in 2016. Their study analyzed 256 published and unpublished placebo-controlled RCTs and concluded that, while placebo responses are quite high, their value have remained constant in the range of 35-40% since 1991 [49]. The correlation between publication year and placebo response was non-significant when correcting for confounding factors, suggesting that prior results were artifacts from underreported rates of response in older studies. Their disagreeing results could be partly explained by different methods of statistical analysis and measurement of placebo responses (a continuous, percentage based measurement in the positive study vs a binary, threshold based measurement in the negative one) [47].

In regards to placebos in difficult-to-treat depression, a meta-analysis looked upon studies involving a wide variety of placebos: pill, parenteral or liquid placebos, as well as sham rTMS or invasive brain stimulation [50]. The authors reported a large placebo effect (g=1.05), irrespective of treatment modalities. Furthermore, they found that open-label, industry funded and novel studies were showing the largest effect sizes. They suggested that their result could be used as a benchmark in further RTCs: if a placebo effect size is greater or smaller than this value (g=1.05), it could mean that the results are false-negatives or false-positives, respectively [50].

Mitsikostas et al. conducted an extensive meta-analysis on 21 RCTs for treatment of depression in order to estimate the magnitude of nocebo effects [51]. His findings suggest that almost half (44.7%) of patients on the placebo arm reported at least on adverse effect, which contributed to almost a 5% treatment discontinuation rate. Surprisingly, these numbers reflected those in the active treatment groups, suggesting that the specific drug of study had no effect on these variables. Overall, effect sizes were on par with those found in migraines, but lower than those in Parkinson's disease or fibromyalgia [51].

An increasing amount of evidence points towards substantial placebo responses in difficult-to-treat disorders as well [52–55]. Welten et al analyzed 10 studies investigating the efficacy of antipsychotics in mania and reported an overall placebo response rate of 32.8% [54]. A higher placebo response was strongly associated with a smaller effect size, and predictors of a higher placebo response included absence of psychotic features at baseline, higher illness severity score at baseline, lower illness severity score at baseline, recent study year, inclusion of three geographic regions compared with one or two, and patients from regions other than the USA and Europe [53,54]. These findings, according to the authors, confirm that the high failure rate of psychiatric trials is partly due to a high placebo response rate. Furthermore, they warn against restricting future studies to patients with psychotic features and recruited solely from the US or EU, as this would limit the generalizability of the findings without significantly reducing the placebo
response or improving the detection of clinically relevant effects of medication [54].

A later, comprehensive meta-regression analysis expanded on this findings, by looking at relative efficacy of both antipsychotics and mood stabilizers on bipolar mania and depression [52]. The authors noted that outcomes in bipolar mania are solely dependent on response rates of active drugs, in contrast with the outcomes in bipolar depression, where treatment efficacy is primarily based on the magnitude of the placebo response. This research also highlights that the placebo response rates were higher and more varied in subjects with depressive symptoms rather than manic symptoms. Taking into account some limitations in their research, the authors nonetheless suggest that future studies should reduce the heterogeneity of placebo responses and clearly define clinically relevant thresholds for treatment response [52].

Anxiety, obsessive-compulsive and stress-related disorders

In contrast with the amount of publication on depression and psychosis, in regards to placebo responses there is a relative sparsity of studies on anxiety, obsessive-compulsive and stress-related disorders. Older studies report considerable heterogeneity in responses across all disorders: but note that placebo responses in anxiety disorders tended to fall in line with those seen in depression, while obsessive-compulsive disorders showed considerably reduced effects [56,57].

A 2017 meta-analysis comparing OCD and anxiety placebo responses corroborated this finding [58]. From the 56 studies they've analyzed, the authors extrapolated medium placebo effects size in OCD (g=0.49) and social anxiety (g=0.70) and large ones in the case of PTDS (g=0.97), panic disorder (g=0.94) and generalized anxiety (g=1.10). Of particular notice in this analysis was the fact that in spite of considerable heterogeneity between the efficacy of placebo interventions, drug-placebo effect sizes did not differ significantly between conditions. This could emphasize the neurobiological overlap, as well as the common psychopathological “internalizing” factor shared in these conditions. On the other hand, it could point out that unblinding is a common caveat shared among all clinical trials [58].

The most recent and extensive review to date on the subject has been published in BMJ Mental Health in May 2023 by Motta et al. [59]. Their systematic review of 366 outcomes in 135 studies showed comparative results to earlier studies regarding placebo responses, while underlining some of their most significant moderating factors, besides patient diagnosis. For instance, the application of a placebo lead-in period appeared to influence the estimated effect sizes across all conditions. Meanwhile, clinician-rated assessments demonstrated greater placebo responses in comparison to self-reported GAD responses. These factors, as well as concomitant benzodiazepine use, baseline severity of symptoms and sample size influence were significant in adults and elderly, but not in children and adolescent, urging further research in pediatric moderators of placebo responses. Despite its high heterogeneity and evidence of small study effects, the study’s large scale, three level design limit biased estimates and confer it significant statistical power [59].

Substance abuse, attention deficit disorders

Despite the relatively poor number of studies on placebo and nocebo responses in externalizing disorders, there seems to be an encouraging resurgence of extensive, high-quality reviews on the subject in the last few years [60–63].

A 2021 meta-analysis analyzed the placebo arms in 128 RTCs of medications for ADHD and reported a particularly intriguing trend regarding their effect sizes [61]. While all pooled placebo responses were statistically significant, they seemed to vary considerably with the type of rater assessing the symptoms. The highest response was seen in clinician rating (-0.75), followed by self-rating (-0.66), parent rating (-0.43) and finally, teacher rating (-0.36). The authors argued the difference could be due to a combined placebo effect acting on both the parent and clinician during interviews, and highlighted the potential risks of elevated placebo responses in trials where clinician ratings are the primary outcome. Significant nocebo effects in the cases of weight gain and drop-outs due to adverse effects were reported as well. It’s worth noting that despite the large placebo effect, prior studies have established the increased efficacy of active medication, especially amphetamines and methylphenidate [62]. Therefore, authors suggested that any intervention increasing the placebo response could potentially enhance the efficacy of ADHD medications, but more research is needed in this area [61].

In alcohol abuse disorder the extent of placebo effects remains poorly understood. One meta-regressive analysis looked at the control arms of 19 RCTs in order to investigate potential drivers of response. Their findings suggest that treatment duration and severity of dependence (defined in the study as the lack of spontaneous abstinence prior to treatment) [60]. The results support previous research [64,65] and suggest that high severity studies show the lowest placebo response rates when compared to mild severity ones (16.8% vs 36.7%). Secondary analyses showed that the placebo response was associated with the mean abstinence duration before treatment initiation, but not with the mean alcohol consumption at baseline. The effects of mean age and gender
on placebo response were not significant. Nevertheless, the authors suggest that other patient-related factors could be involved.

Unfortunately, research involving other substances still lags behind. Most studies investigate abstinence rates and reports low rates of responses on control arms, ranging from 5-10% in the case of opioid dependence [63], 22% for cannabis [66], 2.5% for amphetamines [67], 14% for cocaine [68] and 4-12% for nicotine [69].

Alzheimer’s disease

Due to decreased cognitive function and brain region connectivity, patients with Alzheimer’s disease show impaired expectations and decreased placebo responses, highlight the role of prefrontal modulation [70]. Amanzio et al studied placebo arms in 19 donepezil RCTs and argued that AD patients report significantly more adverse effects when given a placebo compared to those with mild cognitive impairment. These adverse effects might be linked to emotional distress manifesting as physical symptoms due to comorbidities, the frailty of AD patients leading to increased susceptibility to negative outcomes, and the greater cognitive impairment limiting positive outcome expectation [70].

Interestingly, a meta-analysis of 20 randomized controlled trials estimated that the nocebo adverse effect rate in AD is 57.8%, with a nocebo dropout rate of 6.6% [71]. Factors like study sample size, BMI, and mini-mental state examination score were negatively associated with adverse effects and dropout rates among placebo-treated populations. In contrast, age was positively linked with these outcomes. Nevertheless, upon meta-regression analysis, only the study sample size showed a negative correlation with both nocebo adverse effects and dropout rates [71].

CONSIDERATIONS IN CLINICAL PRACTICE AND STUDY DESIGN

Given their ubiquity and significance in basically every aspect of psychiatric practice and research, placebo and nocebo effects engender a host of ethical dilemmas and practical considerations regarding their use and mitigation. Particularly in the case of placebo, clinicians and researchers stand in opposition, with the former trying to maximize the effect in order to provide the best care possible, while the latter group looks to separate and eliminate it as a confounding factor in study design.

Clinical practice

Historical attitudes toward placebos evolved alongside societal norms regarding the medical profession and its scientific rigour [72]. Up to the early 20th century, placebos were a main tool in a doctor’s practice, in accordance to the principles of beneficence and non-maleficence and implied widespread use a deception. This was rooted in a paternalistic paradigm that minimized or even disregarded the involvement of the patient in his own treatment [73]. In light of better scientific understanding and a more refined ethical framework that included the principle of autonomy, views regarding deceptive placebos have shifted towards negative, emphasizing the role of informed consent [74]. Some authors even argued for banning such a practice [75]. Nevertheless, the use of placebos in clinical practice continues to be widespread.

Open-label placebos have been suggested as a viable alternative to deceptive prescribing [76]. This practice aims to harness neurobiological and social modulators of expectation in order to improve treatment response. By emphasizing adequate physician training, a positive patient-clinician relationship and sensible information of patients on placebo and nocebo effects, open-label prescriptions could prove a viable intervention in selected groups of patients [1,77,78]. Miller and Colloca argue ethical use of placebos in clinical practice requires two fundamental considerations [79]. First of all, there should be high-quality scientific proof for significant clinical benefit of placebo compared to no intervention. Second of all, the clinician must offer patients full, transparent and honest disclosure [79]. Other authors defend deceptive placebos altogether, suggesting that in some cases, such as pain and depression, their efficacy can match or even surpass conventional medications, especially where prior trials have proven ineffective [6,73,80].

Research on the nocebo effect highlights the importance of contextualized informed consent in medical practice. This approach takes into account the power of patient-physician interactions and the framing of information about potential side effects, which can significantly influence patients’ experiences. As such, physicians should strive to optimize patient outcomes while maintaining patient autonomy, by tailoring discussions about potential adverse effects in a way that best serves the patient. Although this approach requires further empirical testing, the pervasive nocebo effect suggests it might be healthier to err on the side of optimism [51,77,81].

Research

Placebo and nocebo effects complicate psychiatric clinical research by muddling the differences between active interventions and controls, as well as contributing to dropout rates [1,2]. These effects necessitate careful consideration in study design, as they can lead to misinterpretation of treatment effi-
cacy and true therapeutic outcomes. Furthermore, the ethical dilemmas they pose, such as potential manipulation of patient responses, undermine the need for thoughtful and transparent research protocols [73,82]. Compliance with the 2013 revision of the Declaration of Helsinki is broadly seen as crucial in developing ethical human clinical trials, yet it continues to be riddled with ambiguities [83]. Despite being thought-of as a guide, the document fails to delineate clear definitions of crucial terms such as “serious harm” and “methodological reasons”, leaving them open to interpretation. Skierka and Michels argue that until further revisions address this issues, the Declaration of Helsinki is not a suitable ethical guideline [83].

While randomized controlled trials are considered the cornerstone of evidence-based medicine, the debate regarding ethical underpinning and statistical relevance is far from over, especially in the field of psychiatry [73,84]. One review grouped the main arguments against RTC as “pragmatic”, which put an emphasis of the potential harms and benefits of enrollment, and “fundamental”, which stress the ethical considerations at the level of the individual [84]. The authors suggest that there is insufficient evidence to discredit their use, but advance complementary trial designs such as naturalistic, superiority or non-inferiority trials [84].

A thorough understanding of the interaction between placebo and treatment effect is crucial. Usually, treatment effect is considered to be a simple sum between specific and non-specific (i.e. placebo) effects, which is known as the additive model [85]. However, this does not seem to always be the case, as the intensity of placebo effects can enhance (synergistic model), diminish or even reverse (antagonistic model) the perceived effectiveness of the intervention [86]. Placebo effects can differ substantially between controlled trial settings and real-word contexts, therefore an adequate validation of interventions, especially in placebo-sensitive conditions, is recommended [86].

In order to aid researchers in this sense, comprehensive guidelines and checklists have been developed, such as CONSORT (Consolidated Standards of Reporting Trials, an evidence-based minimum set of requirement for RCTs [87]), TIDieR-Placebo is a subsequent extension that formulates an user-friendly, checklist based guide for reporting placebo and sham interventions [88]. The structured framework encompasses most aspects of placebos such as their names, underlying rationale, materials used, delivery procedures, providers’ expertise, delivery modes, locations, schedules, potential personalization or adaptations, any modifications made during the study, and measures of intervention adherence and success of blinding. This ensures comprehensive transparency and replicability in clinical trials, facilitating the discernment of true intervention effects from placebo effects [88].

Novel study designs that look to reduce the placebo effect also exist. Fava et al identified a series of factors that can be involved in this phenomenon: diagnostic miscategorization, issues concerning inclusion/exclusion criteria, outcome measures’ lack of sensitivity to change, measurement errors, poor quality of data entry and verification, waxing and waning of the natural course of illness, regression towards the mean, patient and clinician expectations about the trial, study design issues, non-specific therapeutic effects and finally, high attrition [82]. Based on a set of practical consideration addressing each of these issues, the authors have proposed the “Sequential Parallel Comparison Design” - SPCD, a methodology adapted for the investigation of psychiatric treatments [82,89]. The SPCD consists of two consecutive stages. The first stage is a conventional parallel group placebo-controlled period where participants are randomly assigned to either the treatment group or the placebo group. The second stage includes only those participants from the placebo group who did not respond to the treatment (i.e., the non-responders) in the first stage. These non-responders are then re-randomized to either the treatment group or the placebo group. By only including non-responders in the second stage, the SPCD reduces the number of placebo responders in the analysis, thereby increasing the ability to detect a treatment effect if one exists. This design also reduces the required sample size and can improve the ethical aspect of the trial by reducing the duration of placebo exposure for the participants [82].

While promising, the novel method still presents inherent limitations. One analysis looked at the SPCD estimand (i.e. quantity estimated in a clinical trial) from a mathematical-centered approach [90]. The study notes that the treatment effect being examined in both stages may differ from the treatment effect in the entire patient population, as stage 2 includes only placebo non-responders identified from stage 1. This discrepancy could potentially skew the perceived effectiveness of the treatment, emphasizing the need for careful consideration when implementing SPCD [90].

Finally, the placebo lead-in design is a type of study in which all participants are given a placebo treatment for up to two weeks before the RCT begins [91]. This method looks to minimize placebo effect, improve treatment adherence and formulate a better baseline assessment of the condition in case. Nevertheless, this design has been criticized on ethical grounds [73] and has been shown to have limited applicability in clinical trials that involve binary outcomes [92].
CONCLUSION
The evolving understanding of placebo and nocebo effects in psychiatry holds vital implications for clinical practice and research. While a robust body of literature delves into these phenomena in the context of depression and psychosis, a notable dearth of research exists in other crucial areas such as anxiety, obsessive-compulsive, and stress-related disorders. Various methodological elements, such as the application of a placebo lead-in period and the use of clinician-rated assessments, seem to influence the observed placebo responses, highlighting the need for a standardized approach.

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