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Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects

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As modern research continues to unravel the details of the placebo phenomenon in CNS disorders, uncertainty about therapeutic outcomes in trials of treatments for several neurological conditions is growing. Advances in understanding the mechanisms of different placebo effects have emphasised the substantial challenges inherent in interpreting the results of CNS clinical trials. In the past few years, new mechanisms and concepts have emerged in the study of placebo, nocebo, and Hawthorne effects in CNS clinical trials. For example, the mere step of recruitment in a trial or social interaction among trial participants can change the baseline conditions and therefore affect the interpretation of therapeutic outcomes. Moreover, different genotypes have been shown to respond differently to placebos—eg, in studies of social anxiety, depression, and pain. Increasing recognition of these factors in the general population raises the question of whether attempts should be made to reduce placebo responses in CNS clinical trials. Both clinical trial design and medical practice could benefit from further investigation of these effects across a range of neuropsychiatric disorders.

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Introduction

The very act of measuring a variable in human beings can modulate the expectations of the person who is being measured, which can in turn change behaviours, attitudes, and body physiology,[1,2] leading to uncertainty in the measurement. This notion of uncertainty is applicable to clinical trials, in which the effects of a treatment (a drug or a non-pharmacological intervention) on patients are usually assessed and measured. In this case, a patient's expectations of therapeutic benefit can interfere with the response to drug administration.[4] Indeed, uncertainty pervades all clinical trials, particularly CNS trials. As placebo research progressively investigates the details of the placebo phenomenon, uncertainty about outcomes in CNS clinical trials is growing. For example, the failure of many recent neurological and psychiatric clinical trials—eg, in pain, Parkinson's disease, and schizophrenia—is related to the high placebo responses reported across different studies. Improved understanding of placebo effects within the context of CNS disorders is therefore urgently needed to design better CNS clinical trials with less uncertainty about treatment effects. Advances in understanding of placebo and nocebo effects in clinical research and clinical practice will lead to the development of more effective treatments and better care for patients.

Rather than providing a comprehensive review of clinical trial methodology or placebo mechanisms, the aim of this Review is to give an overview of recent findings about the mechanisms of placebo, nocebo, and Hawthorne effects (panel 1) and how these effects might contribute to uncertainty in clinical trials.[3,4] We outline the problem of uncertainty in CNS clinical trials and suggest possible ways to improve trial design, first and foremost by assessing patients' expectations. We also consider ways in which these effects and the issue of uncertainty could be addressed in future studies.

Uncertainty of drug action

The concept of uncertainty in measuring therapeutic outcomes (panel 1) is exemplified by a clinical trial of postoperative pain[5] that was reported in 1995, in which the cholecystokinin antagonist proglumide was shown to be better than placebo for relieving pain (figure 1).[5] These results seemed to indicate that proglumide is a good painkiller. However, this conclusion proved to be erroneous, because proglumide was totally ineffective when the act of proglumide administration was eliminated by means of a hidden injection (ie, unknown to the patient). How is it possible that a drug seems to work as a painkiller when administered overtly, according to routine clinical practice, but shows no analgesic action when patients do not know that they are receiving it? The explanation is that proglumide does not act as a painkiller but, rather, as a placebo (or expectation) enhancer, by blocking cholecystokinin receptors. This action, in turn, potentiates the opioid-mediated placebo analgesic response. In other words, proglumide induces a reduction in pain if, and only if, it is associated with a placebo procedure.[5]

The findings from this trial clearly show how the uncertainty principle can be applied to biological macro-systems, and more specifically to the therapeutic setting and clinical trials. In fact, the act of administering a drug and measuring its effects can activate patients' expectations of analgesia, with the drug offering some benefit not by an action on pain pathways, but through the mechanisms of expectation. Of course, this effect can lead to an erroneous interpretation of the trial outcome—ie, the outcome is pain relief, but the interpretation that the drug is an effective analgesic is wrong.

This effect of expectation on drug action has been confirmed by findings from studies of narcotic drugs.[6,7] Expectation of receiving the μ-opioid receptor agonist remifentanil, where the patient is given remifentanil and is told it is remifentanil, produces more pronounced analgesic effects than does the no-expectation condition, where the patient is given remifentanil but is told it is saline (figure 1). Moreover, expectation of interruption, where the patient is given remifentanil but is told its administration has been interrupted, abolishes the

overall analgesic effect. These effects are associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex in the positive-expectation condition, and with activity in the hippocampus in the negative expectation of interruption.

In view of findings about the neurobiology of treatment expectation—one of the main mechanisms of placebo responses (panel 1)—in which various neurotransmitters have been implicated,[8–13] it seems possible that interference between pharmacodynamic and psychological (placebo) effects could take place in the following way. A drug—eg, a narcotic—binds to opioid receptors, but the act of its administration induces expectations of benefit in a patient that activate endogenous ligands, which might compete with the narcotic for the same receptors, thereby interfering with its action. The only way to eliminate this interference is to administer the narcotic in such a way that the patient is unaware that he or she has received it. This method eliminates the ritual of the therapeutic act, and thus the positive expectation of therapeutic benefit.[14,15]

An alternative explanation could be that, rather than competing for the same receptors, the drug and the placebo might act on the same type of receptor but in different regions of the brain.[16] Some experimental evidence suggests that this second mechanism is the most likely explanation in the case of narcotics. For example, remifentanil binds to μ-opioid receptors in one region of the brain, whereas placebos act, through the activation of μ-opioid receptors by endogenous ligands in a different region, which has an overall additive effect (ie, without mutual interference).[17] Nonetheless, as far as is known, an interactive and synergistic relation between endogenous ligands and narcotics—the first interference mechanism—cannot be ruled out completely.[18] Whatever the case, the potential pharmacodynamic–placebo relation raises several ethical and methodological questions that need further research and discussion. For example, should drug A, which amplifies placebo effects and results in better outcomes, be used in clinical practice in preference to drug B, the action of which is based purely on disease-specific influences? Although, to date, little is known about which drugs can modulate placebo effects, virtually all drugs are potentially capable of such an action, and this possibility should stimulate further pharmacological investigation in this direction.

The notion of uncertainty of drug action embraces adverse events as well as therapeutic benefits, whereby patients who take placebos often show side-effects (nocebo effects). For example, in clinical trials of three classes of antimigraine drugs—non-steroidal anti-inflammatory drugs, triptans, and anticonvulsants—the adverse events reported in the placebo arms of these trials corresponded to those of the antimigraine drug against which the placebo was compared.[19] In fact, anorexia and memory difficulties, which are typical adverse events with anticonvulsants, were present only in the placebo arm of these particular trials.[19] These results suggest that the adverse events in the placebo arms of clinical trials of antimigraine drugs depend on the known adverse events of the active medication against which the placebo is compared. These findings are in keeping with the expectation mechanism of placebo and nocebo effects. Similar findings have been shown in trials for depression,[20,21] headache,[22] fibromyalgia,[23] diabetic peripheral neuropathy,[24] and neuropathic pain.[25] These nocebo effects are a major drawback of such trials, because

***Panel 1:* Terms related to uncertainty in clinical trials**

Placebo

A placebo is an inert treatment, be it pharmacological or non-pharmacological, with no specific therapeutic properties for the condition being treated. A placebo effect or placebo response—ie, a positive effect on the therapeutic outcome—might follow the administration of the inert treatment. A source of confusion about this term relates to its different meanings for the clinical trial investigator and the neuroscientist or psychologist. An investigator regards any improvement that takes place after placebo administration—including spontaneous remission, regression to the mean, and patient's or experimenter's biases—as a placebo response. By contrast, a neuroscientist or psychologist considers only the psychobiological factors that arise in the patient's brain after placebo administration, such as expectations of therapeutic benefit.[1]

Nocebo

In contrast to the placebo effect, a nocebo effect or nocebo response encompasses negative rather than positive therapeutic outcomes (adverse events) that follow the administration of an inert treatment. For the neuroscientist or psychologist, the nocebo effect is related to negative expectations of clinical worsening.[1]

Expectation

Patients' expectations have a crucial role in the placebo response,[2] and the term placebo effect is often replaced with the term expectation effect. However, although expectation is the most important mechanism that mediates placebo effects, it is not the only one.[1]

Hawthorne effect

This term is used in clinical research to describe changes in behavioural, clinical, and physiological variables (ie, baseline conditions), that occur in response to a participant's awareness of being under study. Improvements that occur after recruitment, but before the start of treatment, could be attributable to several factors, including more attention from clinicians, better observation, improved care, better compliance and adherence to treatment, and increased expectations of health benefits.[3]

Uncertainty in physics and biology

The concept of uncertainty is best explained in physics by the Heisenberg uncertainty principle. The principle imposes limits on the precision of a measurement by asserting that a dynamical disturbance is necessarily induced in a system by the measurement per se. Although this principle holds true at the subatomic level—ie, in microsystems—it can also be applied at the level of biological macrosystems, whereby the act of measuring can change the biological macrosystem itself.[4]

Uncertainty in clinical trials and health care

Experimental and clinical evidence suggests that an important component of uncertainty in CNS clinical trials derives from placebo responses related to expectations, such that the effect of a molecule (the drug) on a biological system (the patient) can be affected by the act of administering the treatment. Thus, the patient's expectations of clinical improvement can interfere with the specific therapeutic effects of both pharmacological and non-pharmacological treatments.

dropouts due to such effects could confound the interpretation of results from many studies.

The clinical-trial setting is perhaps not appropriate to understand the mechanisms of placebo and nocebo effects, because many factors could contribute to improvements that take place after placebo administration, such as spontaneous remission, regression to the mean, selection biases, experimenters' measurement biases, and patients' report biases.[1] By contrast, these elements can be ruled out in the experimental setting, in which genuine psychobiological placebo effects can be identified. The experimental approach has been translated to the clinical arena for some medical conditions, such that patients have been studied under strictly controlled laboratory conditions. To date, some neurobiological mechanisms of genuine placebo responses are known for only a few CNS disorders and therapeutic interventions, including pain, Parkinson's disease, depression, anxiety, addiction, deep brain stimulation, Alzheimer's disease, and headache (panel 2).[1,26]

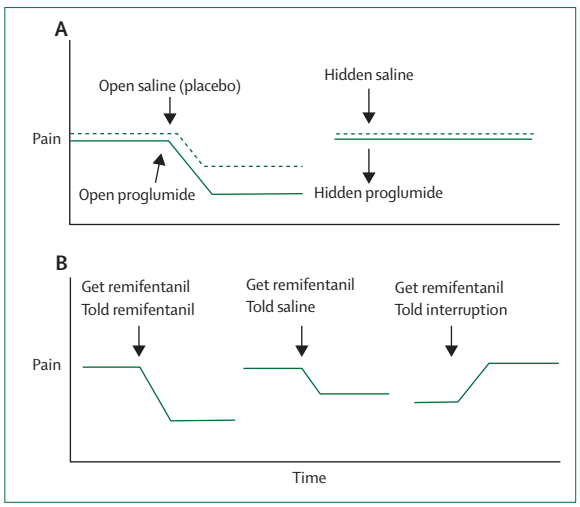

Figure 1: **Uncertainty of drug action**
Ambiguity in defining a painkiller. (A) The cholecystokinin receptor antagonist proglumide (solid line) is better than placebo (dotted line) in relieving pain, suggesting that it is a painkiller. However, the hidden administration of proglumide (unknown to the patient) is totally ineffective and does not differ from a hidden injection of saline solution. (B) The analgesic action of the μ-opioid receptor agonist remifentanil is not always the same, depending on the verbal suggestions given to patients. If they are told that the drug is being delivered, the analgesic effect is larger than when they are told saline is being given. If patients are told that the drug administration has been interrupted, even though it is still being delivered, pain perception can even increase.

Failed trials and the progressive increase in uncertainty

Many failures to detect a significant difference between the effects of medication and placebo are due to high placebo responses, although the mechanism of high placebo responsiveness is unknown in most cases. Failure to show benefit of active treatment over placebo in CNS clinical trials has become the norm over the past few years, and pain is one of the conditions for which the number of trials without a positive outcome for the active treatment is high. Analgesic trials in which the outcome does not support the efficacy of a treatment include studies of drugs such as lamotrigine for mixed neuropathic pain conditions,[27] levetiracetam for postherpetic neuralgia,[28] lacosamide for painful peripheral diabetic neuropathy,[29] and pregabalin for painful HIV neuropathy.[30]

Studies of many drugs are discontinued after phase 2 or 3 clinical trials because the treatments are not better than placebos. For example, more than 90% of drugs for the treatment of neuropathic and cancer pain were dropped from 1990 to 2013 because of the failure rate of putative new painkillers.[31,32] In 2011, ClinicalTrials.gov listed 4152 pain trials, yet in a period of 3 years, the only new approvals were given for already existing drugs—eg, duloxetine, oxycodone, and fentanyl as new formulations or doses.[32] In neuropathic pain, the difference between responses to medication and placebo is greater in studies published earlier, a fact that might be attributable to larger placebo responses in more recent studies and to longer and larger trials.[33,34] This absence of benefit of painkillers over placebo echoes the findings of clinical trials in depression,[35] which suggests that similarities might exist in patients' placebo responses in neuropathic pain and neuropsychiatric disorders.[36] For example, evidence of significant and increasing rates of placebo responses in antidepressant trials has been documented in several studies,[35,37,38] although the reason for this increase is not clear. One explanation could be the greater expectations of participants in clinical trials, but this theory needs further research. In a study by Kirsch and Sapirstein,[39] the response to placebo was always about 75% of the response to active antidepressant therapy, regardless of antidepressant class or mechanism, which indicates that the effects of all antidepressants were much smaller than the effects of placebo.

A progressive increase in placebo responses has been noted in studies of other brain disorders, such as schizophrenia.[40] Evidence for this increase was provided by a comparison of placebo effects in studies from two different phase 3 clinical-development programmes that were used to support registration of two antipsychotic medications. These programmes were completed about 10 years apart and had similar designs. In these trials, placebo effects measured by the reduction in the Positive and Negative Syndrome Scale (PANSS) total score increased over time.[41] In a different study, ten schizophrenia drug programmes that were submitted to the US Food and Drug Administration between December, 1993, and December, 2005, were identified.[42] The investigators noted 31 trials (22 with a positive outcome for active treatment and nine with a negative outcome) that included 12 585 patients from 37 countries (8054 [64%] from North America). In the US trials, placebo effects measured by a reduction in the PANSS total score increased over time, with no apparent trend

Panel 2: **Mechanisms of placebo or nocebo responses in different CNS disorders and therapeutic interventions**[1,25]

Pain
Activation of endogenous opioids, endocannabinoids, and dopamine (placebo); activation of a descending inhibitory network from the dorsolateral prefrontal cortex to the periaqueductal grey and to the spinal cord (placebo); activation of cholecystokinin and deactivation of dopamine (nocebo); activation of the spinal dorsal horns (nocebo)

Parkinson's disease
Activation of dopamine in the striatum and changes in neuronal activity in the basal ganglia and thalamus (placebo)

Depression
Changes in electrical and metabolic activity in different brain regions (eg, the ventral striatum; placebo)

Anxiety
Changes in activity of the anterior cingulate and orbitofrontal cortices; modulation of amygdala activity; involvement of genetic variants of serotonin transporter and tryptophan hydroxylase (placebo)

Addiction
Changes in metabolic activity in different brain regions (eg, the thalamus and cerebellum; placebo)

Autonomic responses to deep brain stimulation
Change in neuronal excitability in limbic regions, as assessed by autonomic responses (eg, heart rate) to brain stimulation

Alzheimer's disease
Involvement of prefrontal executive control and functional connectivity of prefrontal areas (placebo)

Headache
Modulation of cyclooxygenase products (prostaglandins and thromboxane) in hypobaric hypoxia headache (placebo and nocebo)

over time in the non-US or mixed (US and non-US) trials. Unfortunately, nothing is known about the reasons for this difference, and a future challenge will be to understand these geographical effects. Additionally, an assessment of expectations in patients with schizophrenia in the context of drug trials would be interesting, although this certainly represents a difficult task.

An increase in nocebo responses (adverse events in patients given placebo) from 1989 to 2009 has been shown in studies of multiple sclerosis. Papadopoulos and Mitsikostas[43] did a meta-analysis of multiple sclerosis trials published between 1989 and 2009, and calculated the incidence of nocebo responses by pooling the percentage of patients given placebo who had adverse events. 56 trials of disease-modifying treatment (ie, treatments that affect the time course of the disease) and 44 trials of symptomatic treatment were analysed. The incidence of nocebo responses was 74·4% in the trials of disease-modifying treatment and 25·3% in the trials of symptomatic treatment, and nocebo severity in the disease-modifying treatment trials was associated with the year of publication, with stronger nocebo responses in more recent clinical trials. Again, the reason for such an increase is not known, although the high rate of nocebo responses in trials of disease-modifying treatment might have occurred because the active treatment is often toxic and the consent form for such trials is worded to reflect this.

Substantial improvements in clinical outcomes in placebo groups of many clinical trials of Parkinson's disease have been noted,[44,45] and many active treatments have not been better than placebos. For example, placebo data from two studies[46] comparing sarizotan to placebo for the management of dyskinesia showed that both sarizotan and placebo ameliorated dyskinesia compared with baseline, but the amount of amelioration did not differ between the active group and the placebo group. Old age, a low baseline parkinsonism score, and low total daily levodopa doses were related to placebo improvement, whereas low baseline dyskinesia was associated with worsening of symptoms for patients given placebo.[46] Additionally, Goetz and colleagues[47] examined rates and timing of placebo responses to identify patient-based and study-based characteristics that affect such responses, predicting a positive placebo response in several clinical trials. The investigators obtained individual patient data from the placebo groups of 11 medical and surgical treatment trials involving patients with Parkinson's disease with differing disease severities and likelihoods of placebo assignment. 858 patients given placebo met the inclusion criteria for analysis. The overall placebo response rate was 16% (range 0–55%). Placebo responses were temporally distributed similarly across the early, mid, and late phases of follow-up.

Substantial improvements in patients who received placebo were also present in studies of surgical treatments for Parkinson's disease. For example, in a study[48] of the effect of intrastriatal implantation of fetal porcine ventral mesencephalic tissue to treat Parkinson's disease, the degree of motor performance improvement at 18 months was substantial in both the real surgery group and the sham surgery group. In another study[49]—a multicentre, randomised, double-blind, sham-surgery-controlled trial of human fetal transplantation—no difference was noted between the transplantation group and the sham surgery group.

A lack of difference between active treatment and placebo groups has also been observed in CNS clinical trials of gene therapy. Although nine clinical trials of gene therapy for Parkinson's disease have been initiated and completed over the past decade, either placebo-controlled or uncontrolled, none has yet shown sufficiently robust clinical efficacy.[50] The targets of these studies include the subthalamic nucleus,[51] the putamen,[52,53] and the putamen and substantia nigra.[54] Although the development of gene therapy differs from traditional drug development—eg, in the establishment of initial dosing and quantification of targeting success—

improvements are needed in terms of trial design and the selection of outcome measures.

These are just a few examples of CNS clinical trials in which the therapeutic effect of active treatment was not shown to differ from that of placebo. Although many factors could have contributed to these failures, the magnitude of the placebo responses probably played a crucial part in many cases. The various mechanisms underlying different placebo effects are not easy to identify across different studies, but evidence suggests that expectation of therapeutic benefit often plays a major part in the placebo response. For example, in some circumstances, when patients' expectations are used to dichotomise study results, those who have high expectations perceive the treatment to be effective, even if it does not produce specific effects. For example, in a clinical trial[55] of human fetal mesencephalic transplantation for Parkinson's disease, McRae and colleagues studied the effect of fetal tissue implant compared with placebo (sham surgery) for 12 months. They also assessed the patients' perceived assignment to either the active treatment or placebo. They noted no differences between the transplantation group and sham surgery groups for several outcome measures, such as physical scores and quality-of-life scores. However, the patients' perceived treatment assignment had a beneficial effect on the overall outcome, and this difference was still present 12 months after surgery. Patients who believed they received transplanted tissue had significant improvements in their quality-of-life and motor outcomes, regardless of whether they received the active treatment. Thus, patients' perceived treatment assignment affected both objective and subjective measures of motor function.

The effects of perceived treatment assignment, and hence of expectation of therapeutic benefit, hold true for pain as well. In a clinical trial of real acupuncture compared with sham acupuncture,[56] no difference was shown between the two groups. However, when patients were asked which group they believed they belonged to, those who believed they belonged to the real acupuncture group showed greater clinical improvements than patients who believed they belonged to the placebo group. In another clinical trial,[57] patients were asked whether they thought that acupuncture was an effective therapy and what they personally expected from the treatment. Patients with higher expectations about acupuncture had larger clinical benefits than those with lower expectations, regardless of their allocation to real or sham groups. Whether the patients actually received the real or the sham procedure did not really matter–what mattered was whether they believed in acupuncture and expected a therapeutic benefit.

These findings clearly show that a major confounding factor in clinical trials is patients' expectations (panel 1). The therapeutic outcome reflects—at least partly and in some circumstances—the patient's expectations; in some clinical trials, patients get what they expect. If expectations are not assessed in clinical trials, uncertainty about the outcome might be high. Younger and colleagues[58] created a six-item scale for measuring positive and negative treatment expectancies, and found that this assessment was capable of predicting between 12% and 18% outcome variance in patients with pain. Because patients' expectations can, per se, produce an improvement, the attitudes and satisfaction of patients are important in clinical practice and should be valued and carefully assessed. In the arena of clinical trials, strategies to randomly assign patients on the basis of their baseline attitudes, and to use patients' expectations as covariables, can be helpful. A crucial question in any clinical trial should be: which group do patients believe they belong to? Needless to say, blinding is crucial within this context.

Changes in baseline clinical or biological variables

The mere act of being recruited into a clinical trial can trigger clinical and biological effects that are much stronger than has so far been supposed. Behavioural, clinical, and biological variables can change even before a patient has received a treatment, thus altering baseline values (baseline drift) of the population being studied. The potential introduction of biases by having research participants complete questionnaires and receive tests has long been recognised by clinicians, psychologists, and scientists.[59] Clinical trialists now know this collection of biases as the Hawthorne effect (panel 1).[3] The term derives from a study from the late 1920s to the early 1930s commissioned in Hawthorne Works, a factory outside Chicago (IL, USA), which investigated whether workers would become more productive in higher or lower amounts of light. Although productivity improved when changes were made, the investigators concluded that improvements occurred because the workers were under observation. Thereafter, the term was used in clinical research to recognise that individuals improve in response to their awareness of being under study. Indeed, any clinical improvement that occurs when a patient is recruited into a trial might be attributable to several factors, including better attention, better observation, better care, better compliance, and better adherence. Unfortunately, the concept of the Hawthorne effect has often been misinterpreted or misunderstood in terms of clinical trial methodology—eg, in studies of a surgical safety checklist to reduce morbidity and mortality, in which the surgeons under observation might change their behaviour and performance, the risk of the Hawthorne effect occurring is often not considered. Indeed, sophisticated studies of the Hawthorne effect are long overdue.[60]

Findings from some studies have shown significant changes in baseline values of several biological or physiological variables between recruitment and the

beginning of treatment—ie, before any therapy has been started. For example, Cizza and colleagues[61] assessed the effects of study participation per se at the beginning of a sleep-extension trial, between screening and randomisation, in patients with obesity. The participants were screened and returned 81 days later for random assignment to treatment. Sleep duration, sleep quality, daytime sleepiness, fasting glucose, insulin, and lipids were measured. The investigators noted significant improvements in these variables between screening and randomisation, well before any intervention. Sleep duration increased, sleep quality improved, insulin resistance decreased, and lipid concentrations improved. Moreover, both abnormal fasting glucose concentrations and metabolic syndrome decreased. Therefore, improvements in biochemical and behavioural variables between screening and randomisation, before the administration of any treatment, changed the true study baseline, thereby potentially affecting outcome. Although this study is interesting, only a few studies of this kind have been done so far, and further research is needed to substantiate these findings.

The Hawthorne effect is a good example of how a measurement can interfere with a biological system, thereby changing the baseline values. In other words, the act of recruitment and measurement in a clinical trial leads to uncertainty in the therapeutic outcome (figure 2). In clinical trials, the Hawthorne effect and effect of regression to the mean are often intertwined, and the fact that only people who currently have the condition of interest are included in clinical trials means that the most likely direction of change is often a reduction of symptoms. In other words, in the same way that the Hawthorne effect is related to participation biases, regression to the mean is related to patient selection biases. Although many factors are surely at work here, some findings suggest that social interaction among trial participants might play a part in changes to baseline measures.

There is now compelling evidence that both placebo and nocebo responses can develop through social learning, and manipulation of expectations can induce mass psychogenic illness.[62] The observation of beneficial effects in other people—eg, through the observation of prerecorded or face-to-face facial expressions with different emotional content[63,64]—induces substantial placebo analgesic responses that are positively associated with empathy scores.[65] The same evidence holds true for nocebo effects.[66,67] After the observation phase, participants who have been exposed to other participants in pain show robust nocebo responses—ie, hyperalgesic responses. These responses have been correlated with empathy scores[66] and pain catastrophising,[67] which suggests that both social and psychological factors are crucial for nocebo hyperalgesia. These findings have implications for clinical trials, because the observation of other participants should be taken into consideration whenever a clinical trial is done. Participants in a trial might be influenced by observing or communicating with other patients belonging to the same trial.

One study[68] tested the possible propagation of negative information, and hence negative expectations, across individuals, and the possible consequences in a clinical trial. In an experimental model of headache pain, a participant (the trigger) received negative information about the risk of headache at high altitude and disseminated this negative information to several other participants (figure 2). After a retrospective assessment of the negative information received, the researchers found that in 1 week this negative information propagated across 36 participants. This (nocebo) group showed a significant increase in headache and salivary prostaglandins (particularly prostaglandin E2) and thromboxane A2 when at high altitude, compared with the control group. Additionally, this inter-individual communication had a crucial role in the outcome of a clinical trial. In fact, the same authors ran two clinical trials of aspirin versus placebo at high altitude for the control of high-altitude headache (figure 2).[68] The first trial was done in controls, whereas the second trial was done in individuals exposed to social learning by communication. No placebo response was noted in the first trial: aspirin was effective in reducing both pain and prostaglandin synthesis in the controls, whereas placebo was totally ineffective. By contrast, high placebo

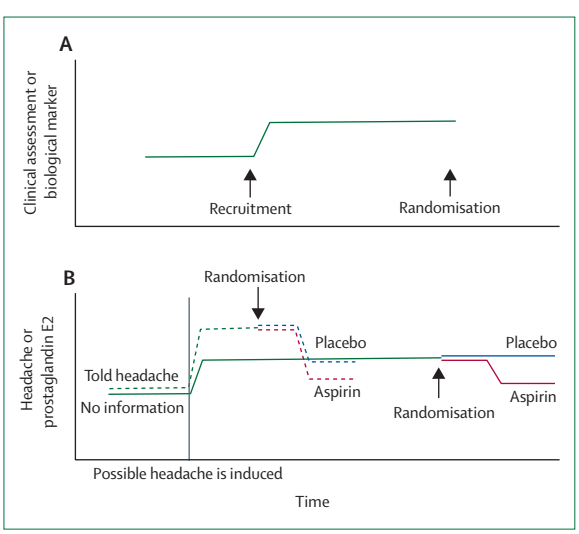

***Figure 2*: Changes in baseline clinical or biological variables before treatment**
(A) In the typical Hawthorne effect, the mere act of recruitment in a clinical trial might change patients' baseline values, thus potentially affecting therapeutic outcomes after randomisation to either placebo or active treatment. (B) Some participants are informed about the risk of high-altitude headache through inter-individual social spread of negative information (dotted line) whereas other participants receive no such information (solid line). A headache is then induced by going to high altitude. The socially affected participants show more severe pain and larger increases in prostaglandin E2 than do those who received no information. This change in baseline produces large placebo responses in the first group (negative information) and no placebo response at all in the second group (no such information).

responses were shown in the second trial: both aspirin and placebo reduced pain and prostaglandins in the socially affected individuals. The difference in placebo response between the two groups is attributable to the different baseline values of headache pain and prostaglandins—eg, prostaglandin E2—induced by the spread of negative information (figure 2). A placebo effect was present only in the socially affected individuals because the placebo acted only on the nocebo component of the prostaglandin and pain increase.[26,68]

Therefore, both the Hawthorne effect[61] and the social propagation of expectations[68] (figure 2) can influence the baseline values of biochemical and behavioural variables before patients are randomly assigned to either placebo or active treatment. Both effects have the potential to affect the outcome of a study.

Should placebo responses be reduced in clinical trials?

Considering the large placebo effects in many CNS clinical trials and their increase over the past few years, a priority in clinical research is the development of study designs that aim to reduce the placebo effect. There are many approaches of this kind.[69–71] For example, a placebo run-in phase is often used to identify placebo responders and exclude them from further random assignment. In this design, patients are given a placebo treatment for several days, and those who respond to the placebo and those who show poor adherence are discontinued from the trial. The remaining participants, who are mainly placebo non-responders and good adherers, are randomly assigned to either active treatment or placebo. In this way, the specific effect of the treatment under investigation is supposed to be isolated.

A variant of the placebo run-in design is the sequential parallel comparative design (SPCD).[72] In the first part of the trial, patients are randomly assigned to either active treatment or placebo. However, unlike other designs, more than half of the patients are assigned to the placebo. After the first part is over, placebo responders and non-responders are identified. The patients who did not respond to placebo are randomly reassigned to another part of the same trial with half the remaining patients receiving active treatment and half receiving placebo. The advantage of this design is that many patients are maintained in the second part of the trial, and thus statistical power is not lost. SPCD is particularly advantageous in trials that involve subjective outcome measures, such as those of antidepressants and analgesics. By using this design in a trial of major depressive disorder, Fava and colleagues[73] were able to reduce the placebo effect from 17% in the first part of the trial to 8% in the second part.

Research into the genetics of placebo responses highlights the possibility of genetic screening for placebo responders and non-responders, with the aim of enrolling only placebo non-responders into a clinical trial.[74,75] In one study,[76] patients with social anxiety disorder were genotyped with respect to the serotonin transporter-linked polymorphic region (*5HTTLPR*) and the G703T polymorphism in the tryptophan hydroxylase 2 (*TPH2*) gene promoter. It was shown that only those patients who were homozygous for the long allele of the *5HTTLPR* or the G variant of the *TPH2* G703T polymorphism showed robust placebo responses and reduced activity in the amygdala, as assessed by functional MRI. Conversely, carriers of short or T alleles were identified as placebo non-responders. In patients with major depressive disorder,[77] polymorphisms in genes encoding the catabolic enzymes catechol-*O*-methyltransferase and monoamine oxidase A were examined. Small placebo responses were found in those patients with monoamine oxidase A G/T polymorphisms (*rs6323*) coding for the highest activity form of the enzyme (G or G/G). Similarly, lower placebo responses were found in those patients with ValMet catechol-*O*-methyltransferase polymorphisms coding for a lower-activity form of the enzyme (two Met alleles). Additionally, the catechol-*O*-methyltransferase functional Val158Met polymorphism was associated with the placebo effect in irritable bowel syndrome. The strongest placebo response occurred in Met/Met homozygotes.[78] The functional missense variant Pro129Thr of the gene coding for fatty acid amide hydrolase, the major degrading enzyme of endocannabinoids, has been shown to affect the analgesic responses to placebo and placebo-induced μ-opioid neurotransmission.[79]

The advantages and disadvantages of controlling and minimising placebo responses are a highly controversial issue in CNS clinical trials. Caution should be applied to the interpretation of the placebo run-in and SPCD trials, as well as the elimination of placebo responders on the basis of a genetic screening, for the following reasons.[80] First, the degree of placebo responsiveness might vary from one time to another within the same individual.[1] Second, reducing placebo responses might not necessarily increase assay sensitivity. In fact, randomly assigning placebo non-responders to placebo and active treatment might lead to low placebo responses in both groups, with no real advantage (figure 3)—ie, no change in the difference between active treatment and placebo. Indeed, a single-blind placebo run-in period is of little use, since it does not differ appreciably, in terms of placebo response or in detecting treatment differences, from trials that do not use such an approach.[81] However, the use of a double-blind, variable duration, placebo run-in period, in which both patients and experimenters are masked to the length of the placebo run-in period and the start of active treatment, has shown better sensitivity in detecting placebo responses.[81] Third, some drugs need an interaction with placebo mechanisms to show their full potential, as shown by the open–hidden administration framework,[14,15] in which the exclusion of the placebo or psychological influence led to a reduction of the drug effect. In other words, the global action of any

treatment, pharmacological or not, is a mix of psychological and specific pharmacodynamic or physical factors. Thus, the exclusion of placebo responders from a clinical trial could lead to artificial situations, and work against the interest of the investigators to detect the full potential of a therapy. Fourth, clinical trials in which only placebo non-responders have been included do not represent the real world. In this regard, the classic distinction between efficacy and effectiveness trials is crucial.[82–84] Whereas efficacy studies are done under ideal and strictly controlled conditions, effectiveness studies are more similar to routine clinical practice (figure 3). In view of the many factors involved in uncertainty—including placebo effects, Hawthorne effects, and social effects—clearly, the more we select patients and circumstances, the further we go from the real world. For example, efficacy trials use strict inclusion and exclusion criteria, whereas effectiveness trials have few exclusion criteria and, additionally, might include patients with comorbid conditions and poor compliance. Moreover, whereas the intervention is standardised in efficacy studies in terms of timing, dose, clinical setting, and trained health professionals, effectiveness studies do not require this standardisation, especially with regard to the medical personnel and equipment or setting. However, effectiveness studies have higher amounts of missing data compared with efficacy trials.

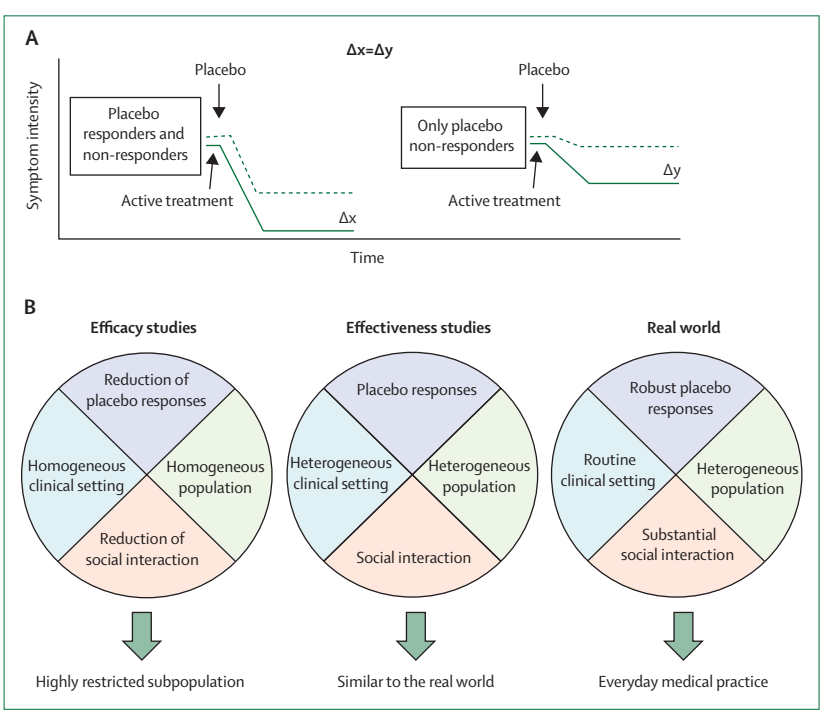

Figure 3: **Problems encountered when reducing placebo responses in clinical trials**
Ethical and methodological problems encountered when reducing placebo responses in clinical studies. (A) Inclusion of only placebo non-responders in a clinical trial might not necessarily increase assay sensitivity, because the placebo effect will be smaller in both groups but the differences Δx and Δy will not change. (B) The more selective we are in the choice of participants, the further we go from the real world. In efficacy studies (with highly selected patients), therapeutic efficacy is studied in a highly restricted subpopulation of patients. In effectiveness studies (less selection), less restrictive inclusion and exclusion criteria are adopted, so the situation is more similar to the real world.

Therefore, the objectives of efficacy studies and real-world effectiveness studies are different and need to be weighed carefully to answer the proper question. Because all the factors contributing to uncertainty in the measurement of therapeutic outcomes are an integral part of the general population, aiming to reduce placebo effects when running a CNS clinical trial is perhaps unrealistic and does not make sense. If we really want to identify placebo responders and non-responders by controlling all these factors contributing to uncertainty, we also need a better discussion about what use we make of this information identifying placebo responders and non-responders. From placebo research, the banes of excluding placebo responders from clinical trials seem to outweigh the boons.

From mechanisms to clinical practice

The study and understanding of placebo and nocebo mechanisms should be a priority in biomedical research, clinical trials, and clinical practice for several reasons. Understanding of the crucial role and biological underpinnings of patients' expectations of therapeutic benefit will help in the design of clinical trials and in the delivery of optimum care for patients. In CNS clinical trials, the assessment of patient expectations should be the rule rather than the exception, and a priority before, during, and after the course of a trial.

All placebos are not equal, and a priority for modern medicine is to elucidate the details of different placebo effects. At present, placebos are used in clinical trials on the assumption that they are inert. However, compelling evidence suggests that different placebos have different mechanisms of action that could, in turn, influence different outcome measures.[85,86] Therefore, in CNS trials, placebos and outcome measures should be selected carefully to avoid erroneous interpretations of study results. For example, Kong and colleagues[85] found that analgesic responses to unique healing rituals might occur through different mechanisms in different situations—eg, in response to placebo pills or acupuncture needles. Likewise, Benedetti and Dogue[86] found that placebo oxygen inhaled through a mask induced a reduction in high-altitude headache with a mechanism of action that differed from that of a swallowed placebo pill. Additionally, and perhaps more importantly, these two different placebos (oxygen mask and pill) affected different outcome measures, such as ventilation, blood pH, and prostaglandin synthesis, which emphasises that the choice of placebo might be crucial in the setting of a clinical trial.

The study of placebo, nocebo, and Hawthorne effects within the setting of clinical trials also provides important information for routine clinical practice. Bearing in mind that patients' expectations often make the difference in terms of therapeutic outcome, clinicians could enhance

the specific effects of a therapy by adding positive psychosocial elements that boost the expectations of their patients (ie, telling their patients how good a treatment is and how great the outcome will be for the patient). Furthermore, testing patients' expectations in phase 4 trials when the drug, or any other treatment, is on the market would be interesting, and both health-care providers and the pharmaceutical industry would benefit from this approach. In fact, the increase in placebo responsiveness over the past few years could be attributed to expectations following the advertisement of new drugs, and this potential association should be assessed.

Conclusions and future directions

Placebo, nocebo, and Hawthorne effects pervade routine clinical practice and produce uncertainty in the measurement of therapeutic outcomes. The more we learn about the mechanisms underlying these effects, the more we need to reframe our approach to clinical trial methodology. Although we believe that placebo responses should not be reduced artificially in clinical trials, some considerations for future trial design should be taken into account (panel 3). For example, social interaction among the participants of a trial should be counted as an important factor affecting baseline values of clinical or biological variables. Because placebo and nocebo effects, Hawthorne effects, and social effects are all at work across various patient populations and CNS disorders, a crucial question is whether these elements should be reduced in clinical trials to show the efficacy of a new treatment. Even if they could be minimised in efficacy studies as a starting point, real-world effectiveness needs to be taken as the main objective. Thus, placebo and nocebo effects should be considered as an integral and essential part of real-world routine clinical practice. Therefore, a better approach in the setting of clinical trials would be to view patients' expectations as crucial determinants of therapeutic outcome, and to consider the assessment of patients' expectations as routine practice in such studies.

Future CNS research should aim to clarify at least three crucial points. First, the nature and the neurobiological mechanisms of placebo, nocebo, and Hawthorne effects need to be understood across various CNS disorders. Second, the CNS diseases in which these effects are large, small, or totally absent need to be identified. Third, once all the elements causing these effects are identified, efficacy and effectiveness trials need to be carefully compared to verify whether steps to control placebo, nocebo, and Hawthorne effects are necessary or desirable to validate a new therapy. Therefore, where, when, and how placebos and nocebos work should be established in future studies. This goal is certainly challenging, because it entails the mapping of placebo and nocebo responses across many conditions, from neurology to psychiatry and many other medical disciplines. A starting point for this exciting enterprise is to understand the role of patients' expectations across various disorders, which will benefit both clinical trial design and clinical practice. An important point that needs to be addressed is why placebo and nocebo effects exist at all. Addressing this question is not simply a matter of advancing evolutionary understanding of human biology, but also a crucial step in improving the doctor–patient relationship.[87–89]

Panel 3: Ten tips for a better future in CNS clinical trials

1. The more placebo non-responders we include in clinical trials, the further we go from the real world; thus, any design that aims to eliminate placebo responders from a trial should be considered carefully.
2. All trials should include an assessment of patients' expectations.
3. All trials should assess patients' perceived assignment by asking participants which group they believe they belong to.
4. Adverse events in placebo arms (nocebo effects) might depend on the adverse events of the active medication against which the placebo is compared; such comparisons could provide important information on the role of patients' expectations.
5. The Hawthorne effect, or the effect of being under study, should be considered in any trial and investigated in detail.
6. Social interactions among trial participants should be avoided to prevent possible effects on baseline clinical and biological variables.
7. The experimenter–patient interaction should be assessed carefully (eg, the number of visits), because these interactions might influence patients' expectations.
8. Different placebos use different mechanisms, which in turn might lead to different outcomes; thus, the careful selection of placebos (pills, injections, delivery systems, etc) and outcome measures is crucial.
9. Longer and larger trials can produce large placebo responses; thus, shorter and smaller trials are sometimes preferable to longer, larger, multicentre trials.
10. A priority for biomedical research, both at the academic and the industry level, should be to understand where (which medical condition), when (which circumstance), and how (which mechanism) placebos and nocebos work.

Search strategy and selection criteria

We searched PubMed for papers published in English between Jan 1, 2000, and Dec 31, 2015, with the following search terms: "placebo effect", "placebo response", "placebo analgesia", "nocebo effect", "nocebo response", "nocebo hyperalgesia", and "Hawthorne effect". We selected reports of studies that aimed to investigate the mechanisms of placebo, nocebo, and Hawthorne effects or that discussed related methodological issues of CNS clinical trials. Because the aim of this Review was to highlight recent findings about the role of placebo, nocebo, and Hawthorne effects in the interpretation of results from CNS clinical trials, we selected mainly studies published between 2010 and 2015, but we did not exclude frequently referenced and highly regarded older publications, especially those that helped in understanding more recent findings. We discarded studies whose main objective was merely to compare an active treatment with placebo.

Contributors

FB, EC, and AP searched and selected the scientific literature, critically discussed the publications, and wrote the Review.

Declaration of interests

We declare no competing interests.

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