for CBT seem to be an example of the latter practice being applied to the results of multiple meta-analyses.

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Authors' reply: We thank Dr McKenna (and colleagues) for his interest in our editorial, and respect his long record of research into schizophrenia. His point about the authors of influential national clinical guidelines such as NICE, the British Association for Psychopharmacology (BAP) and the Scottish Intercollegiate Guidelines Network (SIGN) needing to take negative evidence into account is well made, and analogous to the AllTrials movement in pharmacotherapeutics. Schizophrenia is such a common and potentially devastating illness that it is incumbent on mental health professionals such as psychologists and psychiatrists to work together to deliver best-evidenced treatments.

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Does previous experience of antidepressants form the expectations necessary for a placebo response?

Leuchter *et al*'s[1] findings extend the current understanding of the placebo response and raise important questions regarding the design of antidepressant trials. An important finding was that expectation of medication effectiveness predicted treatment response in the placebo group only, which suggests that expectations of treatment benefit are required for a placebo response.

It is thought that the placebo response results from an interaction between expectations and learning.[2] In studies of placebo analgesia, experimental paradigms often involve a conditioning procedure to induce an expectation of benefit from treatment. One widely used paradigm involves thermal pain stimulation and application of an inert cream. Following application of the cream, the thermal energy is reduced to non-painful levels to condition the participant to believe the cream has analgesic properties. Subsequently, laser stimulation continues at painful levels, and participants report the stimulation as less painful.[3–6] The implication is that an expectation of analgesia, induced by exposure to the cream's 'analgesic' properties, results in a placebo response.[3] Learning to expect an effect has also been shown to influence emotional processing. Petrovic *et al*[7] measured responses to aversive pictures in healthy volunteers following administration of placebo 'anxiolytic' medication and its reversal, and found that participants reported aversive pictures as less distressing when they thought they had received anxiolytic medication, and more distressing when they believed this had been reversed. This result shows that a learned expectation, induced through exposure to a medication, can cause changes in emotional processing.

In the study reported by Leuchter *et al*,[1] there was a relationship between expectation of benefit and treatment response in the placebo group. However, these patients did not undergo a conditioning procedure to induce an expectation of benefit. What caused these patients to expect a benefit? Could the therapeutic environment and consent process for starting an antidepressant engender a powerful expectation of benefit on its own? Or does this expectation come from previous experience of benefit from antidepressant treatment? The data from this study suggest the latter, as the expectations seemed to be formed at the time of enrolment. We could perhaps answer this question more fully through assessment of the relationship between previous response to antidepressant treatment and placebo response in this trial. It is possible that more patients in the placebo group had previously benefitted from treatment than in the medication group, and if this were so, it would lend support to the idea that previous experience of benefit from antidepressant treatment could cause a placebo antidepressant response. This could be an important consideration in future antidepressant drug trials.

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Authors' reply: Huneke & Baldwin raise important points regarding the interpretation of our study results and the relationship of our findings to the broader placebo literature. It is challenging to compare the results from our study with the literature cited by them. As they note, studies of placebo analgesia generally are performed in healthy volunteers not being treated for a chronic illness. Such studies examine the placebo effect, namely the relief of transient, experimentally induced symptoms during manipulation of expectations. By contrast, our study examined placebo response, which involves relief of naturally occurring symptoms of a chronic illness (in this case major depressive disorder, or MDD) within the context of a clinical trial. Because patients with MDD have long courses of illness and treatment, they commonly enter treatment studies with pre-existing expectations and beliefs, and our participants had indeed formed expectations about medications at the time of study enrolment. We concluded that these expectations were probably formed by factors external to the study, and speculated on the role that