Author's response

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We thank Dr Fountoulakis for his interest in our work. He suggested that there may be four factors that could explain the increase in placebo response rates up to 2000, namely the introduction of operationalised diagnostic criteria in 1987, the decrease of baseline depression severity in randomised trials over time, the use of HAMD-D or MADRS (which are not differentially sensitive to depressive or anxiety symptoms), and the co-administration of benzodiazepines (to which anxiety symptoms are responsive). Historically speaking, the concept of endogenous versus neurotic depression was "officially" abandoned by DSM-III in 1980. All studies included in our systematic review used operationalised diagnostic criteria including DSM-III or their forerunners, so this cannot explain the apparent increase in placebo response in the data.[1] Furthermore, we showed in Table 2 that baseline depression severity and the use of rescue medication (i.e. sedative drugs, such as benzodiazepines, or sleeping pill) were not associated with the relationship between placebo response rates and year of the study before 2000. We agree that HAM-D and MADRS may not be the best tools to assess the severity of depressive symptoms; however there are psychometric reasons to include anxiety symptoms in scales that measure the overall severity of depressive disorders (because people with depressive disorder present with both symptoms), but not to include them in the diagnostic criteria (because a differential diagnosis is needed and both people with depressive disorder and those with many other psychiatric disorders present with anxiety symptoms).

A previous commentary to our paper by Dr Enck was in some way misleading [2] and we would like to clarify the following points to allow readers to judge and interpret our findings correctly. The average placebo response rates in antidepressant trials remained stable (at about 35% to 40%) across all trials performed since 1991 (and not in 2000, as wrongly written in the commentary). The previously reported increase in placebo response rates before 2000 [3] was replicated in our dataset but it became non-significant when controlling for potential effect modifiers. In our paper we thus examined what caused the increase of the placebo response observed before 2000. Our analyses showed that multi-centre studies, fixed dosing and longer trial duration were the statistically significant factors contributing to the increase in placebo response rates up to 2000. We think that

these are relevant findings that should help clinicians and researchers not only to interpret the literature but also to inform future trial design in major depression. While it is true that "design variability between RCTs is not what a systematic review or meta-analysis can cope with" [2], antidepressant trials remarkably display a lack of important variation in their design. Consequently, systematic reviews, meta-analyses and ideally network meta-analyses[4] are not only desirable but indispensable to make sense of the vast amount of information in the field.[5]

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