Methodological issues in studies of major depression and schizophrenia. Implications for the "Committee for proprietary medicinal products" guidelines
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7. General discussion
Major depression

The ethical concern that patients in the placebo condition are not getting active treatment during for the duration of a placebo-controlled study is a valid argument against the conduct of such studies and should be taken very seriously. Participation in a placebo-controlled study places a heavy burden on the depressive patient, family, friends and caregivers.

Patients in the placebo condition of a placebo-controlled study run the risk of becoming even more severely depressed, and desperate, and may eventually show psychotic symptoms. On the other hand as most depressive episodes improve over time, the symptoms of patient in the placebo condition might also gradually improve. It should also be said that patients in the placebo condition do not suffer from adverse events that they would have experienced eventually if they were treated with an active compound. This might be an advantage for them.

Moreover, although active treatment improves symptomatology this does not mean that all patients respond. We have shown in our meta-analysis that the effect of the well-established tricyclic antidepressants is modest (1). Moreover we have shown that in 70% of these studies active treatment was not superior to placebo. This means that the curtain drops for equivalence studies in major depression. Because there is evident and historical inconsistency of trial results there is lack of trial sensitivity and therefore there is no way of knowing whether or not a potential lack of difference between treatments in an equivalence study is not actually due to the failure of the study. This finding supports the CPMP opinion concerning the need for placebo to demonstrate efficacy. On the other hand, a superiority study versus an active compound in an adequate dosage, might be an option demonstrating efficacy by-passing placebo.

Another ethical concern in the conduct of placebo-controlled studies, is the risk of (attempted) suicide in the placebo condition. The results of our investigation (2), confirm the findings of Khan et al (3), who found that in short-term placebo controlled studies there is no increased risk of (attempted) suicide when appropriate measures are taken such as the exclusion of suicidal patients. We also demonstrated that in long-term studies there is no increased risk of (attempted) suicide in the placebo condition, even though suicide was not an exclusion criterion in these studies. We conclude, therefore, that an important ethical concern (increased risk of suicide or attempted suicide) against the conduct of placebo-controlled studies in major depression has not been substantiated.

Though it might appear that excluding suicidal patients from the short-term studies would affect generalization of the results to the whole population of depressed patients, the long-term data give sufficient assurance on this point. Moreover there is no indication in the literature to suggest that patients with a major depression with suicidal ideation would react essentially differently to pharmacological treatment than patients without suicidal ideation (4-6).

Our investigation concerning the methodology of long-term withdrawal studies showed that the methodology of these studies do not distinguish between prevention of relapse and recurrence. As there were major methodology differences between the studies (e.g., definition of relapse and recurrence) the results of the separate studies could not be compared fairly. Moreover the duration of these studies
considerably differed from study to study making comparisons of the results impossible.
The only conclusions drawn from these studies are that the design of a "classic" placebo-controlled withdrawal study only allows a statement concerning maintenance of effect (i.e. the short-term efficacy is maintained over time). Extension studies in short-term responders without randomisation, are not even suitable for demonstrating long-term efficacy.
If a company wants to obtain the claim recurrence prevention in Europe a specially designed study has to be conducted: one option might be a long-term randomised placebo-controlled study in patients who at baseline have been free of medication for a substantial period of time and who fulfil the criteria of major depression (recurrent) in remission (e.g. HDRS < 7) for the duration this drug-free period (7).

Schizophrenia
There is also a degree of ethical concern about conducting placebo-control studies in schizophrenic patients again on the grounds that patients in the placebo condition are not given active treatment. We have shown that, for the moment, alternative studies by-passing placebo are inadequate in demonstrating efficacy (8). As there is no effective treatment for negative symptoms in schizophrenia, the concern of conducting placebo-controlled studies is really not relevant.
Efficacy on negative symptoms has recently been tested with amisulpride, in specially designed placebo-controlled studies (9-12). We used the results of these studies to show that there was a surprisingly high success rate in the placebo-groups, indicating either that primary negative symptoms are not as persistent as had previously been thought, or that the concept of primary negative symptoms should be reconsidered according to the theory of Greiden and Tandon (13); primary, enduring negative symptoms that are intrinsic to the disease process and primary non-enduring negative symptoms that are intrinsic to the disorder but wax and wane like positive symptoms. Amisulpride is probably efficacious on these non-enduring primary negative symptoms but can by no means be considered to be gold standard in the treatment of negative symptoms (14). To prove efficacy on negative symptoms therefore, placebo-controlled studies will still be necessary. The addition of a third arm, e.g. low doses haloperidol, also could be very informative in future studies and might be useful as a further validation of the results.

Conclusion
In the development of the depression guideline we investigated the need for placebo-controlled studies to demonstrate efficacy. We have shown that the placebo effect in short-term placebo-controlled studies varies considerably from study to study, and that tricyclic antidepressants in 70% of the studies were not superior to placebo. Equivalence studies with a tricyclic antidepressant as comparator without a placebo-control therefore are not sufficient for demonstrating efficacy. In major depression, placebo-controlled studies are still necessary to demonstrate efficacy. We have also shown that there was no increased risk of (attempted) suicide in the placebo-group. This can not therefore be an used as an argument against the conduct of short-term and long-term placebo controlled trials in major depression. Randomised long-term withdrawal studies are suitable for demonstrating that short-term efficacy is maintained for the duration of the study period. However, this design
does not allow a differentiation between relapse and recurrence in the case of reappearance of symptoms. Therefore this design is not suitable for demonstrating unequivocally relapse or recurrence prevention.

In order to demonstrate recurrence prevention, a long-term randomised placebo controlled study in patients free of medication for a substantial period of time fulfilling the criteria of major depression (recurrent) in sustained remission (e.g. HDRS < 7) might be a worthwhile option.

In schizophrenia we have shown that the responder rates varied considerably from study to study. Moreover, the magnitude of the responder rates in the arms of the equivalence studies were, in two of the three studies, in the same order as the responder rates of the placebo-arms in the placebo-controlled studies.

It is perfectly feasible to conduct placebo-controlled studies in patients with predominantly negative symptoms. These studies show an unexpected, considerably and variable high placebo effect.

In this population too therefore placebo-controlled studies are needed to show efficacy.

In conclusion we affirm that the CPMP guideline for major depression and schizophrenia in terms of the need for placebo-controlled studies is both evidenced-based and ethically justified.
References


