Methodological issues in studies of major depression and schizophrenia. Implications for the "Committee for proprietary medicinal products" guidelines
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Summary
The purpose of the investigations presented in this thesis are introduced in Chapter 1.

Chapter 2 describes a meta-analytic study that was conducted to give answer to the question whether placebo-controlled studies are still necessary in order to show efficacy in major depressive episode or that it is sufficient to conduct active-control equivalence trials (inferiority trials). Moreover, the objective of this study was to provide an accurate estimation of the magnitude of the effect of tricyclic antidepressants.

We illustrate in this study that in 69% of the placebo-controlled studies no statistically significant difference was found in favour of tricyclic antidepressant and that the placebo rate varied considerably from study to study. Equivalence studies with tricyclic antidepressant as comparator without a placebo-control therefore are not sufficient for demonstrating efficacy.

We also show that tricyclic antidepressants are efficacious in the short-term treatment of major depressive episode. However, the magnitude of the effect is rather modest.


Chapter 3 describes a study that was conducted to determine whether there was an increased risk of (attempted) suicide in the placebo-arms of (short-term and long-term) placebo-controlled double-blind studies. We reviewed all short-term and long-term placebo-controlled double-blind studies that were part of a registration dossier for the indication major depressive episode that were submitted to the Medicines Evaluation Board (MEB), the regulatory authority of the Netherlands in the period 1983 - 1997, for (attempted) suicide. In addition, all published long-term placebo-controlled studies conducted in the last decade in patients with a major depressive episode, were assessed for (attempted) suicide. We show that fear of an increased risk of (attempted) suicide in the placebo-group, should not be an argument against the conduct of short-term and long-term placebo-controlled trials in major depressive episode.


Chapter 4 describes a study that was aimed to evaluate what might be concluded from the results of the long-term placebo-controlled studies in major depression that were carried out in the last decade.

We show that randomised withdrawal studies are suitable for demonstrating that short-term efficacy is maintained for the duration of the study period. This design does not, however, allow a differentiation to be made between relapse and recurrence in the case of reappearance of symptoms and is therefore, not suitable for demonstrating unequivocally relapse or recurrence prevention. Extension studies in short-term responders without randomisation are not even suitable for
demonstrating long-term efficacy. We also suggest a study design to demonstrate recurrence prevention: a long-term randomised placebo-controlled study in patients free of medication for a substantial period of time and fulfilling the criteria of major depression (recurrent) in sustained remission (e.g. HDRS < 7) might be a valid option.


Chapter 5 contains a review of all efficacy studies of the atypical anti-psychotics submitted to the MEB in the period 1992-1997. Our aim of this study was to provide an answer to the question of whether it is still necessary to conduct placebo-controlled studies in order to show efficacy, or whether it might be sufficient to conduct active-control equivalence trials (inferiority trials). We show that responder rates in the placebo-arms varies from study to study and that responder rates in the atypical and haloperidol arms of the non-placebo-controlled studies are, in two of the three studies, in the same order of magnitude as the responder rates of the placebo-arms in the placebo-controlled studies. Active-control equivalence studies are not a good option to show efficacy in studies in schizophrenia. We also show that alternatives to avoid placebo-controlled studies are inadequate to demonstrate efficacy in these studies.


Chapter 6 presents a meta-analysis of the specially designed clinical studies which have been conducted with amisulpride in the treatment of negative symptoms and discuss their methodology and findings. Four placebo-controlled studies were conducted in patients with predominantly negative symptoms. In all studies a significant improvement was observed on the SANS in the amisulpride groups (50-300 mg daily) as compared to placebo. The improvement on the SANS was not accompanied by a simultaneous improvement on the SAPS or a decrease in EPS in three of the studies, indicating a genuine effect on primary negative symptoms. The overall analysis shows that the improvement on the SANS was accompanied by a small simultaneous improvement in the SAPS. Moreover in the studies where depressive symptoms were measured, also a significant improvement was shown in favour of amisulpride. However, as the SAPS and MADRS baseline scores were rather low, the improvement on both scales in favour of amisulpride was probably not responsible for the improvement on the SANS.

A positive correlation was found between the severity on the mean SANS score at baseline and mean improvement at endpoint. In addition a surprisingly high placebo-response was observed. This suggests 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; primary, enduring negative symptoms that are intrinsic to the disease
process and primary nonenduring negative symptoms that are intrinsic to the disorder but wax and wane in the same way as positive symptoms. It is likely that amisulpride is efficacious on these nonenduring primary negative symptoms.