Methodological issues in studies of major depression and schizophrenia. Implications for the "Committee for proprietary medicinal products" guidelines
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1. General introduction and objectives of the studies
Introduction

Before a medicinal product can be marketed, a marketing authorisation license has to be issued by the appropriate regulatory authority. The judgment is based on three criteria: efficacy, safety and pharmaceutical quality. To obtain this marketing authorisation, a company must submit to that authority a dossier with relevant information on the quality, safety and efficacy of the medicinal product concerned, as well as a proposed draft text for the official product information texts (i.e. the "summary of product characteristics" and the "patient information leaflet"). In the Netherlands the assessment of this dossier is a task of the government and the name of the official regulatory authority in the Netherlands is the Medicines Evaluation Board (MEB).

Medicines Evaluation Board of the Netherlands
The Medicines Evaluation Board was established by law in 1963. It is an independent administrative body with a maximum of 18 members (mainly doctors and pharmacists) appointed by the Crown. The MEB is responsible for decision-making with regard to the authorisation of medicinal products for human use. The executive staff and those involved in the evaluation of registration dossiers are employed by the Medicines Evaluation Board Agency (MEB Agency), which is part of the Ministry of Health, Welfare and Sport. The Director of the MEB Agency is also Secretary of the MEB.

The MEB Agency is responsible for the preparation of assessment reports of the dossier submitted by pharmaceutical companies. This assessment is carried out by experts employed by the MEB Agency or, at the request of the MEB Agency, by
experts attached to the National Institute for Public Health and the Environment (Rijksinstituut voor de Volksgezondheid en Milieu; RIVM). On the basis of the assessment reports, the MEB decides whether or not a marketing authorisation should be granted and, in the case of a positive opinion, then finalises the product information texts, following which a marketing authorisation is issued. The MEB is not only responsible for the authorisation of medicinal products, but also for monitoring the range of authorised products. It may, for example, be necessary to limit the conditions under which a product has been authorised, or even to suspend the authorisation or revoke it completely, if and when new information on adverse reactions becomes available. Finally, the MEB also has the task of determining the legal status of medicinal products (prescription only or over-the-counter).

**Organisation structure**

**MEB and MEB Agenecy**

**Authorisation of medicinal products and the European Union**

Until 1995, marketing authorisations were issued nationally within the European Union (EU) and were only valid within the territory of the member state that had issued the authorisation. Since 1995, however, it has become possible to obtain a central marketing authorisation, issued by the European Commission and valid throughout the EU. In order to obtain an EU marketing authorisation, an application must be submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) in London. A so-called Centralised Procedure is then followed. The scientific committee for human medicinal products of the EMEA is the Committee for Proprietary Medicinal Products (CPMP) The CPMP is responsible for
advising the European Commission as to whether or not medicinal products should be granted a marketing authorisation.

Every member state of the EU is represented on the CPMP by two experts, the Dutch members being appointed by the MEB. In addition to the above-mentioned procedure, a so-called decentralised procedure is in place. It makes use of the recognition of a marketing authorisation issued at a national level. If a company wishes to introduce a medicinal product for which in a member state a marketing authorisation has been issued the Mutual Recognition Procedure must be followed. In case the decision of the first member state is not accepted by one or more member states the case may be referred to the CPMP for arbitration. After the judgement of the CPMP the involved member states implement the decision.

*Efficacy Working Party*

The work of the CPMP is supported by various working parties, one of which is the Efficacy Working Party (EWP). The EWP consists of a chairman and 15 members, one from each Member State, acting as independent experts. The main task of the EWP is to prepare guidelines for the CPMP. An important reason for drafting a guideline is to increase harmonisation and mutual understanding in Europe, which has not always been the case in the past, and thus to facilitate the work of the
CPMP. These guidelines address methodological issues in drug development and thereby give direction to future drug development.

**CPMP guidelines**

In the process of drafting a guideline, differences in methodological approaches, medical culture and ethical views will inevitably be discussed. The aim is to reach a consensus on, for instance, the most relevant endpoint, the possibility of placebo control, the need for (additional) active control, the duration of trials and other design issues. In these discussions one of the major considerations is that the development of a product should be conducted in such a way that, in the end, clinically relevant results can be obtained, and benefit and risk can be assessed. Guidelines will also ensure consistency in assessing products in the same area and improving the transparency of the decisions concerning the licensing of a product. Guidelines also give companies directions in future development of their medicinal products. The preparation of such a guideline calls for a specific operational procedure. In short, the procedure will start by drafting a Concept Paper, indicating the reason for a guideline, the problems to be addressed and the intended time frame. Based on this Concept Paper, the CPMP will then decide whether a guideline is indeed necessary. If so, the EWP will appoint one or more experts to draft it. These experts are all members of the EWP, who, depending on their expertise, will work in close co-operation with experts in the field. Several drafts will be discussed within the EWP until an acceptable document is produced, which will then be sent to the CPMP to be distributed for further consultation. During the six months consultation time, National Authorities, European Industry, European Professional Societies and other interested parties will be asked for their comments. Some member states, such as The Netherlands, also consult their national professional organisations. After discussing the comments within the EWP, a final draft will sent to CPMP for adoption. Concept Papers, the draft guidelines sent out for consultation, and the final guidelines are put on the Internet as part of the EMEA website. A guideline is a scientific document, reflecting the state of the art at a particular moment. Guidelines are not binding, which means that companies have room to develop a product in a creative way, instead of being obliged to copy each other. Of course, deviation from the guideline has to be justified, bearing in mind that the guideline is the product of lengthy scientific thought and discussion. As science evolves, so too will the guideline.

One of the major problems in developing guidelines is that the need to prove efficacy and safety of a compound in a certain patient population, may sometimes interfere with the treatment needs of the individual patient. In conclusion, guidelines are important instruments for the harmonisation of requirements concerning the methodology of clinical trials within Europe. They are not straitjackets- they are living documents – valid for their times- doorways to the future. Although not science in themselves, guidelines, when used correctly should in no way hamper scientific development, but rather stimulate the clinical development of medicinal products and ensure relevant and open discussion within the CPMP.
CPMP guideline for major depression and schizophrenia

To grant a licence in Europe a relevant effect has to be shown in both short-term and long-term efficacy studies (1). This applies to both major depression and schizophrenia. When these guidelines were being developed the rapporteurs of these guidelines decided to investigate ethical and methodological aspects of the kind of studies needed for a valid risk/benefit assessment. The objectives of these investigations were to compile evidence-based and ethically justified CPMP guidelines.

In the case of the depression guideline, the following aspects were raised: the need for short-term placebo-controlled studies, the risk of (attempted) suicide during the course of these studies, the need for placebo-controlled long-term studies, and the claims to be included in the product information text, that might be derived from them.

In the development of the schizophrenia guideline, the need for placebo controlled studies was also an important topic, as well as the question of the methodology to be used in studies to show efficacy on negative symptoms. These topics will be discussed in detail below.

Do we need placebo controlled studies in major depression and schizophrenia?

Major depression:

In recent years, objections have been raised against the conduct of placebo-controlled studies when known effective therapy is available for the condition being studied (2,3). The rationale for the resistance lies in the facts that part of the patients at least are not treated with an active compound during the study period. It could be therefore that these patients might suffer unnecessarily, and that this might also be a needless burden for family, friends and caretakers.

Rothman and Michels (2), strongly against the conduct of placebo-controlled studies, wrote in their provocative article concerning the conduct of placebo-controlled studies in major depression: "A 1992 report of randomized trial of treatment for major depression began with the statement "Effective antidepressant compounds have been available for over 30 years". Nevertheless, the investigators in that study assigned half of the seriously depressed patients in the trial to receive placebo and the other half to receive paroxetine. Placebo controls are common place in trials of antidepressants drugs, despite the availability of therapies whose success is acknowledged".

Recently, Rothman and Michels (3) again disputed the morality of performing placebo-controlled studies when there is an existing accepted treatment offering suggestions to strengthen the protection of patients participating in medical experiments by strengthening the Declaration of Helsinki. This would make it very difficult to conduct placebo-controlled studies. The question is: are active controlled equivalence studies an option?

Assay sensitivity should be ensured in demonstrating efficacy in active controlled equivalence studies. Assay sensitivity is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective treatment (4,5). Leber (6) examined the results of all three-arm studies (n=6) comparing nomifensine (the test drug) imipramine (TCA: tricyclic antidepressant) and placebo. In none of
these studies was there a difference between the test drug and imipramine in mean improvement on the Hamilton Depression Rating Scale (a primary outcome measure in studies conducted in patients with major depression) at endpoint whilst the changes from baseline seemed to be substantial and of clinical relevance. It might therefore be concluded that the test drug is as effective as imipramine. However in five of the six studies imipramine was not found to be superior to placebo. The only conclusion to be drawn from these studies therefore is that there was a lack of assay sensitivity; i.e it was not possible to distinguish active from inactive treatment. The Leber study (6) limited as it was by the number of studies and the inclusion of only one product (nomifensine), illustrates the importance of including both a placebo and an active drug in major depression studies.

In order to assess the size and consistency of the difference between placebo and TCA in placebo-controlled studies in major depression and thus to investigate the degree of assay sensitivity, we analysed the original data from the placebo-arms and the tricyclic-arms of all parallel randomised controlled three-arm studies conducted in the period 1979-1991 submitted to the MEB for the indication major depression. These files contain all studies which were conducted with a test drug, including all short-term, parallel, randomised studies with both a tricyclic antidepressant and placebo as control. Not all these studies are published. Moreover, these files do not contain aggregate and/or separate center studies from multicenter studies as is often found in the literature. Therefore, although one company did not participate in submitting studies, the studies included in our meta-analysis are sufficiently informative for the purpose of our investigation. Moreover the original data were analysed.

In placebo-controlled studies with patients with major depression, there is a specific ethical concern to deal with, as the lifetime risk of suicide in major depression is 15% (7). Patients in the placebo condition might thus run an increased risk of committing suicide, and could, as such constitute an additional ethical argument against the use of placebo in studies in major depression. We were prompted therefore, to review all previous placebo-controlled studies (short-term as well as long-term) to determine the risk of (attempted) suicide in the placebo group.

Schizophrenia:
In schizophrenia too, there are also ethical concerns which need to be confronted in terms of the “yes” or “no” of placebo-controlled studies. Carpenter et al (8) recently addressed the question of the use of placebo in schizophrenia studies and argued that antipsychotic medications have been shown to be effective for a substantial proportion of patients in alleviating or reducing positive symptoms of schizophrenia and thus reducing the risk or delaying the recurrence of psychotic exacerbation. The risk inherent in placebo-controlled studies in schizophrenic patients includes the prolongation, or the re-emergence of psychosis. This might lead to a situation of loss of judgement and insight, personal harm to others, job or housing loss, increased burden to family or other caregivers or other complications of psychosis. There might also be a long-term risk for untreated patients. Wyatt (9) reviewed the literature in order to address this question and argued that the longer a person is ill before treatment, and the more prolonged the psychotic experience is after initial treatment, the worse the ultimate treatment response and the poorer the long-term outcome.
However, the question of whether psychosis itself is neurotoxic and that it may alter long-term disability has not been resolved unequivocally (8,10). New antipsychotic agents have recently been developed, the pivotal clinical trials of which incorporated a placebo-arm and, in many cases, a third arm (haloperidol). These studies are very informative in respect of the placebo-effects in schizophrenia and might thus provide an answer to the question of whether placebo-controlled studies are still necessary or that active-control equivalence studies are sufficient to prove efficacy. In order to answer to this question we reviewed all efficacy studies from the atypical anti-schizophrenia (from 1992-1997), using the original registration files submitted to the Medicines Evaluation Board of the Netherlands.

Do we need long-term studies in major depression? Before a licence can be granted in Europe, a relevant effect has to have been shown by means of in both short-term and long-term efficacy studies. It may be that long-term placebo controlled studies are even more unethical than short-term studies because patients receiving placebo will be denied active treatment for a longer period of time. It is probably because of these ethical concerns, that no placebo-controlled studies have been conducted with schizophrenic patients in last few decades.

In major depression, however such studies have been carried out and claims concerning relapse and recurrence prevention have been made based on their findings. We critically reviewed the designs of these studies with the objective of evaluating what might reasonably be concluded from them.

What kind of methodology should be used in studies to show efficacy on negative symptoms? Efficacy on negative symptoms has been associated with classic antipsychotic treatment (11, 12) and claimed for clozapine (13) although this has never been shown in placebo-controlled studies conducted in patients with predominantly negative symptoms. Efficacy on negative symptoms has been claimed in most of the pivotal short-term randomized placebo-controlled trials of recently developed anti-schizophrenic agents (14-26). Bearing in mind, however, that patients with predominantly positive symptoms were included in these studies, these findings could be explained by the primary beneficial effect on positive symptoms, causing secondarily an improvement on the negative symptom score (27,28). An improvement on the negative symptom score might also be explained by the lower Extra-Pyramidal Symptoms (EPS) properties of these new compounds compared to the classic antipsychotics. In conclusion, it is impossible in these studies to disentangle which part of the improvement on negative symptom score is due to the improvement on positive symptoms to less EPS, to an improvement on depressive symptoms or to an actual effect on primary negative symptoms. For this reason specific study designs have been developed with the primary objective to show efficacy on primary negative symptoms (28,29). Placebo-controlled studies with this specific design have recently been conducted with amisulpride, a substituted benzamide with high affinity for dopamine (D_2/D_3) receptors (30). We used these studies as they are very informative with regard to efficacy on negative symptoms in schizophrenia. A meta-analysis of these studies was conducted and the
methodology of these studies are discussed together with the clinical implications of the use of amisulpride.
References


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