Methodological issues in studies of major depression and schizophrenia. Implications for the "Committee for proprietary medicinal products" guidelines
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4. Relapse and recurrence prevention in major depression: a review of placebo-controlled efficacy studies with special emphasis on methodological issues.

SUMMARY

Long-term studies in major depression have been conducted claiming relapse and recurrence prevention. This article critically reviews the designs of these studies with the objective to evaluate what might be concluded from the results of these studies. A literature search in MEDLINE was performed with the medical subject headings “depression” “recurrence” “relapse” “prevention” and “study”. This search covered the period from 1990 to July 1999. Only long-term placebo-controlled studies including patients with non chronic major depression were selected. Two types of design could be distinguished: randomised withdrawal studies in responders/remitters (n = 11) and extension studies in responders without re-randomisation (n = 3).

Randomised withdrawal studies are suitable for demonstrating that short-term efficacy is maintained during the duration of the study period. However in this design it is not possible to differentiate between relapse or recurrence in case of a reappearance of symptoms. Therefore this design is not suitable for demonstrating unequivocally relapse prevention or recurrence prevention. Extension studies in short term responders without randomisation are not even suitable for demonstrating long-term efficacy.

To demonstrate recurrence prevention a long-term randomised placebo controlled study in patients who are free of medication for a substantial duration of time and who fulfil the criteria of major depression (recurrent) in sustained remission (e.g. HDRS < 7) might be an option.
INTRODUCTION

Five theoretical outcome definitions can be distinguished in major depression. These are the five R's; Response, Remission, Recovery, Relapse and Recurrence [1]. Response can be defined as a significant level of improvement such that a responder should be qualitatively different from a nonresponder [2] or as a clinically relevant reduction (i.e. ≥ 50%) on a severity scale such as the HDRS or MADRS [3]. Remission is defined as a condition where only “few signs of illness remain” (HDRS <7) [4]. Recovery is a sustained period of remission representing resolution of the index episode. Relapse is the condition of a symptomatic exacerbation occurring after a response but before achieving sustained remission during the same episode. Recurrence is a new episode of depressive illness following recovery.

In the treatment of major depression three stages can be distinguished. The first stage is the treatment of the acute symptoms. The second stage, the continuation phase, strives to prevent relapse, and the third phase, the maintenance phase is intended to prevent recurrence [5].

In the last decade many short-term and several long-term placebo-controlled studies have been conducted to assess the effects of antidepressant agents; the short-term studies claiming efficacy while in the long-term studies relapse and/or recurrence prevention is claimed.

The claim “relapse prevention” indicates that the treatment should be continued during the index episode while the claim “recurrence prevention” has far-reaching consequences as it might implicate lifelong treatment. This paper provides a review of the long-term placebo controlled studies conducted in the last decade with special emphasis on the study design and methodology and its implications for the validity of the claims that have been or can be made based on these studies.

METHOD

A literature search in MEDLINE was performed with the medical subject headings “depression” “recurrence” “relapse” “prevention” and “study”. This search covered the period from 1990 to July 1999. Long-term placebo-controlled studies including patients with non chronic major depression were selected. Long-term studies were defined as all studies with duration longer than 12 weeks. Studies which were published separately as aggregate of a large study were excluded. Moreover studies in elderly or in other languages than English were excluded.

RESULTS

The survey resulted in 14 long-term placebo-controlled studies. Two general types of study design could be identified:

1. The randomised withdrawal studies in responders/remitters (n = 11)
2. The extension studies in responders without re-randomisation (n = 3).

The design of the randomised withdrawal study in responders (RWS) is characterised by a phase where patients are treated (open label usually) and a phase where predefined responders/remitters from this open label phase (phase 1)
are randomised to either placebo or to one or more active compound arms. In some RWS an extra open treatment phase is included (phase 3) where only responders/remitters are included.

The design of the extension study in responders without re-randomisation has a preliminary phase (phase 1) which is a short-term placebo-controlled study (possibly with several arms). Phase 2 is a placebo-controlled extension study. Phase 1 responders continue treatment with the same medication during phase 2 under double-blind conditions. This design is a variant of the long-term placebo-controlled parallel study in which all patients continue.

Table I.
Table I presents the most important methodological characteristics of the randomised withdrawal studies. The explicit objective in four studies [6,7,14, 16] was (a/o) recurrence prevention. Especially in these studies patients with a relatively high number of episodes were included. In some studies where only relapse prevention was claimed no data are available with regard to former episodes [8,11-13, 15]. In one study where relapse prevention was the objective of the study patients with relatively high number of episodes were included [10].

The design of four studies [6,9,13,14] included an extra open treatment phase (phase 3), with a duration of 4-18 weeks, only including phase 2 responders/remitters.

Study 15 was multiple transfer point randomised withdrawal study. The randomised withdrawal phase of this study had several arms. At various time points, the transfer to placebo was made in all but one arm.

The duration of the withdrawal phases (between 24 weeks and 3 years) and the inclusion criteria of phase 2 (and phase 3) differed from study to study as well as the definition for relapse and recurrence.

Table II.
Table II presents the most important methodological characteristics of the extension studies in responders without re-randomisation. In these studies also the duration of the extension phase and the inclusion criteria for phase 2 differed from study to study as well as the definition for relapse.

DISCUSSION

Two different designs have been used in placebo controlled long-term studies in patients with major depression in the past decade; the randomised withdrawal study in acute phase responders/remitters (WSR) and the extension study in acute phase responders without re-randomisation (ESR).

Randomised withdrawal studies

The design of the randomised withdrawal study can be used to demonstrate differences between treatments in reappearance of symptoms. The placebo-controlled withdrawal studies that were conducted in the last decade claim relapse prevention and/or recurrence prevention. In these studies the first 4-6 months after response are considered as the continuation phase in which relapse might occur.
while appearance of symptoms after 4-6 months is considered as recurrence (maintenance treatment). However as the duration of an episode varies from patient to patient [20,21,22] and as some patients are included in a study at an early stage of their episode while others are included at the end of the index episode the duration of the continuation phase (relapse prevention phase) differs considerably from patient to patient. Therefore for some patients included in the studies reappearance of symptoms within 4-6 months in fact is a recurrence while reappearance of symptoms after 6 months is for some patients not a recurrence but a relapse. Moreover the inclusion of patients with a relative high number of former episodes [6,7,10,14,16] also does not guarantee that the appearance of symptoms in acute phase responders/remitters after 4-6 months indeed is a recurrence. Therefore the withdrawal design is not suitable for demonstrating relapse or recurrence prevention as it is impossible to differentiate between the two in case of re-appearance of symptoms. Moreover the inclusion of patients with relative high number of former episodes makes generalisation of the results to the general population of patients with a major depression problematic. In some placebo-controlled withdrawal studies [6,9,13-15] an extra open phase, the stabilisation phase, was included with a duration that varied between 1 month to 18 weeks. The assumptions underlying the use of a stabilisation phase is that the incidence of reappearance of symptoms after randomisation was expected to be related to patients who still had mild symptoms after short-term treatment [23]. After randomisation this could lead to reappearance of symptoms especially in the placebo-group causing a significant difference in favour of active treatment. However the patterns of the survival function of studies with or without an extra open stabilisation phase are not essentially different with most reappearance of symptoms occurring in the first weeks after randomisation indicating that the advantage of the stabilisation phase is questionable. A possible disadvantage of the stabilisation phase is the longer duration of the study with the consequence of (high) drop-out. This might lead to diminishing of the statistical power to detect treatment effects. Moreover in case of a high dropout rate in the stabilisation phase it is questionable whether the patients that are still in the study at the end of the stabilisation phase represent the patients who were included at baseline making generalisation of the results disputable.

All withdrawal studies have the disadvantage that symptoms occurring after abrupt discontinuation from active medication might be misinterpreted as reappearance of symptoms while in fact the symptoms might be discontinuation/withdrawal symptoms [24]. Finally there might be ethical concerns about randomised withdrawal studies when patients who are treated for depression and are responders/remitters are switched to placebo. These ethical concerns are based on the concept that longer treatment is necessary and that there might be an increased suicide risk in patients treated with placebo. However long-term efficacy first has to be shown and (attempted) suicide in the placebo-group is not higher than in the active compound group in long-term studies [25]. Moreover a fail-safe provision whereby a serious deterioration of the patients' condition would allow withdrawal from the study and standard therapy to be given under open conditions might remove the ethical concerns concerning the use of placebo.
The only conclusion that can be drawn from results of withdrawal studies is that maintenance of effect from short-term treatment may or may not be demonstrated. In all withdrawal studies reviewed maintenance of effect was demonstrated for the active compounds for the duration of the study period indicating that the treatment should be continued at least over that period of time in responders/remitters. A comparisons concerning long-term efficacy between the different compounds cannot be made because of differences in designs concerning the duration of the studies, the duration of phase 2 and phase 3 and because of differences in definitions of relapse and recurrence between the studies reviewed.

Extension Studies in responders without Re-randomisation
The extension study in responders without randomisation (ESR) is a variation on the common placebo-controlled parallel long-term design the difference being that in the ESR only responders in both arms at a predefined time point (usually 6-8 weeks) will continue in the study. Ethically this might be an advantage over withdrawal studies where part of the patients responding to active treatment are randomised to placebo while in ESR short-term responders continue their treatment. Moreover an advantage of the ESR design is that withdrawal phenomena cannot interfere with the outcome of the study. However since withdrawal may be overcome by tapering off the active compound this does not appear to be a major issue. There are also important drawbacks of ESR. In ESR the decision on who is and who is not a responder has much more impact on the study than in randomised withdrawal studies. This is illustrated by the fact that most patients relapse during the first few weeks after the decision to continue has been taken even when the medication is unchanged. This might be an illustration of patients having re-appearances of symptoms because they still had mild or moderate symptoms after short-term treatment[23]. Another explanation might be investigator bias as investigators might assess responders incorrectly only to include enough patients in the study.

The major methodological shortcoming of the ESR design is that the patients entering in the extension phase might be a different patient population than the patients at the start of the study. In ESR only placebo responders are included in the placebo-group and this group of patients might be different from responders on active medication in unexplained and unforeseen ways making interpretation of the extension phase results difficult. Moreover extrapolation of the results to the baseline population is impossible. In the randomised withdrawal design short-term responders/remitters are randomised to active treatment or placebo leaving less room for potential bias. Additionally high and differential dropout during the first double-blind phase of the ESR design may affect extrapolation of the results more than in the randomised withdrawal design. All in all the results from ESR are very difficult to interpret concerning long-term efficacy.

Implications
The methodological considerations concerning the designs of long-term studies have implications for licensing an antidepressant. To grant a licence in Europe a relevant effect has to be shown in both short-term and long-term efficacy studies [26]. To demonstrate long-term efficacy RWS are suitable as they are able to show that short-term efficacy is maintained. However because the impossibility to differentiate
between relapse and recurrence the European Regulatory Authorities are less likely
to grant a special claim "relapse prevention" or "recurrence prevention based on
results of RWS.
Although of clinical relevance, the demonstration of recurrence prevention is not a
requirement for granting a license in Europe. When a pharmaceutical company
however would like to obtain the claim "recurrence prevention" a long-term
randomised placebo controlled study in patients who are at baseline free of
medication for a substantial duration of time and who fulfil the criteria of major
depression (recurrent) in remission (e.g. HDRS < 7) during this drug free period
might be an option. The advantages of this design are that increase of symptoms
cannot be due to withdrawal symptoms. The assumption that any appearance of
symptoms might be considered as a recurrence, is a weak point of this design as it is
still possible that re-appearance of symptoms is a relapse. However if the duration of
the drug free period is long enough this might be a guarantee that every
reappearance of symptoms is indeed a recurrence. In our view this design might be
much better that the WSR for demonstrating recurrence prevention and has little
ethical concern since only patients who are free from medication will be included. On
the other hand if one assumes that recurrent depression should always be treated
preventively this design may have ethical concerns. It should be kept in mind
however, that a prophylactic effect has not been shown unequivocally up to now.

CONCLUSION

The randomised withdrawal study design is suitable for showing that short-term
efficacy is maintained during the duration of the study period. However in this design
it is not possible to differentiate between relapse or recurrence in case of a
reappearance of symptoms. Therefore this design is not suitable for demonstrating
unequivocally relapse prevention or recurrence prevention. The design of the
extension study in responders without re-randomisation is not even suitable for
demonstrating long-term efficacy. To demonstrate recurrence prevention a long-term
randomised placebo controlled study in patients who are free of medication for a
substantial duration of time and who fulfil the criteria of major depression (recurrent)
in sustained remission (e.g. HDRS < 7) might be an option.
REFERENCES


25. Storosum JG, Zwieten van BJ, Brink van den W, Gersons BPR, Broekmans AW. Increased suicidal risk no argument against placebo-controlled trials in major depression. Submitted for publication.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of episodes as inclusion criterion</th>
<th>Duration of treatment periods</th>
<th>Inclusion criterion for Phase 2</th>
<th>Inclusion criterion for Phase 3</th>
<th>Primary outcome measure</th>
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</table>
| [6]    | ≥ 3; preceding episode < 2.5 years before onset of present episode | Phase 1: open label acute treatment of imipramine and IPT with a flexible duration n=230.  
Phases 2: open label treatment n=157.  
Phase 3: placebo-controlled study for 3 years n=128. | HDRS ≤ 7 + Raskin ≤ 5 for 3 weeks | HDRS ≤ 7 + Raskin ≤ 5 for 17 weeks | Recurrence: Twice within 7-day period; RDC criteria for Major Depression + HDRS ≥ 15 + Raskin ≥ 7 + independent evaluation |
| [7]    | > 2 episodes | Phase 1: preliminary 8 weeks open label maprotiline treatment n=141.  
Phase 3: one year placebo-controlled study in short-term responders n=841. | MADRS < 10 | | Relapse: MADRS > 27 at one visit or MADRS > 25 at two consecutive visits or modification of medication with MADRS < 27  
Relapse and recurrence: CGI ≥ 4 |
| [8]    | No data | Phase 1: preliminary 8 weeks open label sertraline treatment n=480.  
Phase 2: 44 weeks placebo-controlled study in short-term responders n=289. | CGI ≥ 2 | | |
| [9]    | Single episodes of at least 1 year or recurrent episodes | Phase 1: preliminary 8 weeks open label nefazodone treatment n=467.  
Phase 2: 8 weeks open treatment in responders n=303.  
Phase 3: 36 weeks placebo-controlled study in sustained responders n=131. | No inclusion criterion | HDRS ≤ 10 on two executive visits from week 6 through week 10 and not two consecutive HDRS scores > 10 thereafter and HDRS ≤ 10 at week 16 | Relapse: HDRS ≥ 18 on two consecutive visits or discontinuation for lack of efficacy |
| [10]   | ≥ 3 episodes in the last 4 years | Phase 1: preliminary 8 weeks open label paroxetine treatment n=172.  
Phase 2: 52 weeks placebo-controlled study in short-term responders n=135. | HDRS ≤ 8 | | Relapse: CGI ≥ 4 or deterioration of the CGI ≥ 2 points or DSM III criteria for major depression minus two weeks criterion or the need for antidepressant medication in the opinion of the investigator or depressive symptomatology for > 5 days  
Relapse: MADRS ≥ 22 |
Phase 2: 24 weeks placebo-controlled study in responders n=147.  
Phase 3: preliminary 8 weeks citalopram treatment n=391.  
Phase 2: 24 weeks placebo-controlled study in short-term responders n=226. | MADRS ≤ 12 | | Relapse: MADRS ≥ 25 or clinical judgement |
| [12]   | No data | Phase 1: open label treatment of amitriptyline for 2 months n= 458.  
Phase 2: 1 month open label treatment in responders n = 303.  
Phase 3: placebo-controlled study for 9 months n= 284. | MADRS < 20 or MADRS < 18 or MADRS < 50% or "favourable evaluation" | MADRS < 20 or MADRS < 18 or MADRS < 50% or "favourable evaluation" | Relapse: DSM III criteria for major depression or dysthymia and MADRS ≥ 20 and ≥ 18 on the MADRS  
Recurrence: Resappearance of ≥ 5 symptoms outlined in the DSM III-R and confirmation after 8 days or attempted suicide or completed suicide  
Relapse: DSM III-R criteria for major depression or HDRS ≥ 14 for 3 consecutive weeks |
Phase 2: 18 weeks open label treatment in responders n=283.  
Phase 3: placebo-controlled study for 1 year n= 204. | MADRS < 10 and CGI ≤ 2 | CGI ≤ 2 | |
| [14]   | ≥ 2 episodes in the last 5 years | Phase 1: preliminary 12-14 weeks open label fluoxetine treatment Phase 2: 50 weeks multiple transfer point withdrawal study | HDRS < 7 for 3 consecutive weeks if HDRS < 10 and at least 50% improvement from baseline | ≥ 50% improvement on the | Relapse and recurrence: ≥ 50% decrease on the |
Phase 2: 46 weeks placebo-controlled study in short-term responders

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<tr>
<th>Source</th>
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<th>Duration of treatment periods</th>
<th>Inclusion criterion for phase 2</th>
<th>Primary outcome measure</th>
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<tbody>
<tr>
<td>[17]</td>
<td>No data</td>
<td>Phase 1: 6-8 weeks double-blind treatment with either nefazodone (n=313) or placebo (n=235)</td>
<td>CGI ≤ 3 and clinically decision of treating physician</td>
<td>Relapse: discontinuation for lack of efficacy</td>
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<td>Phase 2: 1 year continuation study in responders with the same medication as in phase 1 under double-blind conditions: nefazodone (n=139;44%) imipramine (n=66;43%) placebo (n=71;30%)</td>
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<td>[18]</td>
<td>No data</td>
<td>Phase 1: 6 weeks double-blind treatment with either venlafaxine imipramine trazodone or placebo *</td>
<td>CGI ≤ 2 part of the patients CGI ≤ 3</td>
<td>Relapse: two consecutive CGI &gt; 3 or withdrawal other reason than &quot;lack of efficacy&quot; and CGI &gt; 3 or &quot;lack of efficacy&quot;</td>
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<td></td>
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<td>Phase 2: 1 year continuation study in responders of venlafaxine and placebo with the same medication as in phase 1 under double-blind condition</td>
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<td>[19]</td>
<td>No data</td>
<td>Phase 1: 6 weeks double-blind treatment with either mirtazapine (n=194) amitriptyline (n=193) or placebo (n=193)</td>
<td>HDRS &lt; 15</td>
<td>Relapse: HDRS ≥ 16</td>
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<td>Phase 2: 104 weeks continuation study in responders with the same medication as in phase 1 under double-blind condition: mirtazapine (n=74;38%) amitriptyline (n=86;45%) or placebo (n=57;29%)</td>
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* no precise results of the number of patients that started phase 1