Blinding in clozapine trials: a problem and a potential solution

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Key words

methodology, Clozapine, agranulocytosis, double blind, clinical trials

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Abstract

Background: A methodological problem arises when efficacy of clozapine is compared with other antipsychotic medication in double blind randomized studies. Due to the risk of leucopenia and agranulocytosis, patients in the clozapine condition need to have regular blood testing. The problem is that in order to maintain blinding, patients in the comparison conditions need to undergo blood testing as well and this can lead to underestimation of treatment acceptability and efficacy of the comparators.

Methods: A thought experiment considering all possible solutions for the methodological problem.

Results: We propose a special study design that preserves randomization and blinding while at the same time prevents underestimation of the effect in the comparator treatments. In addition, the necessity for blood testing is limited to only a small number of patients who receive comparative treatments. The design involves initial randomization to a sub-study including clozapine and a small comparator arm or to a sub-study that includes only comparator arms. Blood testing is only necessary in the first sub-study.

Discussion: Limitations of the proposed design are discussed. It is noted that this study design may offer a solution to similar situations where blood testing or other types of monitoring (e.g. as with lithium) is required in one but not in all of the treatment arms of a double blind randomized study. Copyright © 2009 John Wiley & Sons, Ltd.

Background

There are several instances where clozapine, the treatment of choice in antipsychotic drug resistant schizophrenia, needs to be compared to other antipsychotic drugs or to placebo in double blind controlled trials. An example is the comparison of clozapine with other newly developed compounds with a potential claim of efficacy in treatment resistant schizophrenia, e.g. new glutamatergic compounds (Afshar *et al.*, 2008; Snyder and Murphy, 2008; Harrison, 2008; Hashimoto, 2006). Another

example is the comparison of clozapine with other atypical antipsychotic drugs that claim to be more effective in the treatment of schizophrenia with comorbid substance use disorders than classical antipsychotics, because there is evidence that clozapine would be especially suited for the treatment of this population with dual diagnosis (Buckley *et al.*, 1994; Zimmet *et al.*, 2000; Kelly *et al.*, 2003a; Kelly *et al.*, 2003b; Green *et al.*, 2003). These claims are based so far on uncontrolled studies and case reports, and thus still need to be substantiated in double blind randomized controlled studies.

However, the methodology of double blind studies involving a clozapine condition introduces a difficulty related to the fact that clozapine treatment necessitates regular blood sampling in order to monitor the number of white blood cells due to the risk of leucopenia and agranulocytosis as a side effect of clozapine, while such testing is not necessary with other treatments. If the blind is to be maintained, similar blood testing procedures need to take place in all treatment arms, not just in the clozapine arm. Indeed, most studies involving clozapine included weekly monitoring of white blood cells according to protocol in all treatment arms (e.g. Meltzer *et al.*, 2008, Volavka *et al.*, 2002, Tollefson *et al.*, 2001). However, blood testing in the control conditions could lead to an underestimation of the acceptability, retention, efficacy, and costs of the comparison treatments, because blood testing is not an inherent part of these treatments under usual circumstances (i.e. outside the trial) and thus the outcome of the double blind trials do not necessarily represent clinical reality.

A potential solution for this situation was sought; one that would both maintain the random nature and blindness of the design, while avoiding underestimation of the effect in the comparison/control conditions. In addition, blood testing in the comparators condition should be kept to a minimum.

Methods

A thought experiment considering all possible solutions for the indicated methodological problem.

Result

The results of this thought experiment in which clozapine is compared to other antipsychotics, is outlined in Figure 1. Eligible and consenting patients are first randomized to one of two sub-studies, sub-study A or sub-study B. In sub-study A, a second randomization allocates most patients to receive clozapine plus regular monitoring including frequent blood testing (group A1) and a small fraction of the patients to the comparator drug X plus regular monitoring including frequent blood testing (group A2). Both treatments are completely double blinded. In study B, patients are randomized to one of several comparator antipsychotics. In the example depicted in Figure 1, only two comparators are used, group B1 receives comparator X and group B2 comparator Y. Both treatments are double blinded but without blood testing.

The main comparison that is made to establish the efficacy of clozapine compared to comparators X and Y is

that between clozapine treated patients from sub-study A (group A1) and patients treated with antipsychotic drugs X and Y in sub-study B (groups B1 and B2). In addition, the comparison between patients treated with antipsychotic X and frequent blood testing in sub-study A (group A2) with those treated with the same antipsychotic drug X without frequent blood testing in sub-study B (group B1) will provide an indication of the effect of frequent blood testing on compliance, retention and outcome.

In order to further safeguard blinding, a double informed consent procedure needs to be set in place. This would involve informing only patients who are randomized to study A about the blood drawing procedure. This will also insure a better assessment of the acceptability of clozapine.

The risk of patients making inferences based on communications in waiting rooms regarding blood testing can be prevented by conduction of the two sub-studies (A and B, see Figure 1) on different days or in separate units.

The study is fully randomized and completely double blinded. In addition, only a small proportion of the patients receive an unnecessary monitoring of blood sampling due to the low proportion of patients ($f_1 \times f_4$) randomized to antipsychotic X with frequent blood testing (group A2).

The total number of patients included in such a trial compared to a trial where all patients get a blood test would be somewhat larger due to the additional group (B1 in Figure 1). However, this group will provide additional information regarding the effect of blood testing on efficacy and acceptability. More importantly, the results of the trial will be more valid, i.e. without underestimation of the effect of the comparator and thus without a relative overestimation of the effect of clozapine.

Discussion

This paper presents a possible solution for a problem in studies investigating the effect of clozapine compared to other antipsychotic medications which do not require frequent blood testing. A similar problem may arise when other treatments requiring special monitoring are to be compared in a randomized clinical trial, e.g. when lithium is to be compared to other medications that do not require frequent blood testing to ascertain plasma levels as with lithium. The solution proposed in this paper could be applied in these other situations as well.

A limitation of the proposed solution is that clozapine cannot be compared to only one other compound, because

Figure 1 Results of the thought experiment in which clozapine is compared to other antipsychotics.

sub-study B will no longer be blinded. The proposed solution is also less suitable when the number of eligible patients is too small to assure adequate randomization in both sub-studies. In these circumstances, the classical blinding through frequent monitoring and blood sampling of all treatment groups seems unavoidable and an overestimation of the real difference in effect should always be considered as a possible explanation for the beneficial effect of clozapine over the comparator drug.

Declaration of interests statement

No conflicts of interest were reported.

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