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Review

Randomized controlled augmentation trials in clozapine-resistant schizophrenic patients: a critical review

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Abstract

Approximately 40–70% of treatment-resistant schizophrenic patients fail to benefit from clozapine monotherapy or are partial responders. During the last years several clozapine adjunctive agents have come into clinical practice. This study aims to critically review all published randomized, double-blind, placebo-controlled clinical trials (RCTs) regarding the efficacy and safety of adjunctive agents in clozapine-resistant schizophrenic or schizoaffective patients. A MEDLINE search for RCTs on clozapine adjunctive agents published from January 1980 to February 2004 was conducted. All identified papers were critically reviewed and examined against several methodological features as well as clinical and pharmacological parameters. Eleven trials including 270 patients, partial or non-responders to clozapine, assessed the efficacy of sulpiride, lithium, lamotrigine, fluoxetine, glycine, D-serine, D-cycloserine and ethyl-eicosapentanoate (E-EPA) as clozapine adjuncts. There were eight parallel-group and three crossover trials. The inclusion criteria varied widely. The duration as well as the dosage of clozapine monotherapy were reported adequate in only one trial. Plasma clozapine levels were assessed in only three trials. Main side-effects reported were hypersalivation, sedation, diarrhea, nausea, hyperprolactinaemia. The outcome favored clozapine augmentation with sulpiride, lamotrigine and E-EPA. Lithium was shown to benefit only schizoaffective patients. However, the methodological shortcomings of trials analyzed limit the impact of evidence provided.

Keywords: Schizophrenia; Clozapine-resistant; Double-blind; Controlled; Augmentation; Adjunctive

1. Introduction

About one fifth to one third of schizophrenic patients derive little or no benefit from treatment with conventional or novel atypical antipsychotics of adequate dosage and duration [11]. Clozapine, the prototypic atypical antipsychotic is a low potency compound that has preferential antagonist activity at 5-HT2 receptors followed by activity at adrenergic, cholinergic and histamine receptors with only modest activity at D1 and D2 receptors. This agent has been shown to be the treatment of choice in treatment-refractory patients, with low motor side-effects [24,35]. However, other troublesome or even serious side-effects (agranulocytosis, seizures, sedation, hypersalivation, weight-gain) limit the range of its use and are often the cause of patients' intolerance or non-compliance [11]. Furthermore, approximately 40–70% of treatment-resistant schizophrenic patients are also clozapine-resistant as they have persistent positive, negative or residual symptoms and cognitive deficits despite clozapine monotherapy of adequate dosage and duration [24,29].

During the last years several clozapine adjunctive agents have come into clinical practice to enhance the antipsychotic efficacy of clozapine [4,7,9,17,43]. Conventional or novel atypical antipsychotics [22,37], various antidepressants [6,39], lithium [40], novel anticonvulsants [44], dopamine agonists [1], glutamate receptor agonists [15], mazindol [8] and omega-3 fatty acids [31] have all been tried as clozapine adjuncts to address resistant positive, negative or cognitive symptoms. For most of these compounds evidence is confounding and comes mainly from case studies or open label trials. Prospective, randomized, double-blind, placebo-controlled clinical trials (RCTs) have, over the last 50 years, become one of the most important tools in medical research in general and psychiatric research in particular and are the hallmark of evidence-based medicine. RCTs of clozapine augmentation

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strategies are still sparse though being published with an increasing frequency during the last years. However, clinical practice still seems to be highly driven by case studies or open label trials, especially when it comes to deal with desperate difficult-to-treat cases.

This study aims to critically review all published RCTs regarding the efficacy and safety of adjunctive agents in clozapine-resistant schizophrenic or schizoaffective patients. Specific attention was paid to whether operational criteria for resistance to clozapine monotherapy (such as dosage and duration of treatment, clozapine plasma levels assessed) were met by patients included in the analyzed trials. We also scrutinized included trials regarding other methodological features as well as clinical and pharmacological parameters.

2. Method

All published RCTs assessing the efficacy and safety of adjunctive agents in clozapine-resistant schizophrenic or schizoaffective patients were searched for in the MEDLINE database from January 1980 to February 2004 using the keywords of 'schizophrenia', 'schizoaffective', 'clozapine-resistant', 'double-blind', 'controlled', 'augmentation', 'adjunctive'. In addition, a manual search of the reference sections of identified papers was performed and main review papers [7,9,17,43] were screened. All citations were independently examined by three psychiatrists-reviewers before inclusion.

All papers included in our analysis were critically reviewed and examined against the following set of parameters: demographic and baseline clinical characteristics of patients, duration of clozapine monotherapy, clozapine monotherapy dosage, trial design, clozapine dosage during the trial, dosage of the adjunctive agent, duration of the trial, clozapine plasma levels reported, clinical outcome, outcome measures used and side-effects reported.

3. Results

Eight trials including 197 patients, partial responders or non-responders to clozapine (152 males, 45 females) assessed the efficacy of sulpiride [37], lithium [40], lamotrigine [44], fluoxetine [6], glycine [15,34], D-serine [46] and D-cycloserine [19] versus placebo as clozapine adjuncts. There were also three trials [14,16,31] comparing the efficacy of ethyl-eicosapentanoate (E-EPA) versus placebo when added to background antipsychotic medication in a total of 242 treatment-resistant patients. Out of those three trials only 73 patients were under clozapine treatment and only these were included in our analysis. This sums up to 11 RCTs comprising 270 clozapine-resistant schizophrenic or schizoaffective patients.

Table 1 summarizes the full set of parameters each of the 11 RCTs was examined against. There were eight parallel-group and three crossover trials. There was only one dose-finding trial [31] while the rest were add-on trials. No drop-outs were reported in only two trials [37,46]. Out of the rest, in five trials [6,15,19,34,40] data analysis was based on the completer group (i.e. drop-outs were excluded from the data chart) and in four trials [14,16,31,44] on the intention-to-treat group (on a last-observation-carried-forward basis).

The clozapine-adjunct and clozapine-placebo groups did not generally differ significantly in demographic and baseline clinical characteristics. However, in one trial the two groups differed in the total duration of previous hospitalizations [37]. In another trial the racial distribution of the patients was unbalanced, with more black schizophrenics (six black versus four white) and white schizoaffective patients (nine white versus one black) [40]. No demographic or other differences were generally reported between those who dropped out and those who remained in the trials, with one exception (in which completers scored higher than drop-outs on the Simpson Angus Scale for extrapyramidal effects) [19].

The duration of previous clozapine monotherapy was at least 12 weeks in six trials [6,14,19,37,44,46], ranged between 6 and 67 weeks (mean 19 weeks) in one trial [40] and was not reported in four trials [15,16,31,34].

The clozapine dosage during clozapine monotherapy was at least 300 mg/day in two trials [6,34] while it was not reported in detail in eight trials. Therefore, the duration as well as the dosage of clozapine monotherapy were reported adequate (i.e. at least 12 weeks and 300 mg/day, respectively) in only one trial [6] with 33 patients (12.22%).

The clozapine dosage remained fixed during the combined treatment in all trials. Patients' mean clozapine dosage during the trial varied between 315 and 635 mg/day across eight trials while it was not reported in the remaining three trials [14,16,31]. In one trial other antipsychotic agents (without dosage change during the trial) were also permitted for seven patients [40]. The use of rescue medications was generally limited (i.e. diphenhydramine, chloral hydrate [40], lorazepam [14] for insomnia or agitation, occasional analgesics [14] for headache).

The duration of the combined treatment varied widely from 6 to 28 weeks. It was at least 12 weeks in seven trials [14,16,19,31,34,40,44] and 6–10 weeks in four trials [6,15,37,46].

Clozapine plasma levels were performed in only three trials [34,40,44] including 78 patients (28.9%), in which no significant changes from baseline levels were reported.

The outcome strongly favored the combined treatment of clozapine with sulpiride [37], lamotrigine [44] and E-EPA (at a dose of 2 g/day) [31]. In another trial regarding E-EPA (at a dose of 3 g/day) a moderate positive effect was noted [14]. Lithium was shown to benefit only schizoaffective patients [40]. The outcome was negative in the rest of the trials, regarding fluoxetine [6], glycine [15,34], D-serine [46], D-cycloserine [19] and E-EPA (at doses of 1, 3 and 4 g/day) [16,31]. It is worth noting that in one trial placebo was found superior to glycine in reducing positive symptoms [34] and