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Review

Pharmacological approaches to treating negative symptoms: A review of clinical trials

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ABSTRACT

Clinical trials of pharmacological agents targeting negative symptoms in schizophrenia are reviewed. The focus is on trials that occurred in patients who were stable on an antipsychotic medication at entry to the trial. A small number of trials compared antipsychotics as monotherapy for negative symptoms. Although the data supporting amisulpride for negative symptoms is promising the trials have limitations and it is plausible that the advantages of amisulpride over placebo may result from effects on secondary negative symptoms. Among available agents, antidepressant medications may have effects in negative symptoms. Other promising agents include minocycline, glutamatergic agents, and alpha-7 nicotinic agents. More than 15 active trials are currently underway to evaluate new treatments for negative symptoms.

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1. Introduction

Negative symptoms are an important target for drug development for a number of reasons: (1) negative symptoms are relatively common with a recent study finding that nearly 58% of outpatients had at least one negative symptom (Bobes et al., 2010); (2) negative symptoms are better predictors of functioning than positive symptoms (Rabinowitz et al., 2012); and (3) there are no accepted treatments for primary negative symptoms. With the possible exception of amisulpride in some countries, antipsychotic medications are relatively ineffective for managing negative symptoms in stable patients. This lack of effectiveness is not surprising since complex disorders such as schizophrenia may include families of related disorders. In schizophrenia, patients may have impairments in a number of psychopathological domains including psychotic symptoms, cognitive impairments, and negative symptoms. As a result, it may be unrealistic to expect a single drug to treat all aspects of the disorder (Hyman and Fenton, 2003; Arango et al., 2004; Carpenter and Davis, 2012). Recent attention has focused on the development of pharmacological agents that have specific activity in treating negative symptoms that can be added to an antipsychotic medication (Arango et al., 2004; Kirkpatrick et al., 2006; Marder et al., 2011).

This review will focus on clinical trials of pharmacological agents for treating negative symptoms. We have selected trials that used specific entry criteria for negative symptoms and excluded trials that measured negative symptom change in individuals with acute psychosis. In most cases, the trials fit recent guidelines for negative symptom trials (Marder et al., 2011). That is, negative symptoms were stable and persistent. In addition, other causes of negative symptoms such as depression, extrapyramidal side effects, and psychosis were not sufficiently severe to cause secondary negative symptoms. Studies used different criteria for assuring that persistent positive symptoms such as hallucinations and delusions were not causing negative symptoms such as emotional withdrawal and avolition. These varied from studies requiring that positive symptoms be no greater than mild to studies that permitted moderately severe positive symptoms. This review includes three sections: (1) trials of drugs that are approved for schizophrenia and other illnesses and have also been evaluated for negative symptoms; (2) newer drugs that are not approved and have been evaluated for negative symptoms; and (3) trials of agents for negative symptoms that are currently underway or that have not published results.

2. Studies with approved agents

This review includes published trials evaluating approved agents in negative symptoms of schizophrenia from 1995 to 2012. Our search found multiple published studies and meta-analyses evaluating monotherapy antipsychotics in patients with prominent or predominant negative symptoms. Most of these studies focused on negative symptom improvement in patients with acute schizophrenia and were not included. As a result, this review is limited to studies of clozapine, amisulpride and asenapine.

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2.1. Clozapine

Early comparisons of clozapine with other antipsychotics in treatment resistant and acutely ill patients suggested that clozapine may be more effective for treating negative symptoms (Kane et al., 1988). Although clozapine may have been more effective when compared with haloperidol and other antipsychotics with substantial EPS liabilities, this advantage is not apparent with lower EPS agents (Essali et al., 2009). In addition, studies of a longer duration have failed to find advantages of clozapine for negative symptoms. For example, a VA Cooperative Study (Rosenheck et al., 1999) evaluated patients over a one year period and did not find that clozapine had independent effects on negative symptoms. A 29 week comparison of clozapine and haloperidol also failed to find an advantage for clozapine on negative symptoms (Kane et al., 2001).

One study (Breier et al., 1994) evaluated the effects of clozapine on negative symptoms in deficit and non-deficit patients. Deficit patients were those who demonstrated primary rather than secondary negative symptoms. Clozapine was only effective for treating negative symptoms in the non-deficit patients. Taken together, studies of clozapine suggest that it has advantages for negative symptoms that may be secondary to extrapyramidal side effects or inadequately treated positive symptoms. It does not appear to be effective for primary negative symptoms.

2.2. Amisulpride

Amisulpride, a substituted benzamide, is a selective dopamine D2 antagonist approved in multiple European countries for the treatment of positive and negative symptoms of schizophrenia. Four studies (Loo et al., 1997; Danion et al., 1999; Moller, 2001) evaluated amisulpride monotherapy compared with placebo in patients with predominant negative symptoms of schizophrenia. Patients were selected based on their high scores of the Scale for the Assessment of Negative Symptoms (SANS), low scores of the Scale for the Assessment of Positive Symptoms (SAPS) and extrapyramidal (EPS) scores. All studies used the SANS as the primary outcome parameter. Study duration varied from 6 to 26 weeks. The dose of amisulpride ranged from 50 to 300 mg.

All studies showed a significant improvement on negative symptoms compared with placebo. This improvement on negative symptoms was not accompanied by an improvement on positive symptoms in 3 out of 4 studies. In the fourth study (Danion et al., 1999), both negative and positive symptoms improved significantly compared with placebo. In all studies, placebo-treated patients improved significantly on negative symptoms compared with their baseline severity.

One study (Lecrubier et al., 2006) evaluated two doses of olanzapine (5 and 20 mg), 150 mg of amisulpride, and placebo in 244 patients with predominant negative symptoms. The 5 mg olanzapine group showed greater improvement than placebo in negative symptoms, but not the amisulpride groups. Two additional studies (Speller et al., 1997; Moller, 2000), with at least 25 patients per treatment arm, compared the efficacy of amisulpride with low doses antipsychotics (haloperidol and fluphenazine) for negative symptoms. Neither studies showed a superior efficacy of amisulpride.

2.3. Asenapine

Asenapine is approved for the treatment of schizophrenia in most countries. Trials in patients with acute exacerbations suggested that asenapine was more effective than risperidone and haloperidol for negative symptoms (Potkin et al., 2007; Kane et al., 2010a). Two randomized double-blind studies (Buchanan et al., 2012) compared the effect of asenapine with olanzapine in stable patients with predominant negative symptoms of schizophrenia. Predominant negative symptoms were defined as a PANSS (Positive and Negative Scale (Kay et al., 1987)) negative symptom subscale total of 20 or greater and a score of 4 on 3 or more of the 7 Marder Negative Symptom Factor Scores (Marder et al., 1997). Patients with a score of 4 or greater on more than 2 items of the positive subscale of the PANSS were excluded. Patients needed to be stable for at least 5 months before screening, and have a low score on the Calgary Depression Scale of Schizophrenia (CDSS) and the abbreviated Extrapyramidal Symptoms Rating Scale (ESRS-A). Patients were excluded if they were treated with olanzapine within 5 months prior to screening and failed to benefit on negative symptoms. The prospectively defined primary efficacy variable was the change on the 16-item Negative Symptoms Scale (NSA-16(Axelrod et al., 1993)) total at Study Week 26. Both test drugs, asenapine and olanzapine, were associated with a significant improvement on persistent negative symptoms compared with baseline. There was no significant difference between asenapine and olanzapine on the total NSA score, the primary outcome parameter.

3. Studies evaluating adjunctive therapy with available medications for the treatment of negative symptoms of schizophrenia

3.1. Antidepressant drugs

A meta-analysis (Singh et al., 2010) evaluated the efficacy of antidepressant adjunctive to antipsychotic therapy. Although there were many case reports and open label trials where antidepressants were added to an antipsychotic, only trials that used well-described criteria for negative symptoms and used double-blind methods to compare the antidepressant to a placebo were included. This resulted in the inclusion of 23 trials from 22 publications (n = 819 patients). In most studies, mean scores of negative symptoms were equally or more severe than those of positive symptoms. Study durations varied from 4 to 12 weeks. However, it is unclear whether patients' with depression or severe depressive symptoms were excluded. The overall standardized mean difference was modest (ES-0.33) in favor of antidepressants. Subgroup analyses revealed significant responses for fluoxetine, trazodone and ritanserin. The results supported some benefit of antidepressants in patients with prominent negative symptoms.

3.2. Minocycline

Minocycline is a tetracycline antibiotic with emerging interest for its neuroprotective properties against glutamate neurotoxicity in cell culture and in rodent models of neurodegenerative disorders. Two studies evaluated the effect of minocycline 200 mg/day in early schizophrenia for negative symptoms.

Levkovitz et al. (2010) reported results from a study evaluating the effects of minocycline. Subjects aged 18 to 35 years, within 5 years from their first episode, not receiving antipsychotic treatment for at least 6 months prior to the current episode, and the antipsychotic treatment was initiated less than 14 days prior to the study. A total of 54 patients with PANSS greater than 60 at baseline were randomized to receive minocycline (36) or placebo (18) adjunctive to atypical antipsychotic therapy. Patients treated with minocycline showed greater improvement in negative symptoms measured by the SANS than placebo patients.

Chaudhry et al. (2012) reported results from a study conducted in Brazil and Pakistan. Subjects were aged 18 to 65 years, within 5 years of diagnosis, stable on medication for 4 weeks prior to baseline. A total of 144 participating patients were randomized to receive minocycline (71) or placebo (73) adjunctive to antipsychotic treatment. Data from both participating countries are presented separately, thus making it difficult to extrapolate the overall results. However, the authors concluded that the addition of minocycline to treatment as usual early in the course of schizophrenia improves negative symptoms.