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Alpha-2 receptor antagonist add-on therapy in the treatment of schizophrenia; a meta-analysis

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ABSTRACT

Introduction: Reduced dopaminergic activity in the pre-frontal cortex may partially explain the negative symptoms of schizophrenia. Animal models have shown that adding an alpha-2 adrenergic receptor antagonist to a D2 antagonist can efflux dopamine into the frontal cortex increasing dopaminergic activity. Trials of alpha-2 antagonist add-on therapy in humans have been limited by small sample sizes. Therefore, a meta-analysis was conducted to determine if adding an alpha-2 antagonist to a D2 antagonist improves schizophrenia treatment by reducing negative symptoms.

Methods: Randomized, placebo-controlled trials of the addition of an alpha-2 antagonist to a D2 antagonist were identified through a PubMed search. Treatment effects were measured using schizophrenia rating scales and meta-analyzed as standardized mean differences using random effects models.

Results: Eight unique studies were identified, each including 18 to 41 patients and lasting four to eight weeks. The overall effect size of add-on alpha-2 therapy across the eight trials was an improvement of 0.16 (95% C.I., −.30 to 0.62) for positive symptoms, 0.84 (95% C.I., .17 to 1.51) for negative symptoms, 0.28 (95% C.I., −.08 to 0.64) for general symptoms, and .80 (95% C.I., .15 to 1.46) for symptoms overall. Negative symptom improvements were independent of improvements in depressive symptoms, measured using the Hamilton depression rating scale, for 3 of the 5 studies.

Conclusions: Add-on agents with alpha-2 antagonist activity appear to improve the efficacy of D2 antagonists for the treatment of schizophrenia by reducing negative symptoms. These results support conducting a more definitive confirmatory clinical trial.

1. Introduction

The treatment of schizophrenia remains inadequate, with over 75% of patients failing to achieve pharmacological remission, despite the introduction of second generation (SGA) antipsychotic medications (Miyamoto et al., 2005; Beitinger et al., 2008; Leucht et al., 2009). These patients experience significantly higher rates of homelessness, hospitalization, and suicidality which are associated with increased mortality and societal burdens (Kooyman et al., 2007; Seeman, 2007). Despite insufficient evidence, attempts to improve these outcomes have many clinicians prescribing add-on medications (Zink et al., 2010). In this report, we highlight the potential benefits of alpha-2 antagonist add-on therapy.

First and second generation anti-psychotic agents primarily alter the function of the D2 receptor in the subcortical regions of the brain (Seeman, 1987). Nevertheless, evidence suggests a regional dysfunction of the dopaminergic system throughout the brain including the pre-frontal cortex (Svensson, 2003; Howes and Kapur, 2009). Poor dopaminergic transmission and chronic low levels of dopamine in the prefrontal cortex have been linked to cognitive impairment and negative symptoms in schizophrenia (Abi-Dargham, 2004; Devoto and Flore, 2006).

Clozapine has been shown to cause the efflux of dopamine into the pre-frontal cortex, an action thought to be mediated by its alpha-2 receptor antagonism (Marcus et al., 2005). A similar effect occurs with other alpha-2 antagonists in combination with D2 antagonists which are administered to rodents (Hertel et al., 1999; Wadenberg et al., 2006).

Mirtazapine and mianserin are structural analogs and used as monotherapy in the treatment of major depression. Both agents act as antagonists at central a2-adrenergic autoreceptors and heteroceptors, and have been shown to efflux dopamine into the pre-frontal cortex in rodents when combined with D2 antagonists (Millan et al., 2000; Wiker et al., 2005).

Trials in schizophrenic patients have been performed, combining these agents with D2 antagonists, but have been limited by small sample sizes and have reached inconsistent results. A prior meta-analysis of add-on therapy was conducted before all of these trials

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were reported and did not examine alpha-2 antagonists specifically (Singh et al., 2010).

We therefore sought to combine the results of these trials using meta-analysis. Based upon the theory described above, we hypothesized that the addition of an alpha-2 antagonist to a D2 antagonist would improve the treatment of schizophrenia, predominantly through negative symptom reduction.

2. Methods

2.1. Search strategy

Article abstracts were located by searching PubMed and PsychoINFO using the combination of two phrases, "mirtazapine or mianserin or idazoxan," and "schizophrenia," (Abstract, Fig. 1). Abstracts were screened

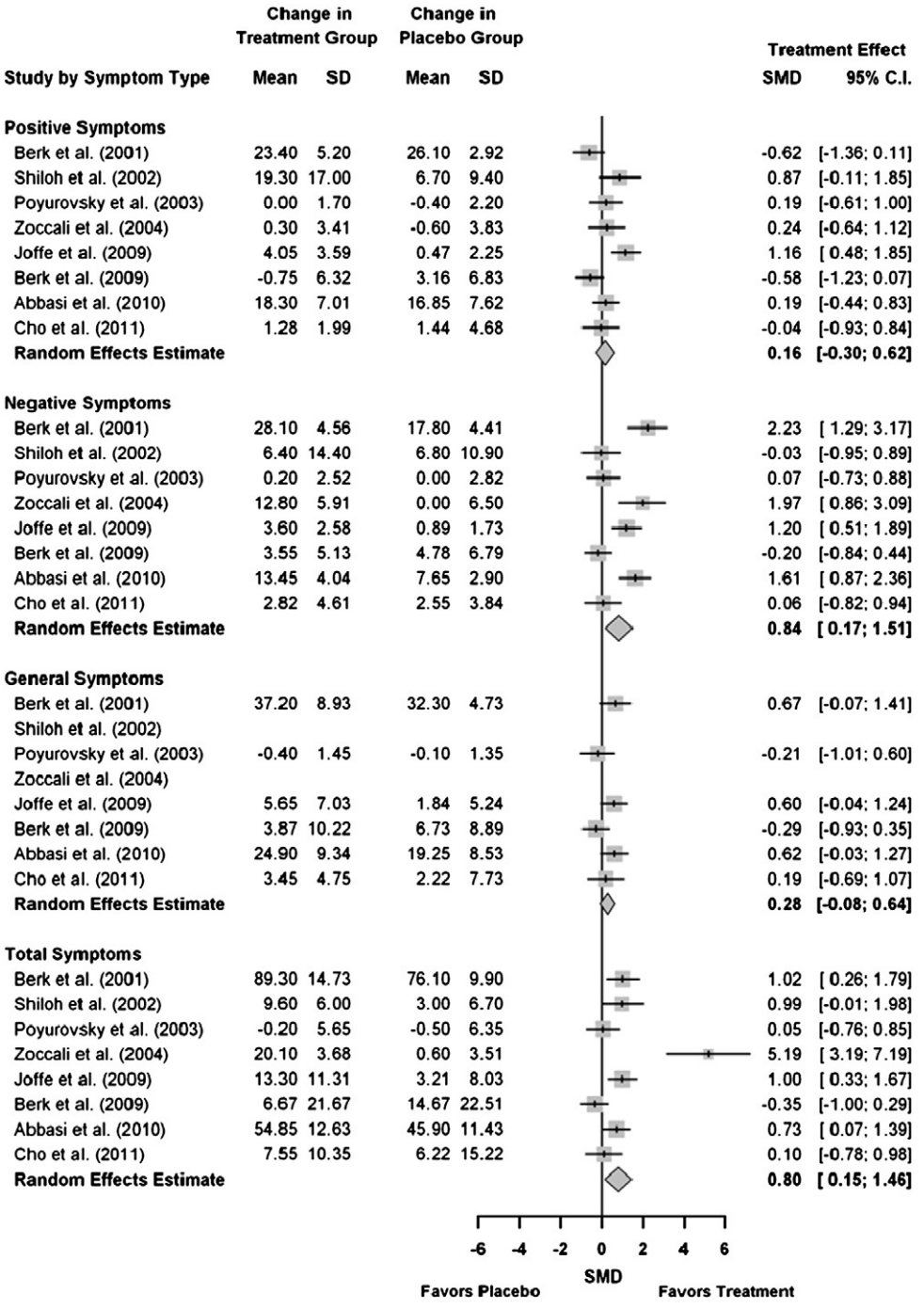

Fig. 1. Forest plot showing the treatment effect, by symptom type for each study. The treatment effect was measured as the standardized mean difference (SMD) of the change pre- to post-treatment for the treatment and placebo groups. The squares represent the point estimates of the treatment effects for each study. The size of the squares is proportional to the weight assigned to that study in estimating the meta-effects. The bars represent the 95% confidence intervals (95% CI) around the treatment effects for each study. The centers of the diamonds represent the estimated meta-effect for each symptom type and the width of the diamonds represents the 95% confidence intervals for the meta-effect estimates. The pre-treatment to post-treatment change, mean and standard deviation (SD), for both the treatment and control groups for each study are presented in the columns on the left side of the forest plot. The standardized mean differences and 95% CI for each study and the estimated meta-effects are presented in the columns to the right of the forest plot.