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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

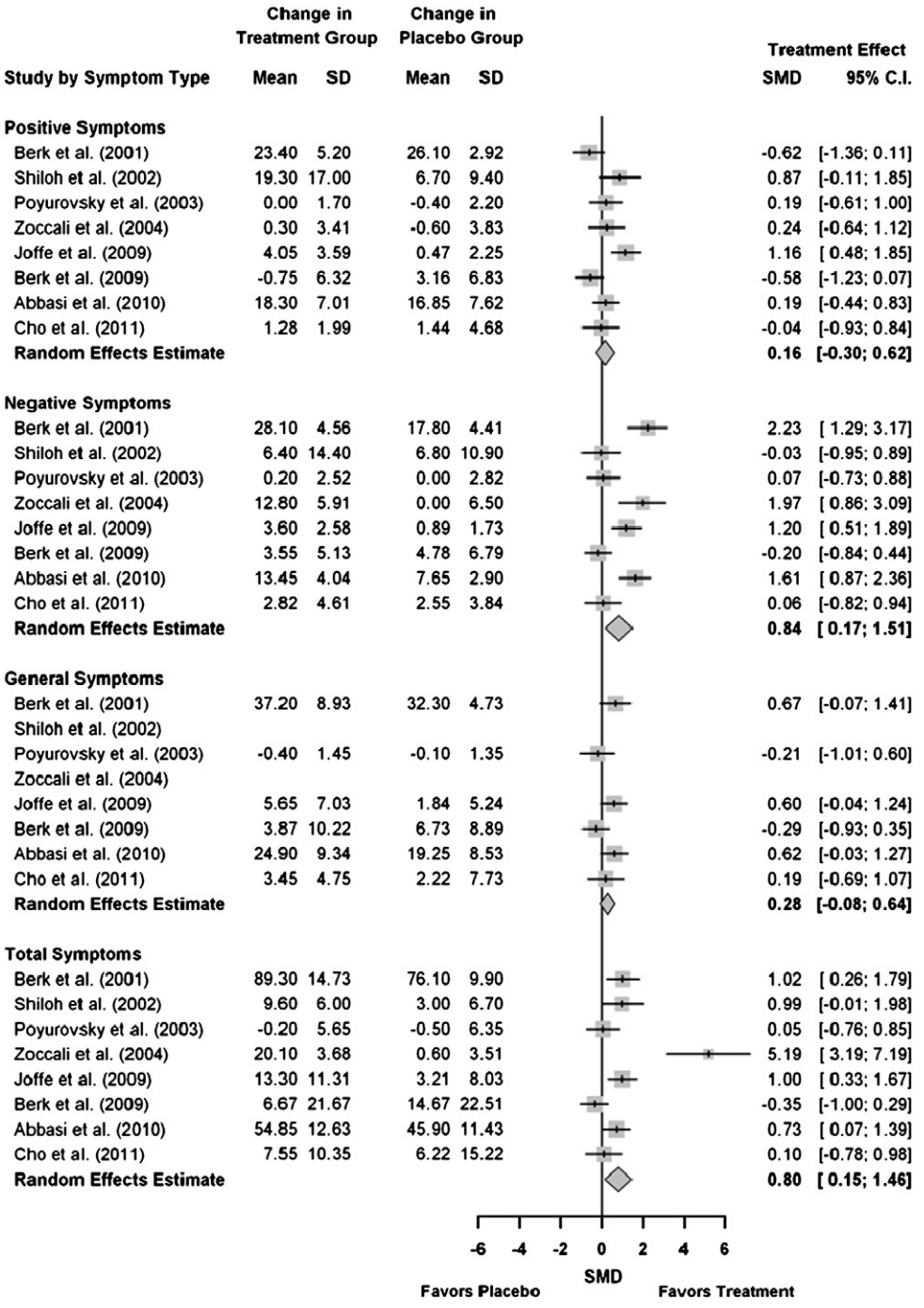

Fig. 1. Forest plot showing the treatment effect, by symptom type for each study. The treatment effect was measured as the standardized mean difference (SMD) of the change pre- to post-treatment for the treatment and placebo groups. The squares represent the point estimates of the treatment effects for 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.

to identify randomized trials of mirtazapine, mianserin, or idazoxan as add-on therapy to a D2 antagonist for schizophrenia treatment. Full texts of these abstracts were reviewed to ensure data originality, use of a placebo control group, and trial duration of at least 4 weeks (Appendix, Fig. 1). One study, in which D2 antagonist use was unclear, was excluded but included in a supplementary analysis yielding results consistent with those reported (Appendix, Fig. 2) (Hayashi et al., 1997).

2.2. Article coding and study effects

Articles were coded in duplicate using an abstraction form to record study characteristics and the results necessary to calculate study effects. Effects included the standardized mean differences of the changes in the treatment group compared to the changes in the placebo control group for positive symptoms, negative symptoms, general symptoms, and total symptoms. When available, the mean change and its standard deviation were recorded for both groups. If unavailable, pre- and post-treatment means and standard deviations were recorded and the mean change calculated as the difference between means and the standard deviation calculated as the pooled standard deviation using the covariance method and correlation of .5.

Only one measure for each effect was used for each study. The preferred positive symptom measure was the Positive and Negative Syndrome Scale (PANSS)-positive subscale score, available for 4 of 8 studies, and the second preference was the Scale for the Assessment of Positive Symptoms (SAPS) score, available for 3 additional studies. The preferred negative symptom measure was the PANSS-negative subscale score, available for 5 of 8 studies, and the second preference was the Scale for the Assessment of Positive Symptoms (SANS) score, available for 3 additional studies. The preferred general symptom measure was the PANSS-general subscale score, available for 4 of 8 studies, and 1 additional study reported a SANS-general score. The preferred total symptom measure was the PANSS total score, available for 4 of 8 studies, and the second preference was the BPRS total score, available for 2 additional studies.

If changes in total symptoms were missing, its mean change and standard deviation were calculated using the other symptom types under the assumption that positive, negative, and general symptoms summed to total symptoms and using a covariance method pooled standard deviation with correlation of .5. This allowed total symptoms to be calculated for 2 additional studies. Supplementary analysis, excluding these 2 additional total symptom estimates, was conducted and yielded results consistent with those reported (Appendix, Fig. 3).

2.3. Statistical analysis

Due to methodological heterogeneity in the included studies, random effects models were employed as the primary method of combining study effects. This decision was made irrespective of fixed effects model results in which the variation in effects is assumed to result solely from sampling error. The homogeneity statistic Q, based on fixed effects models, and its associated P value are reported to provide empirical support for this decision.

3. Results

One hundred thirteen unique abstracts were identified through the PubMed and PsychINFO searches. Of the 19 articles reviewed, 7 did not report original data, 2 were of less than 1 week duration, 1 lacked a placebo-control group, and in 1 the underlying D2 antagonist use was unclear. The 8 included trials used a variety of D2 antagonists as underlying agents and differed in their exclusion criteria, wash out period, and severity of illness (Table 1). Of these studies, 7 were single center, and only 2 were registered.

There was significant variation across studies in the standardized mean difference for positive symptoms (Q [df] = 19.9 [7], P<.01), negative symptoms (Q [df] = 37.4 [7], P<.01), and total symptoms (Q [df] = 35.1 [7], P<.01), but not general symptoms (Q [df] = 7.6 [5], P = .18). There was a larger improvement in the treatment group relative to the control group for total symptoms (SMD = 0.80, 95% C.I. = 0.15–1.46) and negative symptoms (SMD = 0.84, 95% C.I. = 0.17–1.51) but not positive symptoms (SMD = 0.16, 95% C.I. = −0.30–0.62) or general symptoms (SMD = 0.28, 95% C.I. = −0.08–0.64) (Fig. 1).

Treatment effects did not appear to differ based upon the underlying D2 antagonist though there were an insufficient number of studies to test this hypothesis. The one trial which used a lower dose, 15 mg/day, of mianserin and had only 4 weeks of follow-up was also one of the trials that did not show a treatment effect. Finally, the combination regiments were well tolerated with no serious adverse events reported in the trials.

The favorable effect on negative symptoms was more pronounced than the other symptom type subscales. Negative symptoms require distinction from depression, and 5 of the studies included in this analysis measured simultaneously the negative symptoms via the symptom type-specific subscale rating, most often PANSS, and depressive symptoms via the Hamilton scale rating. Three of these 5 studies demonstrated statistically significant improvements in schizophrenia sub scale negative symptomatology while at the same time showed no change in the Hamilton scores.

Table 1
Characteristics of 8 included studies included in meta-analysis of alpha-2 antagonist add-on therapy in schizophrenia.

First author	Journal	N[a]	Underlying D2 antagonist	Baseline score[b]	Participant sex, N male/N female	Add-on alpha-2 antagonist, dose (mg/day)	Duration	Outcome
Berk et al., 2001	Int. Clin. Psychopharmacol.	30	Haldol	136	25/5	Mirtazapine, 30	6 weeks	PANSS
Shiloh et al., 2002	Int. Clin. Psychopharmacol.	18	Haldol/Perphen	54	11/7	Mianserin, 30	6 weeks	BPRS
Poyurovsky et al., 2003	Eur. Neuropsychopharmacol.	30	FGAs	13	17/7	Mianserin, 15	4 weeks	SAPS/SANS
Zoccali et al., 2004	Int. Clin. Psychopharmacol.	24	Clozapine	45.5	13/7	Mirtazapine, 30	8 weeks	BPRS
Berk et al., 2009	Hum. Psychopharmacol.	40	SGAs	85.6	32/6	Mirtazapine, 30	6 weeks	PANSS
Joffe et al., 2009	Schizophr. Res.	41	FGAs	106.1	20/19	Mirtazapine, 30	6 weeks	PANSS
Abbasi et al., 2010	Schizophr. Res.	40	Risperadone	114.05	27/27	Mirtazapine, 30	8 weeks	PANSS
Cho et al., 2011	Prog Neuropsychopharmacol Biol. Psychiatry	21	Risperadone	79.9	10/10	Mirtazapine, 30	8 weeks	PANSS

[a] N refers to the total number of study subjects across both groups.
[b] Baseline score is the average score for total schizophrenia symptoms across both the treatment and control groups prior to the start of therapy as assessed using the scoring system reported in the outcome measures column of this table.

4. Discussion

In this meta-analysis, we found that the addition of an alpha-2 antagonist to a D2 antagonist improved the treatment of schizophrenia, mostly by reducing negative symptoms. Of biological interest is that the selected alpha-2 antagonists demonstrate the ability to efflux dopamine into the pre-frontal cortex in pre-clinical models (Millan et al., 2000; Wiker et al., 2005). The estimated magnitude of the improvement in the standardized mean difference in total schizophrenia symptoms was .8, meaning that schizophrenic symptoms in patients receiving add-on alpha-2 antagonists improved .8 standard deviations more than those in patients receiving a placebo add-on. This is an indication that agents which have alpha-2 antagonist activity have important adjunctive clinical effects in schizophrenia possibly through increasing dopamine efflux into the frontal cortex.

Our meta-analysis addressed short term effects, nevertheless, one of the studies provided an extension portion of the study which was open label and not included in our analysis (Stenberg et al., 2010). This extension study demonstrated additional benefit over time. Also not included were results addressing neurocognitive benefits although two included trials and one additional study have shown that enhanced cognitive functioning is consistent with improved dopaminergic function in the frontal cortex (Poyurovsky et al., 2003; Stenberg et al., 2010; Cho et al., 2011). Though no trials using idazoxan, a highly-selective alpha-2 antagonist, met our inclusion criteria, a prior study has demonstrated a significant benefit in schizophrenic patients, consistent with our findings (Litman et al., 1996).

The sample sizes of the studies included in the analysis, which averaged 31 patients, are consistent with many trials in schizophrenia which are generally small (Thornley and Adams, 1998). Additionally, the included studies had an average follow-up of 6 weeks which is consistent with the finding that most clinical trials in schizophrenia have a 6 week follow-up (Thornley and Adams, 1998).

Possible limitations of our study include the possibility of publication bias and that the validity of our results relies upon the quality of the included studies. Our analysis also does not address which D2 antagonist works best in combination to an alpha-2 antagonist though it is possible that this interaction may be clinically important and explain part of the variation between the individual studies. Future research exploring alpha-2 combination therapy should ascertain which D2 antagonists provide the greatest benefit and also seek to determine if the D2 antagonist dose can be lowered to reduce side effects while still achieving the same therapeutic benefit.

The large meta-effect size, the biological plausibility and confirmation of a pre-specified hypothesis suggest that a large randomized clinical trial should be undertaken to confirm or refute the results of this analysis. These results also highlight the need for future studies to explore whether specific add-on therapies are indicated for specific patient subpopulations such as the use of alpha-2 antagonists for patients with a high level of refractory negative symptoms but without depression.

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There was no funding source for this project.

Contributors

E.H. and D.L. designed the study and managed the literature searches and analyses. D.L. undertook the statistical analyses. E.H. wrote the manuscript, and all authors contributed to the final version of the manuscript. All authors had access to all data in the study and each author held final responsibility for the decision to submit this manuscript for publication.

Conflict of interest

To our knowledge, no conflict of interest, financial or other, exists for the authors of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.schres.2011.11.030.

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