Meta-Analysis of Efficacy of Mirtazapine as an Adjunctive Treatment of Negative Symptoms in Schizophrenia

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Abstract

Context: Despite advances made in treating the positive symptoms of schizophrenia, treatment of negative symptoms remains an unmet therapeutic need. Adjunctive mirtazapine has shown promise for treatment of negative symptoms in several small clinical trials. **Objective:** To assess the efficacy of mirtazapine as an adjunctive treatment of negative symptoms in patients with chronic schizophrenia via meta-analysis. **Data Sources:** A systematic literature review of articles in English and Spanish was conducted in November 2011 by searching PubMed, the Cochrane Library, the Clinical Trial Registry of the NIH, and SIGLE (System for Grey Literature in Europe). Free text search terms for PubMed were "schizophrenia," "negative symptoms" and "mirtazapine." Publication date was not a limitation. **Study Selection:** Studies of people with schizophrenia/schizoaffective disorder were included in the meta-analysis if they were randomized, double-blind, and used the Positive and Negative Syndrome Scale (PANSS) as an outcome measure. Nine studies were initially identified. Five studies were included in the meta-analysis; 1 study was excluded for not using the PANSS, 3 were excluded as representing duplicate publications and open-label phases of one of the selected randomized control trials. Studies varied in the quality of their selection for participants with primary negative symptoms. **Results:** Three of the 5 studies showed significant improvement in negative symptoms individually. The overall analysis showed improvement in negative symptoms with an effect size of 1.00 (0.084–1.918), which was statistically significant (p=0.032). Data from the negative symptoms subscale of the PANSS from 169 subjects was used in a forest plot to illustrate the relative strength of treatment effects. The variation in standard median deviation (SMD) attributable to heterogeneity was 27.35 %, indicating a high degree of heterogeneity. **Conclusions:** This meta-analysis supports the hypothesis that adding mirtazapine to treatment with antipsychotics can improve negative symptoms in schizophrenia. However, additional studies with more stringent negative symptom selection criteria and homogeneous use of antipsychotics are needed.

Key Words: Schizophrenia, Mirtazapine, Negative Symptoms, Meta-Analysis

Introduction

The negative symptoms of schizophrenia "represent a loss or diminution of normal function" (1, p. 215) such as apathy, anhedonia, lack of affect, or alogia. While often overlooked in the face of florid psychosis, negative symptoms are more closely related to poor functional outcome than is psychosis (2, 3). However, treatment of negative symptoms remains an unmet therapeutic need (1, 4).

Several clinical trials have investigated augmenting antipsychotic treatment with medications and dietary supplements for treatment of negative symptoms. Some studies have included adjunctive treatments with lamotrigine (5), n-acetyl cysteine (6) and a number of antidepressants. Antidepressants as adjunctive treatment to antipsychotics have shown some promise in treating negative symptoms. Studies showing positive results have included imipramine (7), MAOIs (8), fluvoxamine (9, 10), fluoxetine (11), and sertraline (12). Hayashi et al. (13) and Shiloh et al. (14) also found

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Clinical Implications

Advances have been made in treating the positive symptoms of schizophrenia. However, negative symptoms, which cause the greatest impairment in patients with chronic schizophrenia, remain untreated (1). During the last decade, efforts to find an alternative treatment to clozapine, which continues to have the most robust effects on negative symptoms but with a high side effect profile, have been unsuccessful. Other alternatives—such as adjunctive treatment with antidepressants and mood stabilizers—have shown inconsistent results. The effects of mirtazapine in the serotoninergic and noradrenergic systems have become of interest and could show some promise.

This meta-analysis reviewed the evidence that mirtazapine is an effective adjunctive medication for the treatment of negative symptoms in schizophrenia. In addition to several of the individual studies producing positive results, the overall meta-analysis demonstrated a statistically significant improvement in negative symptoms in response to mirtazapine. Additionally, the study by Zoccali and colleagues, although excluded from our meta-analysis for not using the PANSS, found a significant improvement in SANS with mirtazapine compared to placebo (21).

improvement in negative symptoms with mianserine. However, the results are not consistent. A meta-analysis conducted by Sepehry et al. (15) concluded that there was not enough evidence to support the efficacy of SSRIs for the treatment of negative symptoms in schizophrenia, while a more recent meta-analysis favored the use of fluoxetine, ritanserine, and trazodone as adjunctive treatment for negative symptoms (16). Despite all of these findings, one agent, mirtazapine, has shown promise (4, 5). Berk et al. (25) hypothesize that the unique pharmacological profile of mirtazapine, with antagonistic effects in the α2-receptors as well as the 5-HT2 and 5-HT3 receptors, could be more beneficial in the treatment of negative symptoms than the solely serotoninergic effect of the antidepressants that have traditionally been studied as potential adjunctive treatments. Recently, Phan and Kreys completed an excellent review of mirtazapine as a treatment for negative symptoms in schizophrenia (18). Our work represents an independently performed meta-analysis on the same topic. We believe this work complements the Phan and Kreys article as they did not perform a meta-analysis in their review.

Methods

Information Sources

A systematic literature review of articles in English or Spanish was conducted by searching PubMed, the Cochrane Library, and the Clinical Trial Registry of the NIH. Additionally, grey literature (referring to documents produced at all levels in print and electronic formats protected by intellectual property rights but not controlled by commercial publishers) was searched by SIGLE (System for Grey Literature in Europe) and GreySource. Free text search terms for PubMed were "schizophrenia," "negative symptoms" and "mirtazapine." The following terms were also included as MeSH terms combined with the Boolean term "and": 1) *randomized controlled trial,* 2) *English or Spanish*, 3) *all adult*. Dates of publication were not included as limitations. This search was completed in November 2011 using the Cochrane randomized control trial filter.

Study Selection

For inclusion in the meta-analysis, studies had to be randomized, placebo-controlled trials of mirtazapine used as an adjunct to antipsychotic treatment for negative symptoms in patients diagnosed with schizophrenia/schizoaffective disorder. There is no valid translation between the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS), so a decision was made to determine the most commonly used rating scale in the mirtazapine studies and restrict the meta-analysis to only those studies using that instrument. Therefore, use of the Positive and Negative Syndrome Scale (PANSS), used by all but one study, became an eligibility criterion. The studies were restricted to adult outpatient samples. Two authors (CV and CR) independently screened all articles for eligibility.

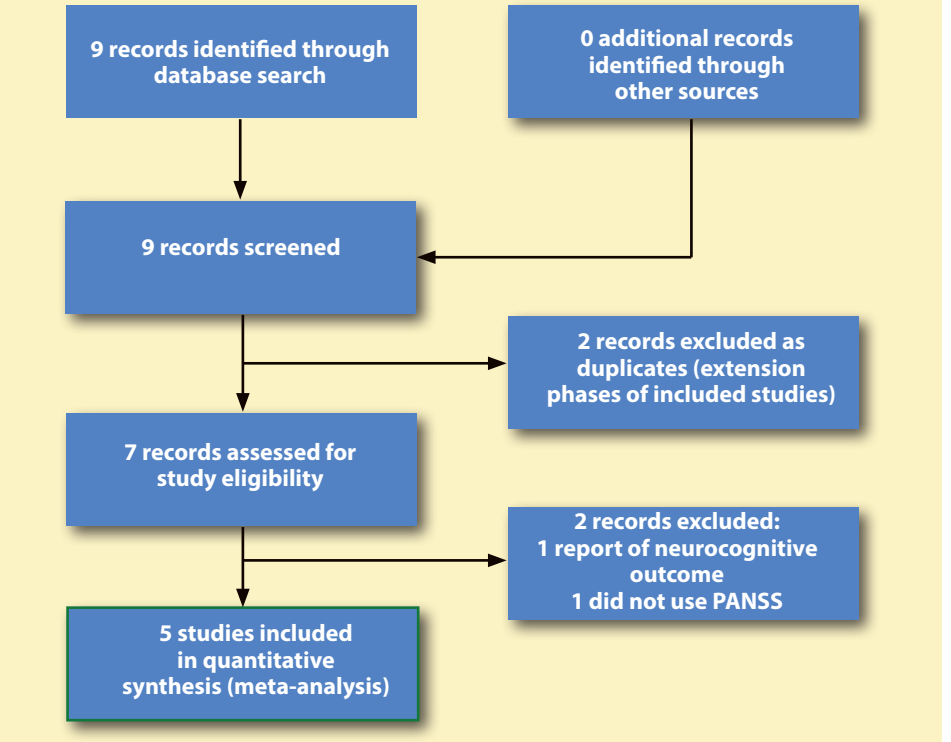
Data Collection and Analysis

Data were abstracted from each of the studies independently by two of the authors (CV and CR). Effect sizes and pooled estimates of effect across studies (Stata 10.0: metan command) were calculated for the studies using analysis of variance models for standardized mean differences (Cohen d). A random effects model was used. The Q statistic and I^2 were used to evaluate heterogeneity. Meta-regression techniques further explored potential moderators. Categorical moderators were dichotomized by a median split and analyzed in the analysis of variance model.

Assessment of Bias

Publication bias was evaluated using a funnel plot as well as the results of Egger's tests. All studies selected for the meta-analysis were individually reviewed for risk of other

Figure 1 Flow Diagram Indicating Selection of Studies Included in Meta-Analysis



biases (e.g., assignment bias, expectancy bias, etc.) using the Cochrane approach, as summarized in the *Cochrane Handbook for Systemic Reviews of Interventions* (Higgins and Green, 2009). This includes an evaluation of each of the following: 1) sequence generation, 2) allocation of concealment, 3) blinding of participants and personnel, 4) reporting of incomplete outcome data, 5) selective outcome reporting, and, 6) other sources of bias. Cohen's kappa for interrater agreement between evaluators was 0.903.

Results

Record Retrieval

Nine records were identified using PubMed, Cochrane library, PsychInfo, and grey literature sites (see Figure 1). Two records were open-label extension phases of an included study and were removed as duplicates during screening (19, 20). The remaining seven records were examined for eligibility. One record was excluded for not using the PANSS (21). One record was excluded because, although the PANSS was used, the study was designed to examine the neurocognitive effects of mirtazapine and not its effect on negative symptoms (22). Five records were then included in the meta-analysis (23-27).

Study Characteristics

All studies included in the meta-analysis were double-blind, randomized, placebo-controlled trials using a 30 mg dose of mirtazapine as adjunctive treatment of antipsychotic medications in patients with chronic schizophrenia or schizoaffective disorder. Three studies consisted of a six-week trial (25-27); two were eight weeks (23, 24).

Berk et al. (27) conducted a 6-week, double-blind, randomized, placebo-controlled trial of add-on mirtazapine as adjunctive therapy to haloperidol in patients with schizophrenia. All patients received 5 mg of haloperidol daily, and they were randomized to placebo or mirtazapine 30 mg daily. The Positive and Negative Syndrome Scale (PANSS) was used as the primary outcome measure. Thirty patients were assigned to the placebo group and 30 to the mirtazapine group, of which 3 dropped out. There was a clear effect of mirtazapine on negative symptoms, evident as early as Week 2, with PANSS negative subscale scores 42% lower in the mirtazapine group.

Joffe et al. (26) conducted another 6-week, double-blind, randomized controlled trial of mirtazapine added to 11 different first-generation antipsychotics. The patients included were receiving one or more first-generation antipsychotics at doses equivalent to 200 mg or more a day of chlorproma-

Table 1 Study Characteristics and Outcomes

Primary	Year	Study Design	N	Retention Rate	Age	Gender	Diagnoses	Intervention	Drug Name, Dose, and Frequency	Outcomes	Types of Measures
Cho et al.	2011	8-week, double-blind, randomized, placebo-controlled trial	21	20/21 1 withdrew consent	21–70	10F 10M	chronic schizophrenia	11 subjects were randomly allocated to risperidone plus mirtazapine and 9 to mirtazapine plus placebo.	Mirtazapine 15 mg a day for 2 weeks and increased to 30 mg for the remainder of the study	SANS[1] and PANSS[2] (negative subscale) scores improved between baseline and Week 8.	PANS, SANS, RBANS[3] for cognitive symptoms (not commented in this meta-analysis)
Abbasi et al.	2010	8-week, double-blind, randomized, placebo-controlled trial	40	38/40 2 withdrew consent	19–49	13F 27M	chronic schizophrenia	20 subjects randomly allocated to risperidone 2 mg/day (increased to 6 mg/day) plus mirtazapine, and 20 to risperidone plus placebo.	Mirtazapine 15 to 30 mg/day	Greater improvement in the negative symptoms and PANSS total scores at end point.	PANSS total score, ESRS[4] , side effect check list
Berk et al.	2009	6-week, double-blind, randomized, placebo-controlled trial	40	38/40 2 withdrew consent	18–65	6F 34M	chronic schizophrenia	Mirtazapine vs. placebo added to an atypical antipsychotic[5].	Mirtazapine 30 mg/day	No significant change from control.	PANSS
Joffe et al.	2009	6-week, double-blind, randomized, placebo-controlled trial	46	39/46 1 non-compliant 5 withdrew consent 1 protocol violation	18–65	19F 20M	schizophrenia or schizoaffective disorder, depressive type	Subjects received mono or polytherapy with 1 antipsychotic, or a combination of 2 or more FGAs[6].	Mirtazapine 30 mg/day	Between-group differences from baseline to Week 6 favored mirtazapine on all scales except the PANSS general subscale, SAS[7], CGIs.	PANSS, CGI[8], PGI[9], SAS
Berk et al.	2001	6-week, double-blind, randomized, placebo-controlled trial	30	27/30 1 left overseas 2 withdrew consent due to side effects (insomnia and dry mouth, respectively)	mean age 29.5	5F 25M	chronic schizophrenia	All subjects received 5 mg of haloperidol daily and were randomized to placebo or mirtazapine.	Mirtazapine 30 mg/day	Robust effect of mirtazapine on negative symptoms since Week 2. At endpoint, PANSS negative scale scores were 42% lower in the mirtazapine than the placebo group.	PANSS, CGI, SAS, HAMD[10]

[1]SANS=Scale for the Assessment of Negative Symptoms. [2]PANSS=Positive and Negative Syndrome Scale. [3]RBANS=Repeatable Battery for the Assessment of Neuropsychological Status.
[4]ESRS=Manual for the Extrapyramidal Symptom Rating Scale. [5]Atypical antipsychotics included: clozapine, quetiapine, risperidone, olanzapine and aripiprazole.
[6]FGA=First-generation antipsychotics. Those included were: haloperidol, trifluoperazine, haloperidol decanoate, fluphenazine decanoate, levomepromazine, chlorprotixene, zuclopentixol decanoate, zuclopentixol, flupentixol, periciazine, sulpiride, or a combination of two or more of these antipsychotics. [7]SAS=Simpson-Angus Scale for Extrapyramidal Side Effects. [8]CGI=Clinical Global Impression.
[9]PGI=Patient's Global Impression. [10]HAMD=Hamilton Rating Scale for Depression.

Table 2 Risk of Bias of Studies Included in the Meta-Analysis

Author (Year)	Sequence Generation	Allocation Concealment	Blind Outcome Assessor	Blind Other	Reporting of Loss to Follow-Up	Selective Outcome Reporting	Other Bias	Comment
Cho et al. (2011)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Methods section lacking in detail.
Abbasi et al. (2010)	Yes (computer-generated code)	Yes (sealed, opaque envelopes)	Yes (rater)	Yes (patient and person who administered the medications)	Unclear	Unclear	Yes	
Berk et al. (2009)	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Methods section lacking in detail.
Joffe et al. (2009)	Yes (blocked randomization table)	Yes (thick envelopes with randomization codes opened only when the database was closed)	Yes	Yes (patient, identical gelatin capsules)	Unclear	Unclear	Yes	
Berk et al. (2001)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Methods section lacking in detail.

zine. Data from 20 patients assigned to mirtazapine and 19 controls assigned to placebo were analyzed. The mirtazapine group presented a statistically significant improvement in the positive and negative subscales of the PANSS when between-group differences from baseline to Week 6 were studied. This effect was not mediated by depressive or anxiety symptoms, as the PANSS general subscale and the depression item scores did not differ between groups. In a cognitive arm of this study (22), the mirtazapine group showed improvement in domains of visual-spatial ability and general mental speed/attention control, assessed with Block design and Stroop dots.

An open-label extension phase of this study consisting of giving mirtazapine for 6 additional weeks (20) studied prolonged treatment with mirtazapine in the relief of cognitive symptoms. The 36 patients included in this open-label study showed improvement in neurocognition after 12 weeks as compared to 6 weeks of treatment. The authors concluded that prolonged treatment with mirtazapine as an adjunct treatment of first-generation antipsychotics may lead to additional benefits in neurocognition enhancement. Positive symptoms in the open-label phase were also measured (19) and the results showed that patients receiving mirtazapine—both in the randomized control trial phase and the subsequent open-label extension phase—presented with an improvement in positive symptoms greater than those who only received mirtazapine during the open-label extension phase. This suggests that longer periods of treatment could be more beneficial for positive symptoms than a 6-week period.

Berk et al. (25) conducted another 6-week, double-blind, randomized, placebo-controlled trial adding mirtazapine to patients with schizophrenia treated with second-generation antipsychotics. Data from 18 patients allocated to the mirtazapine group and 20 allocated to the placebo group were analyzed. The atypical antipsychotics included clozapine, quetiapine, risperidone and olanzapine. The authors found a trend for participants in both groups to improve on the PANSS negative subscale and general psychopathology subscale, but the differences between the two groups were not significant.

Abbasi et al. (24) conducted another double-blind, randomized, placebo-controlled trial with add-on mirtazapine in patients with schizophrenia. Subjects were treated with mirtazapine or placebo in addition to risperidone for 8 weeks. Data from 19 subjects and controls were analyzed. The results showed that there was a significant difference between the two groups on the PANSS total score at the end of the trial compared to baseline. There were differences in the negative symptoms subscales between the two groups at endpoint. There were no differences in the positive symptoms and the general psychopathology symptoms between both groups.

Cho et al. (23) conducted another 8-week, randomized controlled trial to study mirtazapine enhancement in patients with schizophrenia treated with risperidone. Of the 74 patients recruited, 21 were randomized to the mirtazapine or placebo groups. Data were analyzed from 11 subjects in the mirtazapine group and 9 in the placebo group. The SANS and PANSS negative subscales improved significantly from baseline to Week 8. There were no significant differences between the groups in the PANSS total, positive and general psychopathology scales. This study also found improvement in vocabulary and immediate memory as cognitive benefits of add-on mirtazapine treatment.

Zoccali et al. (21) was the study excluded from this meta-analysis due to its use of the SANS as the only outcome measure for negative symptoms. This trial looked at the effect of mirtazapine augmentation of clozapine to treat negative symptoms of schizophrenia in an 8-week, double-blind, placebo-controlled study. This study did find significant differences in negative symptomatology as assessed by the SANS between baseline and end-point measures in the mirtazapine group when compared to the placebo group. The improvement was significant in the subscales of avolition/apathy and anhedonia/asociality. Positive symptoms and depressive symptomatology did not change in either one of the two groups. (See Table 1 for more details on the individual studies, including type of antipsychotic.)

Risk of Bias

There was no evidence of publication bias as determined by funnel plot and Egger's test t=2.56 (CI 95% -2.130056–19.81137, p=0.083). Three studies (23, 25, 27) had too little detail in their methods section to determine risk of other biases (see Table 2). The methods of Abbasi et al. (24) and Joffe et al. (26) provided adequate information to determine their studies contained minimal risk of other biases.

Results of Meta-Analysis

A forest plot was used to illustrate the relative strength of treatment effects in the included studies (see Figure 2). Three of the studies (23, 24, 27) showed significant effects on negative symptoms individually. Cho et al. (23) found a standardized mean difference (SMD) of 0.68 in the PANSS (95% CI -0.23–1.58). Abbassi et al. (24) found an SMD of 1.09 (95% CI 0.42–1.8). The study that demonstrated the most pronounced effect, Berk et al. (27), with an SMD of 3.5 (95% CI 2.3–4.7), was also the one with the least weight in the meta-analysis (16.7%).

Heterogeneity refers to the variation between studies being evaluated in a meta-analysis. Heterogeneity can be evaluated using the Q statistic. If significant, the Q statistic rejects the null hypothesis that there is homogeneity and suggests that there is a greater variability between studies than would be expected by error alone. The I^2 statistic evaluates the percent of variation across the studies that is associated with heterogeneity. Publication bias is concerned with the possible overestimation or underestimation of the reported effect associated with a meta-analysis based on the hypothesis that studies with statistically significant results may be more likely to be published compared to those with non-significant results.

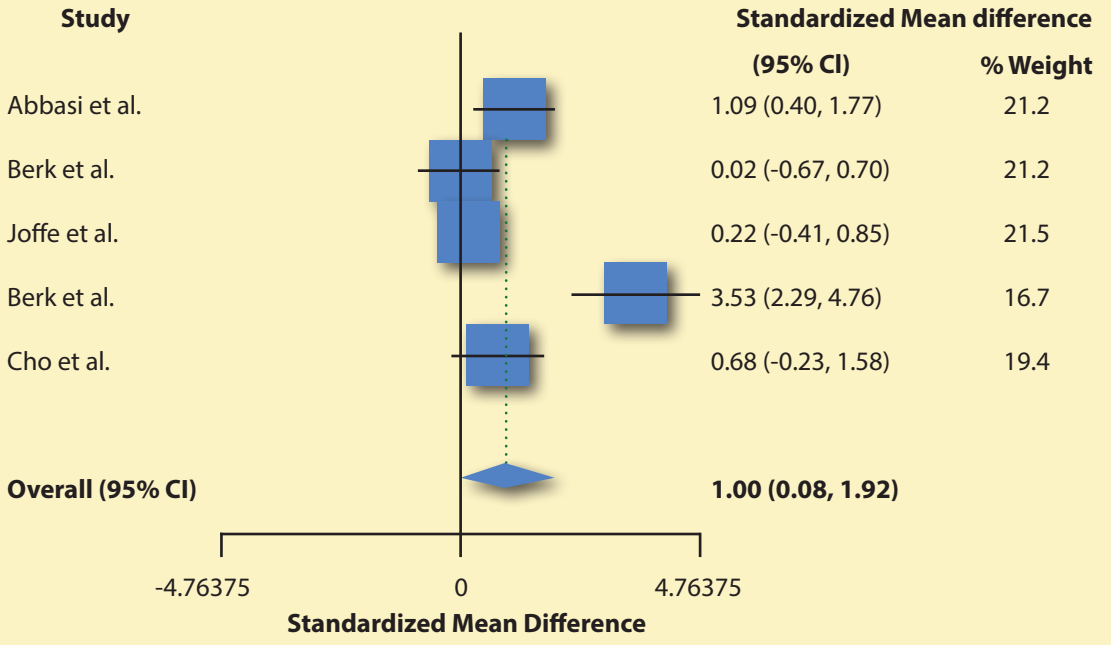
In this meta-analysis, the variation in SMD attributable to heterogeneity was 89.03%, indicating a high degree of heterogeneity between the studies. The Q statistic was 27.35, meaning that the null hypothesis is rejected and there is heterogeneity. I^2=100% x (27.35-1)/27.35=91.27%. Heterogeneity was both clinical and statistical. Clinical heterogeneity was due to differences in the study populations. There was also statistical heterogeneity in that there was a greater difference between trials than expected by chance. This could be due to different interventions or different populations. In this case, the heterogeneity is explained by the one study (27) that used haloperidol as the only antipsychotic. The overall analysis showed a difference that was statistically significant 1:00 (95% CI 0.08–1.92), with a p=0.032 favoring mirtazapine. As a side note, a meta-analytic calculation of the global and positive symptoms subscales did not find any differences between the mirtazapine group and the placebo with p=0.872 and p=0.638, respectively.

Discussion

Advances have been made in treating the positive symptoms of schizophrenia. However, negative symptoms, which cause the greatest impairment in patients with chronic schizophrenia, remain untreated (1). During the last decade, efforts to find an alternative treatment to clozapine, which continues to have the most robust effects on negative symptoms but with a high side effect profile, have been unsuccessful. Other alternatives—such as adjunctive treatment with antidepressants and mood stabilizers—have shown inconsistent results. The effects of mirtazapine in the serotoninergic and noradrenergic systems have become of interest and could show some promise.

This meta-analysis reviewed the evidence that mirtazapine is an effective adjunctive medication for the treatment of negative symptoms in schizophrenia. In addition to several of the individual studies producing positive results, the overall meta-analysis demonstrated a statistically significant improvement in negative symptoms in response to mirtazapine. Additionally, the study by Zoccali and colleagues, although excluded from our meta-analysis for not using the PANSS, found a significant improvement in SANS with mirtazapine compared to placebo (21).

Figure 2 Forest Plot with Data from Four Studies Included in the Meta-Analysis



However, there are several limitations to the available data. First—and most important—is the distinction between primary negative, or deficit, symptoms and secondary negative symptoms. There are many causes for secondary negative symptoms: restricted expressive movement and a masked face may be due to Parkinsonism, depression can cause anhedonia, and paranoia could lead to social isolation. Many secondary negative symptoms can be significantly improved in clinical trials and can lead to a "pseudospecificity" where decreased paranoia or depression seems to improve negative symptoms (1). Most claims of antipsychotic efficacy for negative symptoms are due to this phenomenon (28). In order to adequately test a medication for efficacy in treating negative symptoms, specific inclusion and exclusion criteria should select for people with high levels of negative symptoms but low levels of psychosis, depression, and movement disorders. The Cho et al. study excluded people with high levels of current depressive symptoms, but did not select for high levels of negative symptoms or low levels of psychosis and movement disorders (23). Abbasi et al. also excluded people with high levels of current depressive symptoms but, although participants had to have a threshold level of negative symptoms, they were off antipsychotics for one week prior to starting the study and were not excluded for high levels of psychosis (24). The Zoccali et al. study, excluded from our meta-analysis because it did not use the PANSS, selected people based on a threshold negative symptom level, but did not exclude based on depressive or psychotic symptoms (21). None of the other studies selected for high levels of negative symptoms or excluded for depression, psychosis, or movement disorders (25-27). Despite this shortcoming, improvements in negative symptoms seen in the above studies were not accompanied by general symptom or psychosis improvement. This lends greater confidence in the results; however, a claim that mirtazapine has efficacy for primary negative symptoms may be premature.

Secondly, the meta-analysis supporting the use of mirtazapine for negative symptoms is based on only five small studies. Larger randomized controlled clinical trials will strengthen confidence in these results. Lastly, the degree of heterogeneity was high, which would question the overall effect. However, this heterogeneity can be explained by one study (27), which used haloperidol as the antipsychotic medication. The rest of the studies used atypical antipsychotics or a combination of first-generation antipsychotics with different effects on dopaminergic, cholinergic and serotoninergic receptors, which could be the cause for the smaller differences in improvement of negative symptoms from baseline.

Assuming mirtazapine is an effective treatment for primary negative symptoms, how does it act? There is evidence that deficit symptoms are associated with decreased dopamine in the prefrontal cortex (29). In rodent studies, mirtazapine increases prefrontal dopamine release almost twofold (30), which may be mediated by antagonism of the serotonergic 5-HT2A receptor (31). Another possibility is action through the cholinergic system. Tandon and Greden have reported induction of negative symptoms through muscarinic agonism (32) and mirtazapine's antagonism of muscarinic receptors may be beneficial.

In summary, we conclude that there is preliminary evi-

dence to support the addition of mirtazapine to antipsychotics to reduce negative symptoms in schizophrenia. Further studies with more stringent negative symptom criteria and homogeneous use of antipsychotics are required.

Search Terms

Search terms included: ((“mirtazapine”[Supplementary Concept] OR “mirtazapine”[All Fields]) AND negative[All Fields] AND (“diagnosis”[Subheading] OR “diagnosis”[All Fields] OR “symptoms”[All Fields] OR “diagnosis”[MeSH Terms] OR “symptoms”[All Fields]) AND (“schizophrenia”[MeSH Terms] OR “schizophrenia”[All Fields])) AND (“humans”[MeSH Terms] AND Randomized Controlled Trial[ptyp] AND (English[lang] OR Spanish[lang]) AND “adult”[MeSH Terms]) to support a firmer conclusion.

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