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Efficacy and safety of noradrenalin reuptake inhibitor augmentation therapy for schizophrenia: A meta-analysis of double-blind randomized placebo-controlled trials

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ABSTRACT

Background: We performed an updated meta-analysis of noradrenalin reuptake inhibitor (NRI) augmentation therapy in patients with schizophrenia treated with antipsychotics based on a previous meta-analysis (Singh et al.).

Methods: PubMed, Cochrane Library databases, and PsycINFO citations were searched from their inception to June 10, 2013 without language restrictions. We conducted a systematic review and meta-analysis of individual patient data from randomized controlled trials comparing NRI augmentation therapy with placebo. The outcome measure for efficacy was the psychopathology of schizophrenia and the measures for safety were discontinuation rate and several side effects. We used standardized mean differences (SMD) to estimate treatment effects for continuous variables, and risk ratios (RR) for dichotomous variables, with their 95% confidence intervals (CIs). A random-effects model was used.

Results: Nine studies (4 atomoxetine studies, 3 reboxetine studies, 1 reboxetine–betahistine combination study and 1 mazindol study, total $n = 298$) were identified. No statistically significant effects of NRI augmentation therapy on overall ($p = 0.90$), positive ($p = 0.81$), and negative ($p = 0.89$) symptoms were found. NRI augmentation therapy was marginally superior to placebo for efficacy of depressive symptoms (SMD = −1.08, $p = 0.05$). Dropout due to all-cause ($p = 0.70$), inefficacy ($p = 0.64$), or adverse events ($p = 0.18$) was similar in both groups. NRI augmentation therapy showed a significantly lower increase or larger reduction in body weight than placebo (SMD = −0.47, $p = 0.03$). Reboxetine augmentation was associated with less weight gain that placebo in antipsychotic treated schizophrenia patients (SMD = −0.78, $p = 0.0001$).

Conclusion: NRIs may exert an effect on depressive symptoms, and seem to be well-tolerated treatments.

1. Introduction

Norepinephrine reuptake inhibitors (NRIs) elevate the extracellular level of the neurotransmitter norepinephrine in the central nervous system by inhibiting its reuptake into the synapse via the norepinephrine transporter (Dell'Osso et al., 2011). They do not act at other monoamine transporters such as serotonin. Atomoxetine, an NRI, is the Food and Drug Administration (FDA) approved for the treatment of attention deficit-hyperactivity disorder (ADHD). Reboxetine, another NRI, is also used for the treatment of clinical depression, anxiety, panic disorder, and ADHD.

The noradrenergic system is reported to be involved in dopamine support in the case of insufficient input, the neuromodulatory action exerted by dopamine being reinforced by norepinephrine in dopamine innervated cortical areas, such as the prefrontal cortex (PFC) (Devoto and Flore, 2006). At the same time, heterologous uptake of dopamine by norepinephrine transporters contributes to buffer the excessive spread of released dopamine (Devoto and Flore, 2006). The increase of dopamine activity in the PFC is thought by many to be essential for efficacy against the psychopathology of schizophrenia such as negative symptoms (Yamamoto and Hornykiewicz, 2004). Progressive damage to a noradrenergic reward pathway is also considered to cause the negative symptoms and long-term downhill course of schizophrenia (Stein and Wise, 1971). Several reports have shown strong relationships between abnormalities in the PFC and cognitive dysfunctions in schizophrenia (Arnsten et al., 2012; Friedman et al., 2008; Gray and Roth, 2007). Moreover, because abnormalities in dopamine and norepinephrine in the PFC are reported to cause some of the

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cognitive impairments of schizophrenia, pharmacological remediation of cognitive symptoms through manipulations of dopamine and norepinephrine in the PFC has been suggested (Arnsten et al., 2012; Friedman et al., 1999). Recently, NRI augmentation therapy has been demonstrated as a treatment for schizophrenia. Nine randomized placebo-controlled trials (RCTs) have shown that atomoxetine and reboxetine were not superior to placebo for positive and negative symptoms (Ball et al., 2011; Carpenter et al., 2000; Friedman et al., 2008; Kelly et al., 2009; Poyurovsky et al., 2003, 2007, 2013; Sacco et al., 2009; Schutz & Berk, 2001). However, while 3 reboxetine studies did show superiority to placebo for depressive symptoms (Poyurovsky et al., 2003, 2007, 2013), 1 reboxetine study (Schutz and Berk, 2001) and 2 atomoxetine studies (Ball et al., 2011; Kelly et al., 2009) did not find greater efficacy for depressive symptoms than placebo. These discrepant results may be due to the small sample sizes of these trials, with 3–31 participants in each treatment arm. A meta-analysis produces a weighted summary result, with more weight given to larger studies. Combining results from more than one study has the advantage of increasing statistical power, which is often inadequate in studies with a small sample size (Cohn and Becker, 2003). Moreover, we can combine outcomes with different measurements using standardized mean difference (SMD) analyses (DerSimonian and Laird, 1986). Moreover, even though all nine RCTs with atomoxetine and reboxetine adjunctive treatment to antipsychotic therapeutics have consistently demonstrated no superiority to placebo for positive and negative symptoms, we believe that it is very important for clinicians and patients to evaluate the evidence for these outcomes. We performed a meta-analysis because the results of the meta-analyses are considered to present a higher level of evidence than individual trials (http://handbook.cochrane.org/). Singh et al. (2010) reported that reboxetine did not seem to have a beneficial effect on negative symptoms in the meta-analysis (3 studies). In this regard, the previous meta-analysis of NRI augmentation therapy for patients with schizophrenia was focused on negative symptoms. A systematic review and meta-analysis is required to determine the clinical pharmacological profile of NRI augmentation therapy in patients with schizophrenia, including which symptoms it effectively treats, and whether it is safe and tolerable. Thus, to overcome the limitations of small studies and cover broader outcome measures, we performed an updated and comprehensive meta-analysis of the nine RCTs of NRI augmentation therapy that have been conducted in patients with schizophrenia.

2. Methods

2.1. Inclusion criteria, search strategy, data extraction, and outcome measures

We selected only open-label or double-blind randomized placebo-controlled trials using NRI treatment in patients with schizophrenia or schizophrenia-like psychoses. We allowed inclusion of non-double-blinded studies to include more studies in the meta-analysis. This meta-analysis was performed according to the guidelines of preferred reporting items for systematic reviews and meta-analyzes (PRISMA) 2009 (Stroup et al., 2000). Included in this meta-analysis were RCTs of NRI augmentation therapies for patients with schizophrenia under treatment with antipsychotics. To identify relevant studies, we searched PubMed, Cochrane Library databases, and PsycINFO citations from their inception to June 10, 2013, using the keywords (Doggrell and Vincent, 1981; Hajos et al., 2004) “Amedalin”, “Atomoxetine”, “Daledalin”, “Edivoxetine”, “Esreboxetine”, “Lortalamine”, “Mazindol”, “Nisoxetine”, “Reboxetine”, “Talopram”, “Talsupram”, “Tandamine”, “Viloxazine” or “Maprotiline”, and “Schizophrenia”. Because mazindol is classified as a reuptake inhibitor of norepinephrine (Inoue, 1995), we included this drug in the meta-analysis. However, mazindol is known to inhibit dopamine and serotonin reuptake, and is approved for the management of exogenous obesity as a short term adjunct in a regimen of weight reduction based on caloric restriction in certain patients by the FDA (Ioannides-Demos et al., 2005). First, we used PubMed for the literature search using above keywords. Next, we used other electronic databases based on the same keywords. Additional eligible studies were also sought by a hand search of reference lists from primary articles and relevant reviews. The first three authors of this review (T.K. T.M. and Y.M.) scrutinized the inclusion and exclusion criteria of the studies identified. When the data required for a meta-analysis were missing, the first and/or corresponding authors were contacted for additional information (including endpoint scores). The three authors of this study independently extracted, checked, and entered the data into Review Manager.

2.2. Data synthesis and statistical analysis

We included the outcome measures of at least 2 studies for each outcome measure. The primary outcome measure for efficacy was the psychopathology of schizophrenia, meaning the overall, as well as positive, negative, and depressive symptoms. The overall outcome measure included the total Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and total Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989). The positive outcome measure included the positive BPRS scores, positive PANSS scores, and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1985) scores. The negative outcome measure included the negative PANSS endpoint scores and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) scores. The depressive outcome measure included the Hamilton (1960) Rating Scale for Depression (HAMD). Because all available data for the depressive symptoms in the studies included the meta-analysis used the HAMD, we used the HAMD for performing the meta-analysis of the depressive outcome measure. The secondary outcome measures included discontinuation for any cause, discontinuation due to adverse events, discontinuation due to inefficacy, and extrapyramidal symptoms, which were derived from the Simpson and Angus (1970) Scale (SAS). In addition, we pooled the data for side effects.

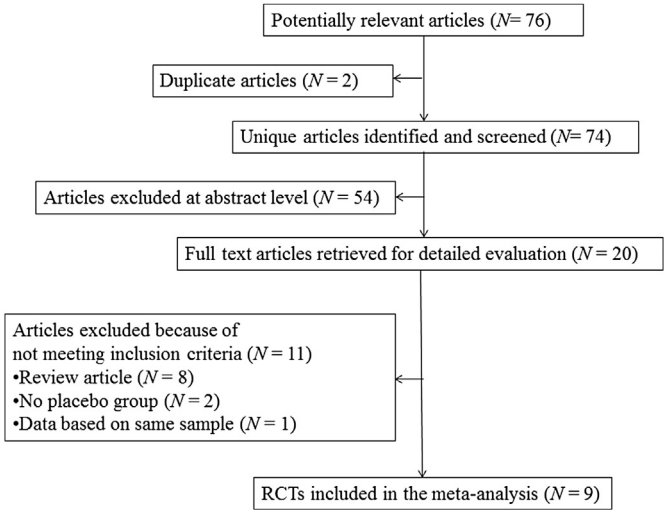

Fig. 1. PRISMA flow diagram.