5-HT$_{2A}$ receptor antagonists for the treatment of neuroleptic-induced akathisia: a systematic review and meta-analysis

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Abstract

Akathisia is a common and distressing extrapyramidal side-effect, which usually results from the use of antipsychotic medication. Previous reviews and meta-analyses have demonstrated a lack of evidence for the effectiveness of treatment strategies, which are traditionally used against neuroleptic-induced akathisia (NIA), i.e. beta-blockers, anticholinergic agents and benzodiazepines. In the last fifteen years, randomized trials have studied the effect of drugs with antiserotonergic properties on NIA. We conducted a systematic review of randomized control trials and used meta-analytic methods to quantify the overall effect size. PubMed and the Cochrane libraries were searched for eligible trials. Six randomized controlled trials were found, five of which included a placebo control group and qualified for our meta-analysis. The overall effect size in the analysis is RR=7.10 with 95% CI 3.08–16.40 (p<0.0001). Our findings suggest that 5-HT$_{2A}$ antagonists are effective in the treatment of NIA.

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Key words: Akathisia, extrapyramidal side effects, serotonin receptor antagonists.

Introduction

Hascovec first used the term akathisia in 1901 in order to describe the inability of two patients with hysteria and neurasthenia, respectively, to remain sitting down for any length of time (Mohr and Voavka, 2002). Today, this term is used to describe a common extrapyramidal side-effect (EPS), which results mainly from the use of antipsychotics. Antidepressants (Koliscak and Makela, 2009) and dopamine receptor antagonists other than antipsychotics (e.g. metoclopramide) (Pasricha et al., 2006) are also associated with akathisia. We will focus here solely on neuroleptic-induced akathisia (NIA). Traditionally, only first generation antipsychotics are defined as neuroleptic medication (Stahl, 2008); however, atypical antipsychotics can also cause akathisia, albeit frequently (Rosenheck et al., 2003; Haddad et al., 2012). The available data on the frequency of NIA in first- and second-generation antipsychotics are not unequivocal and some studies (among them the CATIE study; Lieberman et al., 2005) detected no difference between them (Peluso et al., 2012). Thus, the term ‘antipsychotic induced akathisia’ (AIA) has been proposed recently (Poyurovski, 2010) and seems to be more appropriate. Nevertheless, we use here the established term NIA in accordance with the majority of the existing literature.

According to DSM-IV-TR, akathisia is characterized by a subjective feeling of restlessness and by objectively observed typical movements such as shuffling of the legs, pacing, rocking from foot to foot, or the inability to sit down or stand still. (American Psychiatry Association [APA], 2000). These movements are typically bilateral and relatively symmetrical. Reports on the prevalence of NIA vary between 20 and 35% (Braude et al., 1983; Halstead et al., 1994). The onset of symptoms is usually rapid. Crane et al. (1971) reported akathisia developing within an hour after receiving droperidol or metoclopramide. The majority of affected patients develop their symptoms within the first days after the onset of antipsychotic medication. Age and gender do not seem to influence the occurrence of NIA. Increasing the dose in the first days of treatment, rather than a high dose per se seems to be the main risk factor for the development of akathisia (Miller et al., 1997). A genetic predisposition may also play a role (Bakker et al., 2012).

NIA is described as a very unpleasant experience and can influence adherence to the medication. Furthermore, it is associated with an increase in the risk for suicide in schizophrenic (Seemueller et al., 2012) and depressive patients (Koliscak and Makela, 2009). This fact stresses the importance of an accurate diagnosis and immediate treatment. It is often reported that clinicians tend to...
overlook akathisia (Weiden et al., 1987). But even after an accurate diagnosis, the majority of available medications for the treatment of NIA have not proven to be sufficiently effective.

Propranolol, anticholinergic agents and benzodiazepines have been traditionally used for the treatment of NIA. Propranolol is a non-selective beta-blocker and is considered to be a first-line agent against NIA. Side effects (e.g. hypotension, bradycardia), contraindications (e.g. diabetes mellitus, bronchial asthma) and drug interactions (propranolol is an inhibitor at cytochrome P450 2D6) set limitations in its use. In a review, Barnes et al. (2004) could identify only three trials, which reported on the effectiveness of beta-blockers on NIA. No firm conclusions could be drawn from this small data set. Anticholinergic agents seem to be less effective against NIA than against other extra-pyramidal symptoms (EPS) (dystonia, parkinsonism). Rathbone and Soares-Weiser (2006) performed a review and mentioned the lack of evidence for the efficacy of anticholinergic agents against NIA. Similarly, another meta-analysis included only two trials, which tested the effectiveness of benzodiazepines on NIA (Resende Lima et al., 1999). The positive-effect size lacked statistical significance. Miller et al. (1990) studied the effectiveness of ritanserin, a 5-HT2A receptor antagonist, against NIA in a single-blind trial without a control group. Since then, the effect of agents with serotonin antagonist properties has been studied in several trials, based on the assumption that the antagonism of the atypical antipsychotics at 5-HT2A receptors accounts for their low incidence of EPS. Here, we give an overview of the current evidence for the effectiveness of these agents in the treatment of akathisia and use meta-analytic methods in order to quantify this effect.

Method

Search strategy

The aim of the present study was to determine whether serotonin antagonists are effective in the treatment of neuroleptic-induced akathisia (NIA). The inclusion criteria for the studies were:

1. Double blind randomized controlled trials (RCTs), either placebo-controlled or head-to-head trials. For the purposes of the meta-analysis only placebo-controlled trials were used.
2. The drug used in the active arm of the trials should have antagonist properties at serotonin receptors (i.e. at the 5-HT2A receptors). Second generation antipsychotics were not included.

We searched for studies in the electronic databases PubMed and the Cochrane Library. The only search term was ‘akathisia’. We aimed towards higher sensitivity and lower precision in this first selection in order not to miss an appropriate study. In particular, we omitted any search term for therapy or treatment, which could reduce the search sensitivity. This approach is suggested by the ‘Cochrane Handbook for systematic Reviews of Interventions’ (Higgins and Green, 2006). The applied limits of the search were that articles should be written in English and that the search term appeared in the title or abstract of the articles. The search was performed on 28 February 2013 and no time limits were applied. We further searched through the reference lists of reviews and relative articles to identify any additional studies.

Article selection and review strategy

The selection of studies involved an initial screening of the title and the abstract in order to find studies, which were appropriate according to the inclusion criteria stated above. If it was not clear from the title or the abstract that the study should be rejected, the full text was obtained. Both authors conducted the process independently in order to reduce the possibility of rejecting a relevant article.

Both authors extracted the data independently. In case of disagreement, a clinician experienced in schizophrenia and psychopharmacology could be involved to mediate consensual decisions. A structured format was used, as presented for the individual studies in Appendix A. Dichotomous data were collected for the primary outcomes of this review (responders and non-responders to treatment). Secondary outcomes were the risk ratios for remission, dropouts, adverse effects and the impact of the outcome on psychotic symptoms.

Statistical methods (meta-analysis)

A random effects model was applied in the meta-analysis on the assumption that the true effect size was not the same in all studies. The risk ratio (RR with 95% confidence intervals) was preferred to the odds ratio for the computation of effect size because it has the advantage of being more intuitive (Borenstein et al., 2009). Calculations were performed using standard formulas (Borenstein et al., 2009) in Microsoft Excel (Excel 2003
### Table 1. Overview of studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Participants (n)</th>
<th>Duration</th>
<th>Antipsychotic medication</th>
<th>Evaluation tools</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Head-to-head trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fischel</td>
<td>2001</td>
<td>Cyproheptadine vs. propranolol</td>
<td>n=30</td>
<td>7 d. (4 d on medication and 3 d drug-free)</td>
<td>haloperidol, perphenazine</td>
<td>BARS, SAS, BPRS</td>
<td>No significant difference between cyproheptadine and propranolol. After discontinuing medication symptoms worsened more in the cyproheptadine group than in the propranolol group.</td>
</tr>
<tr>
<td><strong>B. Placebo-controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poyurovski</td>
<td>1999</td>
<td>Mianserin vs. Placebo</td>
<td>n=30</td>
<td>5 d</td>
<td>haloperidol, perphenazine, fluphenazine, haloperidol, perphenazine</td>
<td>BARS, LAS, SAS, BPRS, HAM-D</td>
<td>The differences between the two groups were significant (6/15 vs. 1/15 responders; p=0.04 by Fisher’s exact test, log odds ratio=2.23) Response rate of 53.8% (7/13) in the mirtazapine group and only 7.7% (1/13) in the placebo group (t=8.3, df=1, p=0.004)</td>
</tr>
<tr>
<td>Miodownik</td>
<td>2006</td>
<td>Mianserin vs. vitamin B6 vs. placebo</td>
<td>n=60</td>
<td>5 d</td>
<td>39 patients on FGA, 21 patients on SGA</td>
<td>BARS, BPRS, CGI</td>
<td>The number of responders was significantly greater in the vitamin B6 group (13/23, 56%) and in the mianserin group (13/20, 65%) than in the placebo group (1/17, 6%; χ²=14.976, p&lt;0.0005) 13 (43.3%) of 30 patients in the mirtazapine group and 9 (30.0%) of 30 patients in the propranolol group were considered responders vs. only 2 (6.7%) of 30 patients in the placebo group (χ²=10.57, df=2, p=0.0051). The difference in the responder rate between the two active treatment groups was not statistically significant (χ²=1.15, df=1, p=0.28). At the end of the first phase, 4 of 8 patients who started with trazodone had a response; there were no responders in the placebo group.</td>
</tr>
<tr>
<td>Poyurovski</td>
<td>2006</td>
<td>Mirtazapine vs. propranolol vs. placebo</td>
<td>n=90</td>
<td>7 d</td>
<td>haloperidol, perphenazine, clothiapine</td>
<td>BARS, SAS, BPRS, HAM-D</td>
<td></td>
</tr>
<tr>
<td>Stryjer</td>
<td>2010</td>
<td>Trazodone vs. Placebo</td>
<td>n=13</td>
<td>6 d in 2 phases of 3 d each (crossover trial)</td>
<td>Not reported</td>
<td>BARS, SAS, PANSS, HAM-D</td>
<td></td>
</tr>
</tbody>
</table>

BARS, Barnes akathisia rating scale; BPRS, brief psychiatric rating scale; CGI, clinical global impression; df, degrees of freedom; FGA, first generation antipsychotics; HAM-D, Hamilton rating scale-depression; LAS, Leeds anxiety scale; PANSS, positive and negative symptoms scale; SAS, Simpson-Angus scale; SGA, second generation antipsychotics.
Heterogeneity $I^2$ was computed in order to assess the percentage of the overall variability attributable to the between-studies variability. The risk of bias in individual studies was evaluated using the Cochrane Collaboration’s domain-based tool, which assesses allocation concealment, sequence generation, blinding, selective outcome reporting and other sources of bias. The risk of publication bias was assessed using a funnel plot and the Egger regression method (Egger et al., 1997).

In the case of crossover studies, we included only the first phase of the trial in our meta-analysis. Crossover trials are most appropriate for symptomatic treatment of chronic or relatively stable conditions or disorders (Elbourne et al., 2002). Akathisia is an acute condition; thus, the treatment or the non-treatment of akathisia alters the condition and on entry to subsequent phases patients may systematically differ from their initial state.

In the case of zero events trials (in one or in both arms), the standard continuity correction of 0.5 was applied (Friedrich et al., 2007).

Results

Search results

The electronic searches provided 1515 references from MEDLINE and 570 references (clinical trials) from the Cochrane Library. The initial scanning of the abstracts excluded all but 12 reports. These reports were further screened and assessed for eligibility and six of them were rejected. The remaining 6 RCTs fulfilled the inclusion criteria for the review. From these 6 citations there was one head-to-head trial (Fischel et al., 2001), i.e. active drugs were compared with each other; and five randomized placebo-controlled studies (Poyurovsky et al., 1999, 2003, 2006; Miodownik et al., 2006; Stryjer et al., 2010) (see flow diagram in Fig. 1). Details of each trial are presented in Table 1 and Appendix A. The complete list of assessed trials is presented in Appendix B.

### Table 2. Relative risk ratios for response in each trial and mean effect size

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug-group</th>
<th>n</th>
<th>Responders</th>
<th>Placebo-group</th>
<th>n</th>
<th>Responders</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyurovsky et al. (1999)</td>
<td>Mianserin</td>
<td>15</td>
<td>6</td>
<td>15</td>
<td>1</td>
<td>6.00</td>
<td>0.82</td>
<td>44.00</td>
<td>0.0780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poyurovsky et al. (2003)</td>
<td>Mirtazapine</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>1</td>
<td>7.00</td>
<td>1.00</td>
<td>49.16</td>
<td>0.0504</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miodownik et al. (2006)</td>
<td>Mianserin</td>
<td>20</td>
<td>13</td>
<td>17</td>
<td>1</td>
<td>11.05</td>
<td>1.61</td>
<td>76.01</td>
<td>0.0146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poyurovsky et al. (2006)</td>
<td>Mirtazapine</td>
<td>30</td>
<td>13</td>
<td>30</td>
<td>2</td>
<td>6.50</td>
<td>1.60</td>
<td>26.36</td>
<td>0.0088</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stryjer et al. (2010)</td>
<td>Trazodone</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>5.82</td>
<td>0.38</td>
<td>88.21</td>
<td>0.2039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>86</td>
<td>43</td>
<td>80</td>
<td>5</td>
<td>7.10</td>
<td>3.08</td>
<td>16.40</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2. Forest plot.**

Edition, Microsoft, USA). The forest plot was also created in Microsoft Excel according to a guide published by Higgins and Green (2008).

Overview of all studies

Head-to-head trials

Fischel et al. (2001) studied 30 patients with akathisia. Propranolol (80 mg/day, $n=12$) was not found to be superior to the serotonin receptor antagonist cyproheptadine (16 mg/day, $n=18$). The efficacy of propranolol in the treatment of NIA has already been demonstrated in other trials (Adler et al., 1986; Reiter et al., 1987; Kramer et al., 1988) and it is traditionally considered as a first line option. However, other studies failed to replicate these positive findings (Irwin et al., 1988; Sachdev and Loneragan, 1993a). The results of Fischel et al. (2001) suggest that cyproheptadine is as effective as propranolol. Both drugs were well tolerated. The authors...
Table 3. Relative risk ratios for remission in each study

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug-group</th>
<th>Placebo-group</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyurovsky et al. (1999)</td>
<td>Mianserin</td>
<td>15</td>
<td>15</td>
<td>4.00</td>
<td>0.50</td>
<td>31.74</td>
<td>0.19</td>
</tr>
<tr>
<td>Poyurovsky et al. (2003)</td>
<td>Mirtazapine</td>
<td>13</td>
<td>13</td>
<td>5.00</td>
<td>0.67</td>
<td>37.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Miodownik et al. (2006)</td>
<td>Mianserin</td>
<td>20</td>
<td>17</td>
<td>7.68</td>
<td>0.44</td>
<td>132.99</td>
<td>0.16</td>
</tr>
<tr>
<td>Poyurovsky et al. (2006)</td>
<td>Mirtazapine</td>
<td>30</td>
<td>30</td>
<td>5.00</td>
<td>1.19</td>
<td>20.92</td>
<td>0.02</td>
</tr>
<tr>
<td>Stryjer et al. (2010)</td>
<td>Trazodone</td>
<td>8</td>
<td>5</td>
<td>4.53</td>
<td>0.29</td>
<td>71.73</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>86</strong></td>
<td><strong>80</strong></td>
<td><strong>4.95</strong></td>
<td><strong>2.01</strong></td>
<td><strong>12.22</strong></td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Table 4. Relative risk for dropouts

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug-group</th>
<th>Placebo-group</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyurovsky et al. (1999)</td>
<td>Mianserin</td>
<td>15</td>
<td>15</td>
<td>0.11</td>
<td>0.01</td>
<td>1.89</td>
<td>0.13</td>
</tr>
<tr>
<td>Poyurovsky et al. (2003)</td>
<td>Mirtazapine</td>
<td>13</td>
<td>13</td>
<td>1.00</td>
<td>0.25</td>
<td>4.07</td>
<td>1.00</td>
</tr>
<tr>
<td>Miodownik et al. (2006)</td>
<td>Mianserin</td>
<td>20</td>
<td>17</td>
<td>0.85</td>
<td>0.02</td>
<td>40.83</td>
<td>0.94</td>
</tr>
<tr>
<td>Poyurovsky et al. (2006)</td>
<td>Mirtazapine</td>
<td>30</td>
<td>30</td>
<td>0.60</td>
<td>0.25</td>
<td>1.44</td>
<td>0.25</td>
</tr>
<tr>
<td>Stryjer et al. (2010)</td>
<td>Trazodone</td>
<td>8</td>
<td>5</td>
<td>0.65</td>
<td>0.01</td>
<td>28.08</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>86</strong></td>
<td><strong>80</strong></td>
<td><strong>0.62</strong></td>
<td><strong>0.31</strong></td>
<td><strong>1.25</strong></td>
<td>0.18</td>
</tr>
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</table>

Table 5. Relative risk for adverse effects (sedation)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug-group</th>
<th>Placebo-group</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyurovsky et al. (1999)</td>
<td>Mianserin</td>
<td>15</td>
<td>15</td>
<td>2.67</td>
<td>0.87</td>
<td>8.15</td>
<td>0.09</td>
</tr>
<tr>
<td>Poyurovsky et al. (2003)</td>
<td>Mirtazapine</td>
<td>13</td>
<td>13</td>
<td>5.00</td>
<td>0.67</td>
<td>37.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Miodownik et al. (2006)</td>
<td>Mianserin</td>
<td>20</td>
<td>17</td>
<td>0.85</td>
<td>0.02</td>
<td>40.83</td>
<td>0.94</td>
</tr>
<tr>
<td>Poyurovsky et al. (2006)</td>
<td>Mirtazapine</td>
<td>30</td>
<td>30</td>
<td>0.60</td>
<td>0.25</td>
<td>1.44</td>
<td>0.25</td>
</tr>
<tr>
<td>Stryjer et al. (2010)</td>
<td>Trazodone</td>
<td>8</td>
<td>5</td>
<td>0.65</td>
<td>0.01</td>
<td>28.08</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>86</strong></td>
<td><strong>81</strong></td>
<td><strong>1.42</strong></td>
<td><strong>0.54</strong></td>
<td><strong>3.73</strong></td>
<td>0.55</td>
</tr>
</tbody>
</table>

Table 6. Impact on psychotic symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Scale</th>
<th>Drug-group</th>
<th>Placebo-group</th>
<th>Mean change</th>
<th>SD</th>
<th>Mean change</th>
<th>SD</th>
<th>Hedge's g</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyurovsky et al. (1999)</td>
<td>BPRS</td>
<td>−6.5</td>
<td>−1.5</td>
<td>7.0</td>
<td>4.55</td>
<td>1.4</td>
<td>6.44</td>
<td>−0.07</td>
<td>0.98</td>
</tr>
<tr>
<td>Poyurovsky et al. (2003)</td>
<td>PANSS</td>
<td>−9.7</td>
<td>0.1</td>
<td>13.6</td>
<td>4.55</td>
<td>5.90</td>
<td>−0.05</td>
<td>3.08</td>
<td>−0.91</td>
</tr>
<tr>
<td>Miodownik et al. (2006)</td>
<td>BPRS</td>
<td>0.5</td>
<td>0.7</td>
<td>4.55</td>
<td>6.30</td>
<td>3.08</td>
<td>6.44</td>
<td>−0.04</td>
<td>−0.05</td>
</tr>
<tr>
<td>Poyurovsky et al. (2006)</td>
<td>BPRS</td>
<td>−0.3</td>
<td>−0.07</td>
<td>6.30</td>
<td>6.44</td>
<td>−0.07</td>
<td>6.44</td>
<td>−0.42</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
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</tbody>
</table>
attributed the positive effect of cyproheptadine on NIA to its 5-HT2A antagonistic properties.

Placebo-controlled studies

Poyurovsky et al. (1999) and Miodownik et al. (2006) compared the tetracyclic antidepressant mianserin (15 mg/d in both studies) with placebo in 30 and 37 patients with NIA, respectively. Both publications reported a significant effect of mianserin on akathisia in comparison to placebo. The anticholinergic properties of mianserin are minimal, so that its effect on NIA can be attributed solely to its antagonism at the 5-HT2A receptors.

Poyurovsky et al. (2003) found in another trial with 26 participants that mirtazapine (15 mg/d) is effective in the treatment of NIA. Poyurovsky et al. (2006) replicated these positive results in a trial with a larger sample (n=60, mirtazapine dose=15 mg/d). A third group with propranolol (80 mg/d) was included in this latter study (Poyurovsky et al., 2006). Both drugs were equally effective, but mirtazapine was better tolerated. Mirtazapine is structurally and pharmacologically similar to mianserin and exhibits marked 5-HT2A antagonism.

Finally, Stryjer et al. (2010) found in a crossover trial that trazodone (100 mg/d) was more effective than placebo in the treatment of NIA. Trazodone is a weak serotonin reuptake inhibitor with potent antagonism at 5-HT2A and 5-HT2C receptors. In the first phase of the study, which lasted 3 days, 8 patients were treated with trazodone and 5 with placebo. There was no washout period between the first and the second phase. As mentioned above, we included only the first phase in our analysis.

Meta-analysis

Effect size

All studies used the Barnes Akathisia Rating Scale (BARS) to quantify the symptoms of NIA and the response was defined as a reduction of the BARS score by at least two points. The overall effect size in the analysis is $RR=7.10$ with 95% CI 3.08–16.40 ($p<0.0001$). Thus, with the 5-HT2A antagonists, a therapeutic response (as defined in the considered studies) is about seven times more likely than in the placebo group (see Table 2 and forest plot in Fig. 2). As can be seen in the forest plot, the error bars of the effect size for the first and fifth study cross the y-axis, which means that these results lack statistical significance. This discrepancy between the results presented here and the ones presented in the original studies results from using a different measure of effect size. Poyurovsky et al. (1999) found a significant odds ratio of responders in their trial (log odds ratio=2.23, $p=0.04$). Stryjer et al. (2010) reported a statistically significant score reduction in the BARS, but did not report an effect size for responders.

Heterogeneity

The computed heterogeneity $I^2$ was −14.07. Values less than zero make no sense and heterogeneity is considered
to be equal to zero in such cases. Heterogeneity between 0 and 40% is of no importance.

Secondary outcomes

Remission rates were significantly higher in the drug groups than in the placebo groups (RR = 4.95, 95% CI 2.01–12.22, p = 0.0005; Table 3). There were no significant differences between patients in either group in dropouts (RR = 0.62, 95% CI 0.31–1.25, p = 0.18; Table 4) and adverse effects (RR = 1.42, 95% CI 0.54–3.73, p = 0.55; Table 5). Two studies (Miodownik et al., 2006; Stryjer et al., 2010) reported no adverse effects in either drug or placebo groups, while two other studies (Poyurovsky et al., 1999, 2003) reported only sedation. Poyurovsky et al. (2006) presented a more extensive list of adverse effects. In order to achieve comparable results, we included only the patients with sedation from this study in the meta-analysis. The treatment of akathisia did not influence the severity of the psychotic symptoms (see Table 6). Here data from four studies were available, since the corresponding author of the fifth study did not provide us with missing data.

Risk of bias and publication bias

The risk of bias for each study can be assessed using the following six domains: sequence generation, allocation concealment, blinding, missing data, selective outcome reporting and other sources of bias (Higgins and Green, 2008). The group of studies was relatively homogenous and the overall risk for bias could be described as low (Fig. 3). The results for each trial are presented in Appendix C. Finally, no indication of publication bias can be derived from the funnel plot; in particular, there was no gap on the bottom left side, which would be indicative of unpublished studies with small to moderate effects (Fig. 4). However, the small number of trials limits the reliability of these results. The estimated intercept in Egger's regression was −0.0007 (Fig. 5). Values near zero indicate no publication bias.

Discussion

This is the first meta-analysis to estimate the effect of agents with antagonistic properties at the 5-HT2A receptor on NIA and the first to report a positive effect of a drug group. The mean effect size was RR = 7.10 (95% CI 3.08–16.40, p < 0.0001), which indicates a substantial drug efficacy. There were no significant differences between drug and placebo groups as far as adverse effects and dropouts are concerned. A reduction in the intensity of akathisia was not accompanied by a reduction in psychotic symptoms severity. Because of the small number of trials, no differences in efficacy among the three agents used (i.e. mirtazapine, mianserin and trazodone) can be detected. Based on the existing literature, mirtazapine have adrenolytic properties, which can cause somnolence, sedation, impairment of cognitive functioning and circulatory problems (Stahl, 2008). Trazodone can also cause priapismus, an infrequent but severe adverse effect (Fagiolini et al., 2012). In contrast, mirtazapine lacks adrenolytic properties and can thus be better tolerated when combined with antipsychotics, which themselves exhibit α1-receptor blockade. Sedation is often observed in low doses, owing to its antihistaminergic properties, for this reason mirtazapine is preferentially administered before sleep. Long-term use is associated with weight gain.

Alternative options

In addition to the medication discussed above, there are trials that show the efficacy of other agents, e.g. vitamin B6 (Lerner et al., 2004; Miodownik et al., 2006),
apomorphine (Sachdev and Loneragan, 1993b) and zolmitriptan (Avital et al., 2009). Only vitamin B6 has been shown to be effective in more than one trial. The lack of significant adverse effects of vitamin B6 and its proven efficacy justify its use in the treatment of NIA. Vitamin B6 has already been found to be effective in the treatment of tardive dyskinesia (Lerner et al., 2001, 2007). The exact mechanism of action is not known; but the fact that a derivative of vitamin B6 is a coenzyme of dopa decarboxylase is suggestive (Amadasi et al., 2007). Apomorphine has dopaminergic properties. However, it is not known to exacerbate psychotic symptoms in schizophrenic patients (Dépatie and Lal, 2001). Zolmitriptan is a 5-HT1A receptor antagonist and is used in the treatment of migraine.

Treatment strategies

The studies in this review provide no data on the adequate duration of a sufficient treatment. Fischel et al. (2001) reported worsening of symptoms after the termination of treatment on day four. On the other hand, the crossover trial by Stryjer et al. (2010) shows that a switch of treatment on day four. On the other hand, the crossover trial by Stryjer et al. (2010) shows that a switch from trazodone to placebo after a three-day trial did not lead to a worsening of the symptoms. At any rate, no concrete recommendations for the duration of the treatment can be made based on the available trials.

Poyurovski (2010), an expert in the treatment of antipsychotics-related side effects, such as akathisia and weight gain, proposes an algorithm for the treatment of akathisia. He presents two main treatment strategies. The first is the modification of the drug regimen (i.e. dose reduction or switching to another agent) and the second is adding an anti-akathisia agent (propranolol and mirtazapine are proposed as first-line treatment options). Taking the available data from meta-analytic reviews of the efficacy of these two agents into account, we believe that low-dose mirtazapine should be preferred.

Limitations and strengths

The main limitation of the present meta-analysis is the small number of trials and the small number of patients included. However, the results attained statistical significance; this can be attributed to the clear and substantial effect of the drugs under study. Another limitation is the definition of the 5-HT2A receptor antagonists. Most drugs exhibit a variety of pharmacodynamic properties and it is not always possible to attribute a clinical effect to a specific action at the molecular level. A strength of our meta-analysis is the absence of inhomogeneity (I² = 0). The trials were of similar study design, they used same scale (BARS) for the evaluation of NIA and all trials assessed psychotic symptoms. Three trials were conducted by the same author, which presumably reduces the between-studies variance.

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Statement of Interests

None.

Supplementary material

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References


