Antipsychotic drugs and extrapyramidal side effects in first episode psychosis: a systematic review of head–head comparisons

Peter M Haddad1, Amlan Das2, Sarvenaz Keyhani1 and Imran B Chaudhry3

Abstract
This systematic review aimed to determine whether the risk of extrapyramidal side effects (EPS) differed between antipsychotic drugs used in first episode psychosis (FEP). We identified 11 RCTs comparing two or more antipsychotics in FEP and reporting on EPS. All trials assessed one or more second generation antipsychotics (SGAs), one assessed chlorpromazine, one zuclopenthixol and seven trials assessed haloperidol. Assessment and reporting of EPS varied. Compared with one or more SGA comparators, haloperidol was associated with significantly higher rates/severity of parkinsonism (seven trials) and akathisia (six trials) and greater use of anticholinergics (five trials) and beta-blockers (two trials). Two trials with low-dose haloperidol (≤ 4 mg) showed significantly worse EPS outcomes versus a SGA. Two of four long-term haloperidol trials (≥ 1 year) found a higher dyskinesia-risk with haloperidol versus olanzapine and risperidone respectively; the remaining two trials found no difference (various SGA comparators). There was an EPS advantage for clozapine versus chlorpromazine (one trial) and risperidone versus zuclopenthixol (one trial). There was little evidence of EPS-differences between SGAs, possibly reflecting use of low doses. We conclude that SGAs offer an EPS advantage over FGAs in FEP though the evidence largely relates to comparisons with haloperidol. Standardized assessment and reporting of EPS would assist future research.

Keywords
Akathisia, antipsychotic, dystonia, extrapyramidal symptom, first episode psychosis, parkinsonism, schizophrenia, systematic review, tardive dyskinesia

Introduction
Extrapyramidal side effects (EPS) were recognized soon after antipsychotic drugs entered clinical practice (Steck, 1954). Four common extrapyramidal syndromes are recognized, namely parkinsonism, akathisia, acute dystonia and tardive dyskinesia. The clinical features of these syndromes are well described (e.g. Braude et al., 1983; Haddad and Dursun, 2008; Swett, 1975; Uhrbrand and Faarbye, 1960). EPS are important as they can impair quality of life, stigmatize patients and lead to poor antipsychotic adherence and relapse.

Meta-analyses show that second generation antipsychotics (SGAs) cause fewer EPS than haloperidol but differences in EPS risk between individual SGAs and between SGAs and low potency first generation antipsychotics (FGAs) are less marked (Komossa et al., 2010; Leucht et al., 2009; Rummel-Kluge et al., 2010a). These analyses largely relate to patients with chronic schizophrenia. For example, the meta-analysis by Leucht et al. (2009) incorporated 150 double-blind studies (21,533 participants) of which only five studies were of first episode patients. These results may not apply to patients with first episode psychosis given that these patients have little or no prior antipsychotic exposure, tend to be treated with lower doses of antipsychotics than patients with chronic schizophrenia and appear more sensitive to develop EPS (Sanger et al., 1999).

A recent meta-analysis showed a greater risk of parkinsonism with FGAs versus SGAs in first episode patients but other types of EPS were not considered (Crossley et al., 2010). The main aim of this study was to investigate whether the risk of a broader range of EPS (parkinsonism, akathisia, dyskinesia and dystonia) differed between antipsychotic drugs used in the treatment of first episode psychosis (FEP). We aimed to achieve this by conducting a systematic review of randomized controlled trials (RCTs) that compared two or more antipsychotic drugs in FEP. A secondary aim was to better understand the reporting of EPS in clinical trials. This was prompted by an observation that meta-analyses of antipsychotic treatment often contain relatively little data on EPS and instead concentrate on drug efficacy.

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Method

Search strategy

We conducted a PubMed search, with no starting date limit, up to April 2011 using terms ‘first episode schizophrenia’ and ‘antipsychotic’ with limits specified as ‘Humans, Randomized Controlled Trial and English’. The abstracts of all papers were reviewed to determine whether they met inclusion/exclusion criteria and if there was doubt the full paper was examined. Additional studies, identified through the reference list of papers in the primary search or known to the authors, were reviewed to see if they met inclusion/exclusion criteria.

Inclusion criteria

1. RCT comparing two or more antipsychotic drugs.
2. Diagnosis of schizophrenia plus related disorders including schizophreniform disorder and schizoaffective disorder made according to standard criteria (any).
3. Patients explicitly described as ‘first episode’ by the authors. Although we did not define this further we recorded key criteria that the researchers employed to define this population, e.g. maximum age, maximum duration of illness and maximum cumulative antipsychotic treatment length.
4. EPS assessed using a standard rating scale.
5. Quantitative data on incidence or severity of EPS provided.

Exclusion criteria

2. Non-randomized studies.
3. Studies of early onset schizophrenia (i.e. samples largely composed of subjects < 18 years old).

Analysis

Key data from the studies that met the inclusion/exclusion criteria were included. This included EPS ratings for parkinsonism, akathisia, dyskinesia and dystonia made using standardized rating scales and the rates of use of medications used to treat EPS, namely anticholinergics, benzodiazepines and beta blockers. The latter can act as a proxy marker for clinically relevant EPS. We extracted data on drop-outs due to side effects where this was provided. In analysing the data from one trial (Kahn et al., 2008) we used Fisher’s exact test with Bonferroni adjustments to make pairwise comparisons of the rates of akathisia and parkinsonism between haloperidol and specific SGAs as pairwise analysis was not provided in the paper. A meta-analysis was not conducted as, concomitant medication use apart, the studies varied markedly in the assessment of EPS and reporting of data.

Results

Included studies and participants

The search strategy identified 112 articles. Eleven trials (14 publications) met the inclusion/exclusion criteria. These are summarized in Tables 1 and 2. Three trials had resulted in two publications each; in each case the two papers detailed EPS assessment at different time points in the trial (trials 4, 6 and 10 in Tables 1 and 2). Although EPS data from all 14 publications is summarized in Table 2, we will refer to the number of trials rather than publications when summarizing our results (e.g. in the Abstract and Discussion) as different publications from a single trial will have a high proportion of common patients.

Nine trials included patients with additional diagnoses to schizophrenia, usually schizoaffective disorder and schizophreniform disorder (Table 1). In keeping with the inclusion criteria all studies explicitly described their subjects as ‘first episode’. Most defined this by using additional criteria that included a maximum age (10 trials), a maximum cumulative exposure period to antipsychotic drugs (nine trials) and a maximum duration of psychosis (six trials) (see Tables 1 and 2).

Trial design including duration

In keeping with the inclusion criteria all trials were randomized. Four trials were open (Crespo-Facorro et al., 2006, 2011; Glenthoj et al., 2007; Kahn et al., 2008; Robinson et al., 2006) though raters were blind to treatment in one (Robinson et al., 2006). The remaining seven trials were double blind. All allowed flexible dosing within a specified dose range. Ten trials allowed the use of concomitant medication, most commonly anticholinergics, as necessary to treat EPS. In the remaining trial prophylactic benzotropine 2 mg b.d. was given to chlorpromazine-treated patients and placebo to the clozapine-treated patients (Lieberman et al., 2003a). Of the 14 publications that were analysed, seven had a follow-up period of 16 weeks or less, five had a one-year follow-up and two had a follow-up period of two years or longer. Nine of the 11 trials had some degree of industry involvement.

Antipsychotics and dose

Haloperidol, risperidone, olanzapine and quetiapine were the only drugs assessed in more than one trial (Figure 1). In terms of FGAs, seven trials assessed haloperidol (Crespo-Facorro et al., 2006, 2011; Emsley 1999; Gaebel et al., 2007; Green et al., 2006; Kahn et al., 2008; Lieberman et al., 2003b; Möller et al., 2008; Sanger et al., 1999; Schooler et al., 2005), one assessed zuclopenthixol (Glenthoj et al., 2007) and one assessed chlorpromazine (Lieberman et al., 2003a).

Several trials specified a maximum daily antipsychotic dose below that given in the summary of product characteristics (SPCs) (Table 2). Of particular note, two haloperidol trials were low-dose (maximum dose ≤ 4 mg/day haloperidol) (Kahn et al., 2008; Schooler et al., 2005) though in Schooler et al. (2005) the dose of haloperidol could be increased to 8 mg in ‘exceptional circumstances’. The authors did not report how often this occurred though as the mean modal dose was 2.0 mg it seems to have been relatively rare. The German Research Network on Schizophrenia (GRNS) trial (Gaebel et al., 2007; Möller et al., 2008) can be regarded as an intermediate-dose haloperidol trial (range 2–8 mg but target dose 2–4 mg after week 1). Most studies of risperidone and olanzapine, the two SGAs assessed most frequently, used comparatively low mean doses (e.g. McEvoy et al., 2007; Schooler et al., 2005). An exception is Emsley et al. (1999), one of the earliest studies, in which the mean dose of risperidone was 6.1 mg.
Assessment and reporting of EPS

Various scales were used to assess EPS and tardive dyskinesia (TD) (see Table 2). The extrapyramidal symptom rating scale (ESRS) (Chouinard, Gerlach et al., 1980) and St Hans rating scale (Gerlach, 1993) are both designed to assess a range of EPS including parkinsonism, akathisia, dystonia and tardive dyskinesia or hyperkinesia. The ESRS was used in three trials and the St Hans rating scale in one trial. Syndrome-specific scales consisted of the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970) to assess parkinsonism (used in seven trials), the Barnes Akathisia Scale (BAS) (Barnes, 1989) (five trials), the Hillside akathisia scale (Fleischhacker, 1989) (one trial) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) for TD (four trials). Occasionally an existing scale was altered. Due to the association of sialorrhea with clozapine, the sialorrhea item was omitted from the SAS in a RCT that compared chlorpromazine and clozapine (Lieberman, 2003a). In another study a dystonia item was added to the SAS (Lieberman, 2003b).

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Some studies presented additional data on the prevalence of EPS syndrome absent at baseline but present at a subsequent
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Methods of analysing continuous EPS data included comparing baseline to endpoint changes on a rating scale (e.g. Sanger et al., 1999), comparing baseline to maximum or ‘worst’ score at any time point during treatment (e.g. Emsley et al., 1999, Schooler et al., 2005) and comparing endpoint scores (e.g. Gaebel et al., 2007). Most analyses of EPS syndromes calculated incidence rates (i.e. syndrome absent at baseline but present at a subsequent

Table 1. RCTs of two or more antipsychotic drugs in first episode psychosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Publication(s)</th>
<th>Diagnosis</th>
<th>Illness duration prior to randomization</th>
<th>Prior cumulative antipsychotic use</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Emsley et al. (1999)</td>
<td>DSM-III-R schizophrenia or schizophreniform disorder</td>
<td>&lt; 3 days emergency antipsychotic treatment</td>
<td>DB</td>
<td></td>
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<td>2.</td>
<td>Sanger et al. (1999)</td>
<td>DSM-III-R schizophrenia, schizoaffective disorder or schizophreniform disorder</td>
<td>&lt; 5 years</td>
<td>DB</td>
<td></td>
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<tr>
<td>3.</td>
<td>Lieberman et al. (2003a)</td>
<td>DSM-IV schizophrenia or schizophreniform disorder</td>
<td>&lt; 5 years</td>
<td>DB</td>
<td></td>
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<tr>
<td>4.</td>
<td>Lieberman et al. (2003b)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder</td>
<td>&lt; 5 years</td>
<td>DB</td>
<td></td>
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<tr>
<td>5.</td>
<td>Schooler et al. (2005)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder</td>
<td>&lt; 1 year</td>
<td>DB</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Robinson et al. (2006)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorders</td>
<td>&lt; 12 weeks</td>
<td>Open (but blind raters)</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Glenthoj et al. (2007)</td>
<td>ICD 10 F20 schizophrenia</td>
<td>Most patients drug naïve. Max. duration of prior treatment 28 days</td>
<td>Open</td>
<td></td>
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<tr>
<td>9.</td>
<td>McEvoy et al. (2007)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder</td>
<td>&lt; 5 years</td>
<td>DB</td>
<td></td>
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<td>11.</td>
<td>Kahn et al. (2008)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder</td>
<td>&lt; 2 years</td>
<td>DB</td>
<td></td>
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</tbody>
</table>

*Eleven trials were reported as 14 publications. CAFE: Comparison of Atypicals in First Episode Psychosis, DB: double-blind, EUFEST: European First-Episode Schizophrenia Trial, GRNS: German Research Network on Schizophrenia
Table 2. EPS rating scale data from RCTs of two or more antipsychotic drugs in first episode psychosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Publication</th>
<th>Sample size</th>
<th>Age range (mean or median; years)</th>
<th>Duration of study</th>
<th>Daily antipsychotic dose (range plus mean/median dose)</th>
<th>EPS rating scales</th>
<th>Rating scale outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Emsley (1999)</td>
<td>183</td>
<td>15–45 (median: 26 risperidone, 24 haloperidol)</td>
<td>6 weeks</td>
<td>Risperidone and haloperidol (both 2–16 mg). Mean dose: risperidone 6.1 mg and haloperidol 5.6 mg.</td>
<td>ESRS</td>
<td>Using baseline to worst scores, haloperidol associated with greater increase in total ESRS score (parkinsonism + dystonia + dyskinesia), several parkinsonian symptoms and akathisia. Greater increase in ESRS scores with high dose (&gt; 6 mg) vs. low dose (≤ 6 mg) of both haloperidol and risperidone.</td>
</tr>
<tr>
<td>2.</td>
<td>Sanger et al. (1999)</td>
<td>83</td>
<td>&lt; 45 (mean 29.0 olanzapine and 27.4 haloperidol)</td>
<td>6 weeks</td>
<td>Olanzapine and haloperidol (both 5–20 mg). Mean modal dose: olanzapine 11.6 mg and haloperidol 10.8 mg.</td>
<td>BAS, SAS</td>
<td>SAS and BAS scores from baseline to endpoint improved for olanzapine but worsened for haloperidol patients. Incidence of treatment-emergent parkinsonism (SAS ≤ 3 baseline to &gt; 3 post-baseline) higher for haloperidol vs. olanzapine (52.6% vs. 18.8%). Incidence of treatment-emergent akathisia (BAS ≤ 2 baseline to ≥ 2 post-baseline) higher for haloperidol vs. olanzapine (38.1% vs. 11.3%). Haloperidol-treated first episode patients had greater increase in SAS total score from baseline to endpoint than haloperidol-treated multi-episode patients.</td>
</tr>
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<td>3.</td>
<td>Lieberman et al. (2003a)</td>
<td>160</td>
<td>16–40 (mean 28.7)</td>
<td>52 weeks</td>
<td>Clozapine max. dose 400 mg (median dose at 1 year: 300 mg). Chlorpromazine max. dose 600 mg (median dose at 1 year: 400 mg).</td>
<td>SAS</td>
<td>SAS scores higher at 12 weeks and 1 year for chlorpromazine vs. clozapine; difference only significant at 12 weeks in LOCF analysis but at both time points in observed cases analysis. Over 1 year of follow-up akathisia and dystonia more frequent with chlorpromazine.</td>
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<td>4.</td>
<td>Lieberman et al. (2003b)</td>
<td>263</td>
<td>16–40 (mean 24)</td>
<td>12 weeks</td>
<td>Olanzapine (5–20 mg) (mean modal dose 9.1 mg) haloperidol (2–20 mg) (mean modal dose 4.4 mg).</td>
<td>AIMS, BAS, SAS</td>
<td>Greater change in SAS and BAS scores from baseline to endpoint for haloperidol vs. olanzapine. Incidence of treatment-emergent parkinsonism (SAS ≤ 3 baseline to &gt; 3 post-baseline) higher for haloperidol vs. olanzapine (54.8% vs. 26.1%). Incidence of treatment-emergent akathisia (BAS ≤ 2 baseline to ≥ 2 post-baseline) higher for haloperidol vs. olanzapine (51.2 vs. 11.9%).</td>
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<td>Green et al. (2006)</td>
<td>263</td>
<td>16–40 (mean 23.8)</td>
<td>2 years</td>
<td>Olanzapine (5–20 mg) and haloperidol (2–20 mg). Mean daily dose at endpoint: olanzapine 10.2 mg and haloperidol 4.8 mg.</td>
<td>AIMS, BAS, SAS</td>
<td>Based on maximal rating scale values, haloperidol associated with more severe parkinsonism (SAS) and akathisia (BAS) but no differences on AIMS. Symptoms of parkinsonism and akathisia greater at 3 months and 6 months with haloperidol but not later. AIMS scores similar for two groups at 3 months but greater for haloperidol group at 6 months, 1 year and 2 years.</td>
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<tr>
<td>Trial</td>
<td>Publication</td>
<td>Sample size</td>
<td>Age range (mean or median; years)</td>
<td>Duration of study</td>
<td>Daily antipsychotic dose (range plus mean/median dose)</td>
<td>EPS rating scales</td>
<td>Rating scale outcomes</td>
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<td>5.</td>
<td>Schooler et al. (2005)</td>
<td>555</td>
<td>16–45 (mean 25.4)</td>
<td>≥ 2 years</td>
<td>Risperidone and haloperidol (1–4 mg unless ‘exceptional circumstances’ when dose could be increased to 8 mg). Mean modal dose: risperidone 3.3 mg and haloperidol 2.0 mg.</td>
<td>ESRS</td>
<td>Maximum change on ESRS total score from baseline greater for haloperidol vs. risperidone. Higher akathisia and parkinsonism sub-scores for haloperidol. No difference in dystonia subscale. More emergent dyskinesia with haloperidol vs. risperidone (13.4 vs. 8.3%) but no significant difference in persistent dyskinesia.</td>
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<td>6.</td>
<td>Crespo-Facorro et al. (2006)</td>
<td>172</td>
<td>15–60 (mean 27.3)</td>
<td>6 weeks</td>
<td>Haloperidol (3–9 mg), olanzapine (5–20 mg) and risperidone (3–6 mg). Mean modal daily dose: haloperidol 5.4 mg, risperidone 4 mg, and olanzapine 15.3 mg.</td>
<td>AIMS, BAS, SAS, UKU</td>
<td>Incidence of treatment emergent parkinsonism (SAS ≤ 3 baseline to &gt; 3 post-baseline) higher with haloperidol (46.4%) vs. olanzapine (5.5%) and risperidone (24.6%). Incidence of treatment emergent akathisia (BAS &lt; 2 baseline to ≥ 2 post-baseline) higher with haloperidol (55.4%) vs. olanzapine (5.5%) and risperidone (26.2%). Change in baseline to endpoint score on BAS and SAS greater for haloperidol vs. olanzapine but not for other pairwise comparisons. No difference between drugs on mean AIMS scores. Higher prevalence of akathisia, rigidity and hypokinesia on UKU with haloperidol vs. comparators.</td>
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<td>7.</td>
<td>Robinson et al. (2006)</td>
<td>112</td>
<td>16–40 (mean 23.3)</td>
<td>4 months</td>
<td>Olanzapine (2.5–20 mg) and risperidone (1–6 mg). Mean dose at 1 year: haloperidol 2.9 mg, risperidone 3.5 mg and olanzapine 10.2 mg.</td>
<td>BAS, SAS</td>
<td>Incidence of treatment emergent parkinsonism at 1 year (SAS ≤ 3 baseline to &gt; 3 at 1 year) did not differ between three groups (range 2.4 to 4.2%). Incidence of treatment emergent akathisia at 1 year (BAS &lt; 2 baseline to ≥ 2 at 1 year) differed between drugs; haloperidol (20.8%), olanzapine (0%), risperidone (4.9%). Change in baseline to endpoint score on BAS greater for haloperidol vs. olanzapine but not for other pairwise comparisons. Change in baseline to endpoint score on SAS showed a trend for difference between three groups with greatest increase with haloperidol ($p = 0.06$). Higher prevalence of akathisia on UKU with haloperidol vs. comparators.</td>
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<td>8.</td>
<td>Glenthoj et al. (2007)</td>
<td>19</td>
<td>No age range specified, mean 25.9</td>
<td>13 weeks</td>
<td>Zuclopenthixol (4–27 mg) or risperidone (1–7 mg). Mean dose at end point: risperidone 3.4 and zuclopenthixol 10.3 mg.</td>
<td>ESRS</td>
<td>Difference that approached statistical significance in total SAS scores that favoured olanzapine over risperidone ($p &lt; 0.07$). Analysis of BAS scores and syndromal rates of parkinsonism showed no significant difference between drugs. Higher ESRS score at endpoint for zuclopenthixol vs. risperidone.</td>
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<tr>
<td>Trial</td>
<td>Publication</td>
<td>Sample size</td>
<td>Age range (mean or median; years)</td>
<td>Duration of study</td>
<td>Daily antipsychotic dose (range plus mean/median dose)</td>
<td>EPS rating scales</td>
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<td>9. CAFE</td>
<td>McEvoy et al. (2007)</td>
<td>400</td>
<td>16–40 (mean 24.5)</td>
<td>52 weeks</td>
<td>Olanzapine (2.5–20 mg/day), quetiapine (100–800 mg/day), or risperidone (0.5–4 mg/day). Mean modal daily dose: olanzapine 11.7 mg, quetiapine 506 mg, and risperidone 2.4 mg.</td>
<td>AIMS, BAS, SAS</td>
<td>Low EPS rates and no significant differences between treatment groups; using maximum values during study, 16% of patients had a rating &gt; 1 (mild) on any SAS item, 7% had a rating &gt; 2 (mild) on the global severity item of the BAS and 1% had a score &gt; 2 (mild) on the global severity item of the AIMS.</td>
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<tr>
<td>10. GRNS</td>
<td>Möller et al. (2008)</td>
<td>289</td>
<td>18–60 (mean 30.1)</td>
<td>8 weeks</td>
<td>Haloperidol and risperidone (both 2–8 mg but dose ‘should not exceed 4 mg by week 2’). Mean daily dose: risperidone 3.8 mg and haloperidol 3.7 mg.</td>
<td>AIMS, HAS, SAS</td>
<td>Prevalence of SAS &gt; 0 and AIMS &gt; 0 at endpoint higher for haloperidol than risperidone (SAS: 51.5% vs 43.8%; AIMS: 21.7 vs. 15.0%). No difference in prevalence of HAS &gt; 0 at endpoint (risperidone 28.5% vs. haloperidol 36.9%). Incident rates of all three EPS syndromes higher for haloperidol using one of two definitions (i.e. shift from total score &lt; 1 at baseline to &gt; 1 at endpoint).</td>
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<td>Gaebel et al. (2007)</td>
<td>151</td>
<td>18–60 (mean 31.6)</td>
<td>1 year extension following acute study</td>
<td>Haloperidol and risperidone (2–8 mg). Mean daily dose: risperidone 4.2 mg and haloperidol 4.1 mg.</td>
<td>AIMS, HAS, SAS</td>
<td>No significant differences between two drugs in total scores at endpoint for each scale. AIMS incapacitation item higher at endpoint for haloperidol. Incidence and prevalence rates of TD did not differ significantly though rates were higher for haloperidol.</td>
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<tr>
<td>11. EUFEST</td>
<td>Kahn et al. (2008)</td>
<td>498</td>
<td>18–40 (mean 26.0)</td>
<td>1 year</td>
<td>Haloperidol (1–4 mg), amisulpride (200–800 mg), olanzapine (5–20 mg), quetiapine (200–750 mg) and ziprasidone (40–160 mg). Mean dose before end of treatment was 3.0, 450.8, 12.6, 498.6 and 107.2 mg for these five drugs respectively.</td>
<td>St Hans rating scale</td>
<td>Significant difference between drugs in rate of akathisia (range 10% olanzapine to 28% ziprasidone) and parkinsonism (range 6% olanzapine to 34% haloperidol). Low rates of dyskinesia (0–3%) and dystonia (0–3%) with all agents. See Figure 2.</td>
</tr>
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</table>

aEleven trials were reported as 14 publications. bAll differences are statistically significant unless otherwise stated (i.e. p < 0.05). cSialorrhea item omitted due to association with clozapine. AIMS: Abnormal Involuntary Movements Scale, BAS: Barnes Akathisia Scale, CAFE: Comparison of Atypicals in First Episode Psychosis, EPS: extrapyramidal symptoms, ESRS: Extrapyramidal Symptom Rating Scale, EUFEST: European First-Episode Schizophrenia Trial, GRNS: German Research Network on Schizophrenia, HAS: Hillside Akathisia Scale, LOCF: last observation carried forward, SAS: Simpson-Angus scale, TD: tardive dyskinesia, UKU: Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale. |
assessment point) but some papers also presented prevalence rates (i.e. syndrome present at a specified time irrespective of whether present at baseline). Syndromal definitions varied between studies in terms of the sensitivity threshold adopted. Crespo-Facorro et al. (2006), Lieberman et al. (2003b) and Sanger et al. (1999) defined treatment-emergent parkinsonism as a total score higher than 3 on the SAS at any post-baseline visit (assuming a total score of 3 or less at baseline) and treatment-emergent akathisia as a total score of 2 or more on the BAS (assuming a total score of less than 2 at baseline). McEvoy et al. (2007) defined parkinsonism as a rating ≥ 1 on any SAS item, akathisia as ≥ 2 on the global severity item of the BAS and dyskinesia as ≥ 2 on the global severity item of the AIMS. Robinson et al. (2006) defined parkinsonism as present if two or more items on the SAS were rated 2 or one item was rated 3 or higher. Möller et al. (2008) calculated incidence rates using two different thresholds on the AIMS, BAS and SAS. Gaebel et al. (2007) calculated incidence and prevalence rates of TD using both the Glazer–Morgenstern criteria (total AIMS score ≥ 3 and at least one AIMS item score ≥ 2) (Morgenstern and Glazer, 2009) and the Schooler–Kane criteria, which have a higher threshold (any AIMS item score ≥ 3 or at least two AIMS item scores ≥ 2) (Schooler and Kane, 1982). Schooler et al. (2005) defined emergent dyskinesia using the Schooler-Kane criteria applied to items of the seven-item dyskinetic movement scale of the ESRS. They also calculated rates of persistent dyskinesia, which was defined as meeting the criteria for emergent dyskinesia on two or more consecutive visits.

Nine trials reported on the number of patients prescribed anticholinergic drugs to treat EPS, i.e. a proxy measure of EPS. A smaller number of studies reported prescribing rates for propranolol for akathisia and benzodiazepines which may be prescribed for akathisia or agitation. Several studies reported drop-out due to all adverse effects.

**EPS rating scale outcomes**

Table 2 summarizes the main outcomes seen on rating scales; all drug differences in Table 2 are statistically significant (*p* < 0.05) unless otherwise stated. Seven trials (10 studies) compared haloperidol with one or more SGAs. Using either continuous or categorical analysis, haloperidol was associated with a significantly higher rate and/or severity of parkinsonism in seven trials and of akathisia in six trials at one or more time points versus one or more comparator SGAs. This summary includes the results of the authors’ using Fisher’s exact test to compare the proportion of patients with akathisia and parkinsonism for haloperidol versus each of the SGAs in the trial reported by Khan et al. (2008) (see Figure 2 for details); the publication provided within-group but not pairwise comparisons. One trial, the German Research Network on Schizophrenia (GRNS) trial (Gaebel et al., 2007; Möller et al., 2008), did not find a significant difference in the rate of akathisia between haloperidol and the SGA comparator (risperidone) in the primary analysis (prevalence at eight weeks). However, a secondary analysis (incidence of EPS over eight weeks) showed a significantly higher rate of akathisia with haloperidol (Möller et al., 2008). Two trials reported more marked EPS with higher doses of haloperidol and risperidone (Emsley, 1999; Möller et al., 2008).

The most consistent definition of treatment-emergent parkinsonism was a total score ≥ 3 on the SAS at any post-baseline visit (total score of ≤ 3 at baseline) and for treatment-emergent akathisia a total score of ≥ 2 or more on the BAS (total score < 2 at baseline). These definitions were used in three studies that assessed haloperidol over six or 12 weeks (Crespo-Facorro et al., 2006; Lieberman et al., 2003b; Sanger et al., 1999). In all three studies the incidence of parkinsonism and akathisia in haloperidol-treated patients was approximately 50% over six to 12 weeks, which was approximately double or greater than the rate seen with the SGA comparator(s) with the differences being statistically significant (Table 2).

Five trials, including four with a haloperidol arm, had a duration of one year or more and employed a rating scale to assess dyskinesia (Gaebel et al., 2007; Green et al., 2006; Kahn et al., 2008; McEvoy et al., 2007; Schooler et al., 2005). Green et al. (2006) reported that AIMS scores were similar for haloperidol- and olanzapine-treated patients at three months but greater for the haloperidol group at six months, one year and two years. Schooler et al. (2005) found emergent dyskinesia was more frequent with haloperidol than risperidone (13.4% vs. 8.3%, *p* = 0.05) though persistent dyskinesia did not differ between the two groups. Gaebel et al. (2007) found no significant difference in rates of TD or total AIMS scores between haloperidol and risperidone treated patients, although the haloperidol group had a significantly higher score on the AIMS incapacitation item at one year. Kahn et al. (2008) and McEvoy et al. (2007) found low rates of dyskinesia with all drug groups (< 3% for all antipsychotics) and this included a low-dose (≤ 4 mg) haloperidol group in Kahn et al. (2008). Between-group differences in rates of TD were non-significant in McEvoy et al. (2007) and the number of events was too small for statistical analysis in Kahn et al. (2008). In summary, the results are variable but suggest that haloperidol may have a greater risk of TD than risperidone and olanzapine.

The only study of a low-potency FGA reported a higher parkinsonism (SAS) score with chlorpromazine than clozapine at 12 weeks and one year, though the difference was only significant in a last observation carried forward (LOCF) analysis at 12 weeks (Lieberman et al., 2003a). Dystonia and akathisia were significantly more frequent with chlorpromazine over one year of follow-up. The only study of a medium-potency FGA reported a higher ESRS score at the 13-week end point for zuclopenthixol versus risperidone (Glenthøj et al., 2007).

Four trials compared two or more SGAs but none reported a significant difference in EPS ratings between individual SGAs.

Figure 1. Number of RCTs assessing antipsychotics in first episode psychosis and reporting on EPS (three RCTs led to > 1 publication).

![Figure 1](image-url)
Crespo-Facorro et al., 2006, 2011; Khan et al., 2008; McEvoy et al., 2007; Robinson et al., 2006). Robinson et al. (2006) noted a non-significant trend favouring olanzapine over risperidone in scores on the SAS and BAS. The European First Episode Schizophrenia Trial (EUFEST) reported by Khan et al. (2008) compared low dose haloperidol (≤4 mg) and four SGAs (Kahn et al., 2008). Rates of parkinsonism and akathisia differed significantly between antipsychotics but pairwise analyses were not reported (Figure 2). The small number of cases of dyskinesia and dystonia prevented statistical analysis. The high rate of akathisia with ziprasidone (28%) was notable.

Concomitant medication use and drop-outs due to side effects

Of the seven haloperidol trials, five found that anticholinergic use was significantly higher with haloperidol versus the SGA comparators and two trials found no significant difference (Figure 3). The rate of anticholinergic prescribing with haloperidol ranged from 34.7% (Möller et al., 2008) to 75% (Emsley, 1999). With regard to other FGAs, Glenthoj et al. (2007) reported significantly higher anticholinergic use with zuclopenthixol versus risperidone. This was despite dose reduction of the antipsychotic being the preferred method to treat EPS in this study rather than the prescription of an anticholinergic.

Three trials reported on the use of propranolol for akathisia, of which two reported significantly high prescribing rates for patients treated with haloperidol versus a SGA comparator, olanzapine in Lieberman et al. (2003b) and risperidone in Schooler et al., (2005). The third trial (Möller et al., 2008) compared haloperidol and risperidone and found no significant difference in the rate of prescribing of propranolol. Four haloperidol trials reported on benzodiazepine use; rates differed in one study, being higher with haloperidol than olanzapine (Lieberman et al., 2003b).

Of four trials with two or more SGA cohorts, only one reported a significant difference in concomitant medication prescribing between SGAs. McEvoy et al. (2007) found that more patients treated with olanzapine received medications for parkinsonism or akathisia than those treated with quetiapine (11% vs. 4%). Robinson et al. (2006) reported a trend for lower prescribing of anticholinergics and propranolol with olanzapine versus risperidone.

Two remaining trials (Crespo-Facorro et al., 2006, 2011; Khan et al., 2008) included a haloperidol arm as well as two or more SGAs (Figure 3). Rates of anticholinergic prescribing varied significantly between groups in both studies, being highest with haloperidol, but neither study reported pairwise comparisons between SGA cohorts.

Total drop-outs due to adverse effects were significantly greater with haloperidol than the SGA comparators in five trials (Emsley, 1999, Green et al., 2006, Kahn et al., 2008; Möller et al., 2008; Sanger et al., 1999) and no different in two trials (Crespo-Facorro et al., 2006; Schooler et al., 2005). Lieberman et al. (2003b) reported significantly more drop-outs due to EPS over eight weeks for haloperidol versus olanzapine.

EPS risk in first episode versus chronic patients

Sanger et al. (1999) conducted a sub-analysis of 83 patients with FEP who had taken part in a large, multicentre, 14 month double-blind trial of olanzapine versus haloperidol (total n = 196) in schizophrenia (Tollefson et al., 1997). Data from the initial six-week acute phase of this study was used to compare the FEP patients (n = 83) with the remaining, multiple episode, patients (n = 1913). The difference in mean age between the two groups...
was 10.5 years. The analysis by Sanger et al. (1999) has the advantage that the same EPS scales and analysis were applied to first episode and multi-episode patients.

For haloperidol treatment, first episode patients experienced a significantly greater increase than multiple episode patients in SAS total scores from baseline to endpoint (4.5 vs. 0.7; \( p < 0.001 \)). In addition, treatment-emergent hypertonia and hypokinesia, both features of parkinsonism, were significantly more frequent in the haloperidol-treated first-episode patients than in the haloperidol-treated multiple-episode patients. These differences occurred despite the mean modal dose of haloperidol being lower in the first-episode group compared with the multiple-episode group (10.8 vs. 12.7 mg/day). In summary, first-episode patients were more likely to experience parkinsonian symptoms with haloperidol treatment than were multiple-episode patients. No difference was seen between the first-episode and multiple-episode patients in baseline to endpoint scores on the BAS with haloperidol treatment. No difference was seen between first-episode and multiple-episode patients treated with olanzapine in change from baseline to endpoint scores on the SAS or BAS.

**Discussion**

**Strengths and weaknesses**

In terms of strengths, the decision to review only randomized studies reduces the impact of confounding factors on the rates of EPS. Seven of the 11 trials were double blind, which reduces rater and patient bias. We considered specific EPS (akathisia, parkinsonism, dyskinesia, dystonia) and reported on a range of outcomes including changes on EPS rating scales, the incidence of emergent syndromes, the rate of prescribing of anticholinergics, propranolol and benzodiazepines, and drop-outs due to side effects. In contrast an earlier meta-analysis of antipsychotic treatment in FEP restricted its review of EPS to parkinsonism (Crossley et al., 2010).

With regard to weaknesses, most of the trials had some industry involvement and this may impact on the results that are presented. Some trials employed doses of antipsychotics that in current practice would be regarded as high in FEP, e.g. the mean modal dose of haloperidol was 10.8 mg in Sanger et al. (1999) and the mean dose of risperidone was 6.1 mg in Emsley (1999). However, in most trials the mean drug doses were clinically appropriate to a first-episode population. In two studies (Kahn et al., 2008; Schooler et al., 2005) the maximum dose of haloperidol was \( \leq 4 \text{ mg/day} \) other than in exceptional cases in one trial (Schooler et al., 2005). Seven of the nine trials with a FGA arm used haloperidol, a high-potency drug, which limits the conclusions that can be drawn about other FGAs. There were no studies of aripiprazole, a dopamine partial agonist and relatively new SGA.

Trials varied in the EPS rating scales used and their analysis of data. In one trial the method of EPS analysis differed in two publications that related to different periods of follow-up (Gaebel et al., 2007; Möller et al., 2008). Lack of consistency has been noted in the reporting of other antipsychotic adverse effects and makes it difficult to make cross-study comparisons (Hamer and Haddad, 2007; Pope et al., 2010). It probably accounts for most meta-analyses of antipsychotic treatment providing comparatively little data on side effects and tending to concentrate on efficacy where trials are more consistent in assessment and reporting of data.

The use of the worst post-randomization value for each subject on a rating scale at any point during a study has advantages, particularly in short-term studies. EPS are likely to be treated, for example with an anticholinergic agent or by reducing the dose of the antipsychotic, leading to a reduction in severity. An analysis of the last observed value on a rating scale will ignore the impact of treatment and may obscure differences between antipsychotics.
Conversely, worst post-randomization data may mean that transient differences between drugs that occur early on in a study are given undue prominence later on. Therefore in long-term studies the change in a rating scale from baseline to endpoint is likely to be more clinically relevant. Rates of treatment-emergent EPS and prescribing rates for concomitant medication will often be more relevant to clinicians and patients than continuous outcome data. In summary, no single EPS measure is ideal and a range of outcomes is needed.

**Rates of EPS**

A potential confounder in studies of drug-induced EPS in FEP is that Parkinsonism and dyskinesia occur in antipsychotic-naïve first-episode patients (Pappa and Dazzan, 2008). This suggests that neurotransfunction of key motor areas is part of the underlying pathophysiology of schizophrenia. As this review examined randomized studies, spontaneous extrapyramidal symptoms are unlikely to affect conclusions about the relative risk of EPS with different antipsychotics, though they may inflate prevalence rates.

A key finding of the review is that haloperidol had a high risk of causing Parkinsonism and akathisia. Six of the seven haloperidol studies showed higher rates/severity of both syndromes as assessed by a standard rating scale at one or more time points versus at least one SGA comparator. This included two low-dose haloperidol studies (maximum dose ≤ 4 mg) indicating that this is not simply an artefact of trials using inappropriately high doses of haloperidol. The data is consistent with a meta-analysis, largely in chronic schizophrenic first-episode patients (Pappa and Dazzan, 2008). This suggests that haloperidol was approximately double or greater than those seen with SGAs (Creso-Facorro et al., 2006; Lieberman et al., 2003a; Sanger et al., 1999). The anticholinergic prescribing data (Figure 3) supports the view that the higher EPS risk with haloperidol was clinically significant. The higher drop-out rate due to all side effects seen with haloperidol in several studies raises the possibility that the increased EPS burden with haloperidol may have led to discontinuation of treatment.

Assessment of TD requires studies lasting a year or more. Four haloperidol trials were a year or more in length and incorporated an assessment of TD. Two trials reported higher rates of dyskinesia with haloperidol versus risperidone (Schooler et al., 2005) and olanzapine (Green et al., 2006). The first trial employed a low dose of haloperidol. The two remaining long-term trials showed no significant difference in rates of dyskinesia for haloperidol versus comparator SGAs (Gaebel et al., 2007; Kahn et al., 2008). The results are variable but suggest that in patients with FEP haloperidol may have a greater risk of causing TD than risperidone and olanzapine. This is consistent with a meta-analysis of patients with chronic schizophrenia that showed a higher risk of TD with haloperidol versus SGAs (Correll et al., 2004). The only study to assess a low-potency FGA showed an EPS-advantage for clozapine over chlorpromazine over one year despite the use of prophylactic benztpine in the chlorpromazine group and a maximum dose of chlorpromazine of 400 mg (Lieberman et al., 2003a). A nine-year follow up, largely naturalistic, of patients from this trial has recently been published (Girgis et al., 2011). Among the 29 patients who remained on chlorpromazine or clozapine for nine years, one person on clozapine (4.8%) and two on chlorpromazine (25%) developed TD (p = 0.18). Glenthoj et al. (2007) reported an EPS-advantage for risperidone over zuclopenthixol, a medium-potency FGA, though only in a small, short-term and open study. The results of Lieberman et al. (2003a) and Glenthoj et al. (2007) are consistent with Leucht et al. (2009), who found that clozapine and risperidone were associated with a small EPS advantage over low potency FGAs in a meta-analysis based largely on patients with chronic schizophrenia.

There was little evidence of EPS differences between SGAs either in terms of rating scales or concomitant prescribing. A high rate of akathisia was seen with ziprasidone in EUFEST (Kahn et al., 2008) and concomitant medication use suggested a slight EPS advantage for quetiapine over olanzapine (McEvoy et al., 2007) and olanzapine versus risperidone (Crespo-Facorro et al., 2006, 2011; Robinson et al., 2006). These tentative differences are consistent with those seen in large meta-analyses, predominantly in patients with chronic schizophrenia (e.g. Komossa et al., 2010; Rummel-Kluge et al., 2010a). Nevertheless even in these analyses, differences in EPS-risk between SGAs are relatively small in relation to differences for other side effects such as weight gain (Rummel-Kluge et al., 2010b). The relative lack of EPS differences in our analysis may partly reflect the use of low doses. For example in the CAFE study the mean dose of olanzapine was 11.7 mg and the mean dose of risperidone was 2.4 mg (McEvoy et al., 2007).

Three studies reported on dystonia (Kahn et al., 2008; Lieberman et al., 2003a; Schooler et al., 2005). The only significant difference between comparator drugs was a lower rate of dystonia with clozapine versus chlorpromazine (Lieberman et al., 2003a). Dystonia was uncommon in all drug cohorts in the EUFEST study including haloperidol (1%), possibly reflecting the low mean dose of haloperidol (3 mg) (Kahn et al., 2008). Methodological issues may contribute to the under-reporting of dystonia in trials. There is no specific dystonia rating scale, although the ESRS and St Hans rating scale have a dystonia item. Other studies rely on reported adverse events to identify the occurrence of dystonic reactions. Acute dystonia is a transient syndrome, often lasting only a few hours, in contrast to other extrapyramidal syndromes that tend to be persistent and this may contribute to under-reporting.

**Implications for clinical practice**

Sanger et al. (1999) showed that haloperidol-treated patients with FEP were more likely than multi-episode patients to develop Parkinsonian symptoms. This needs to be considered alongside studies that suggest that first-episode patients are particularly vulnerable to develop acute dystonia when treated with haloperidol (Aguilar et al., 1994; Boyer et al., 1987). Clinical experience also tends to support the view that patients with FEP are more sensitive to develop EPS and other antipsychotic side effects such as sedation. These data support the recommendation in various guidelines that antipsychotic treatment in FEP should start with a low dose (e.g. Barnes et al., 2011; Moore et al., 2007; NICE, 2009; Royal Australian and New Zealand College of Psychiatrists, 2005).

The differences in EPS-risk between antipsychotics seen in this review may assist patients and clinicians in selecting an antipsychotic, though other factors will influence choice, including the risk of other adverse effects (Haddad and Sharma, 2007).
In particular the EPS advantage of SGAs over FGAs needs to be balanced against a relatively high risk of weight gain and metabolic disturbance with several SGAs, most notably olanzapine (e.g. Green et al., 2006; Kahn et al., 2008; Lieberman et al., 2003b; Robinson et al., 2006). Balancing the benefits against the risk of a range of side effects for different antipsychotics is not simple and is likely to depend on patient to patient. Consequently prescribing decisions are best made on an individual basis involving the clinician and patient.

Regular screening for EPS, and other adverse effects, is required throughout antipsychotic treatment. Screening tools such as the Liverpool University Neuroleptic Side Effect Rating Scale (LUNERS) (Jung et al., 2005) and the Glasgow Antipsychotic Side-effect Scale (GASS) (Waddell and Taylor, 2008) can aid this process. In practice EPS are often undiagnosed and untreated (Mitra and Haddad, 2007; Weiden et al., 1987). Possible explanations include clinicians’ lack of knowledge and skills, being too time-pressured to address this aspect of care, or underestimating the distress that antipsychotic side effects cause.

**Implications for research**

It would be an advantage if future trials adopted a more consistent approach to the assessment and reporting of EPS as well as other antipsychotic side effects. This recommendation has been made previously (Hamer and Haddad 2007; Pope et al 2010). This would facilitate comparison of study results and inform clinical decisions about medication choice. This is important as, clozapine apart, antipsychotics differ more in terms of their side effect profiles than efficacy. Guidance from drug licensing bodies and professional organizations could facilitate the introduction of standards for side effect reporting.

The proportion of RCTs in schizophrenia that relate to FEP is small and more studies are needed. Future trials in FEP should not use haloperidol as a FGA comparator given its high risk of EPS, even at low dose. We identified only two RCTs that used a FGA other than haloperidol in FEP. The CATIE study found that in chronic schizophrenia perphenazine, a low potency FGA, had an EPS-liability similar to that of several SGAs but had a relatively low risk of weight gain and metabolic disturbance (Lieberman et al., 2005; Meyer et al., 2008). Further trials of low-potency FGAs are warranted in FEP given that many SGAs carry high risks of weight gain and metabolic disturbance.

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**Conflict of interest**

In the last three years PMH and IBC have received lecture and consultancy fees, as well as conference expenses, from the manufacturers of several antipsychotics, including AstraZeneca, Bristol Myers Squibb, Eli Lilly and Janssen. PMH has also received a lecture fee from Lundbeck.

**References**


