Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis

Nicolas A. Crossley, Miguel Constante, Philip McGuire and Paddy Power

Background
There is an ongoing debate about the use of atypical antipsychotics as a first-line treatment for first-episode psychosis.

Aims
To examine the evidence base for this recommendation.

Method
Meta-analyses of randomised controlled trials in the early phase of psychosis, looking at long-term discontinuation rates, short-term symptom changes, weight gain and extrapyramidal side-effects. Trials were identified using a combination of electronic (Cochrane Central, EMBASE, MEDLINE and PsycINFO) and manual searches.

Results
Fifteen randomised controlled trials with a total of 2522 participants were included. No significant differences between atypical and typical drugs were found for discontinuation rates (odds ratio (OR) = 0.7, 95% CI 0.4 to 1.2) or effect on symptoms (standardised mean difference (SMD) = –0.1, 95% CI –0.2 to 0.02). Participants on atypical antipsychotics gained 2.1 kg (95% CI 0.1 to 4.1) more weight than those on typicals, whereas those on typicals experienced more extrapyramidal side-effects (SMD = –0.4, 95% CI –0.5 to –0.2).

Conclusions
There was no evidence for differences in efficacy between atypical and typical antipsychotics, but there was a clear difference in the side-effect profile.

Declaration of interest
None.

Over the past decade, atypical (or second-generation) antipsychotics have been increasingly used in the treatment of schizophrenia in preference to ‘conventional’ typical (first-generation) drugs. However, meta-analyses of clinical trials in participants with chronic schizophrenia have suggested a limited advantage of the newer agents in terms of efficacy and two recent large trials failed to find a difference between these two classes of antipsychotics. Furthermore, economic analyses have raised doubts about the cost-effectiveness of the newer drugs. Cost is an important factor for low- and middle-income countries, particularly if, as suggested by a previous meta-analysis, the cost of treatment could partly explain the inverse association between longer duration of untreated psychosis and per capita income. In this context, it has been suggested that typical antipsychotics are as useful as atypicals in the treatment of schizophrenia.

Individuals presenting with a first episode of schizophrenia differ from those in whom the disorder is well established in that a higher proportion show a good symptomatic response. Moreover, the dose of antipsychotics required to achieve symptomatic remission is usually lower than in individuals with chronic schizophrenia, and those with a first episode are more susceptible to extrapyramidal side-effects. Their younger age also puts them at risk of longer exposure to the potential metabolic complications of newer antipsychotics. Avoiding adverse effects when individuals first start treatment is particularly important as it may colour their attitude to medication and psychiatric treatment more generally thereafter. Antipsychotics with a benign side-effect profile thus offer an advantage in this phase of schizophrenia. This is particularly important considering the high rates of non-adherence to medication in this population, reported to be as high as 50%. Regarding the question whether atypical or typical antipsychotics are better for this population a Cochrane meta-analysis from 2003 found that there was not enough evidence at that time to make recommendations.

In the UK, a recent update to the National Institute for Health and Clinical Excellence (NICE) guideline has moved away from the previous recommendation of atypical antipsychotics as a first-line treatment in people presenting with a first episode of psychosis. We performed a meta-analysis to look at the efficacy and side-effects of atypical versus typical antipsychotics in the treatment of the early phase of psychosis.

Method
We included randomised controlled trials comparing atypical and typical antipsychotics in individuals in the early phase of psychosis. To be included in the meta-analysis, studies had to use a validated diagnostic system and explicitly define whether their participants were antipsychotic naive, experiencing a first episode of psychosis or were in the early phase of psychosis. We expected to find varying definitions of first episode and early psychosis, and therefore we accepted any definitions used and modelled the effects of the different duration of illness in the analyses. We excluded studies that recruited only participants with an affective psychosis, or individuals younger than 13 or older than 65 years of age. Studies needed to report at least one of the following outcomes: adherence with antipsychotic medication, symptom scales, weight or any validated measure of extrapyramidal side-effects.

In line with a recent long-term study, we selected ‘discontinuation for any cause’ at 12 months of the assigned antipsychotic (or when this was not reported, between 6–24 months), which includes drug efficacy and tolerance, as our primary measure of effectiveness. We also selected a measure of medication efficacy consisting of symptom scores at 12 weeks (or when this was not reported, between 6–18 weeks), as this is the time point at which a previous study showed that 90% of individuals with a first episode who responded to medication achieved symptomatic remission. When more than one symptom scale was reported, we chose to use the Positive and Negative Syndrome Scale (PANSS) first, then the Brief Psychiatric Rating Scale (BPRS)
and then any other validated scale. Two major groups of side-effects were assessed: weight gain and extrapyramidal side-effects, using the last reported observation of each study. When studies reported more than one arm of atypical or typical antipsychotics, effect sizes and variances of the different drugs were pooled together per group using number of participants as a weight factor.

Pertinent randomised controlled trials were identified using an electronic and a hand-based search. A computer-based search was performed using the following databases: MEDLINE (1966 to 20th January 2009), EMBASE (1980 to January Week 3 2009), PsycINFO (1806 to January Week 2 2009) and Cochrane CENTRAL (The Cochrane Library 2008, Issue 4). No language constraints were applied. Subject headings including Psychosis, Schizophrenia, and Atypical Antipsychotic Agent were used as well as text words such as ‘first episode’, ‘never medicated’, ‘naïve’ and names of atypical antipsychotics. Details of the search strategy can be found in the online supplement. Two of the authors (N.A.C. and M.C.) independently reviewed all the identified abstracts from the electronic search, selected the studies included and extracted the data. Any conflicts were discussed with a third reviewer (P.P.).

References of the identified studies and published reviews on pharmacological management of first-episode psychosis were also searched. One of the authors (N.A.C.) undertook to hand-search data of published abstracts of the 3rd to 5th Conference on Early Psychosis and 8th to 14th Biennial Winter Workshop on Schizophrenia to complement the electronic search. Authors were contacted if data were missing.

As we anticipated different definitions of early psychosis or first-episode psychosis we expected to find significant clinical heterogeneity among the studies and therefore decided that using a random-effects analysis would be appropriate. When looking at adherence rates for antipsychotic medication, we preferred to use odds ratios instead of ratio risks in spite of their more difficult interpretation. This allowed us to avoid giving too much weight to trials with high event rates. For continuous variables, weighted means or standardised mean differences using Hedges’ g were used. The latter was used when more than one scale was reported in the outcomes. Heterogeneity was explored using χ². I² is another measure of heterogeneity that refers to the proportion of the variance explained by the between-trial variance. Due to the easiness in the interpretation, it is also reported in this study. We used meta-regression to look at potential confounders in our summary measure. Knowing that we would find a limited amount of trials to include in each comparison, we only performed the regression if the variable being controlled for was reported in all the included studies. We used meta-regressions to look at the effects of the dose of typical antipsychotic used and the proportion of antipsychotic-naïve participants included. The European First-Episode Schizophrenia Trial (EUFEST) suggested that masking status might cause a bias in discontinuation rates (e.g. unmasked clinicians might discontinue typical drugs sooner than atypicals if complications arose). Masking status was therefore also included in the model for discontinuation rates. For the side-effects analysis, we included the assessment point in time. Given the known difference in side-effect profiles for some atypicals, we also included in the regression the proportion of participants taking olanzapine or clozapine when looking at weight gain, and amisulpride or risperidone when looking at extrapyramidal symptoms. In order to avoid spurious results by overfitting the data (e.g. when more than one factor was reported in all the studies), we opted for a repeated univariate meta-regression rather than a multiple regression approach. Results of these meta-regressions should be considered exploratory because of the multiple comparisons performed.

Publication bias was explored using Egger’s test. All analyses were done using STATA 10.0 running in Windows XP.

**Results**

Combined searches of the four databases yielded 1053 references. In total 105 articles were retrieved for further assessment from which 14 different randomised controlled trials were identified. Two further trials were identified in the manual search, one of which could not be included because of a lack of data (the trial looked at ziprasidonie versus haloperidol and was published as a conference abstract). As a result, we included 15 randomised controlled trials that recruited a total of 2522 patients. Figure 1 summarises the study selection and exclusion process.

Risperidone was used in nine studies as the atypical antipsychotic, olanzapine was used in seven trials, and two studies used quetiapine and clozapine. Amisulpride and ziprasidone were used in one study. Twelve of the fifteen studies used haloperidol as the first-generation antipsychotic. The other three studies used chlorpromazine, oral zuclopenthixol and sulpiride. All but one study reported using low doses of typical antipsychotic, below the usually described cut-off point of 12 mg of haloperidol or equivalent. Eight studies reported using doses lower than haloperidol 5 mg, accounting for more than two-thirds of the total sample of participants treated with typical antipsychotics included in this review. Characteristics of the included trials and selected references are shown in online Table DS1.

Seven studies reported long-term data of discontinuation rates suitable for pooling, with a total of 1823 participants. Studies used different definitions of discontinuation, but most reported that participants were considered as discontinuing the drug due to

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**Fig. 1** Flowchart of study selection. RCT, randomised controlled study.
side-effects or lack of response among other reasons. Only one study considered discontinuation rates as their primary outcome and explicitly defined how they measured it.\textsuperscript{22} There was a non-significant greater proportion of individuals prescribed atypical antipsychotics who were adherent around 1 year (Fig. 2, odds ratio (OR) = 0.73, P = 0.22). On visual inspection, results appeared to differ between the different studies and not surprisingly, heterogeneity was significant as assessed with $\chi^2$ ($P < 0.001$). There is an outlier finding from a small study that used quetiapine,\textsuperscript{35} and excluding this study did not change the overall result (OR = 0.64, $P = 0.09$) and had little effect on the heterogeneity observed. Masking status was reported in all seven studies. A meta-regression including masking status as the independent variable and the odds ratio of each study as the dependent variable was non-significant. In other words, masking status was not a significant moderator of the effect sizes of the studies included.

For the short-term symptomatic outcome, 12 trials were pooled with a total of 1949 participants. Most studies reported PANSS scores, although a few reported BPRS scores. Therefore standardised effect sizes were pooled. A small non-significant trend favouring atypicals was found (s.d. = 0.1, $P = 0.12$) as shown in Fig. 3. Heterogeneity was not statistically significant in the comparison according to $\chi^2$ ($P = 0.17$). Since there was no significant heterogeneity found, we repeated the analysis with a fixed-effect approach as some authors have suggested, but the difference remained non-significant (s.d. = −0.08, 95% CI = −0.17 to 0.02). We performed a meta-regression using the dose of atypical as a covariate of the effect size. There was a non-significant trend for comparisons that used higher doses of typical antipsychotics to report larger effect sizes that favoured atypicals (1 mg of haloperidol equivalent accounting for standardised mean difference (SMD) = 0.02 favouring atypicals, $P = 0.09$).

For weight gain, a total of seven studies were pooled including 1444 participants. Pooling of the seven studies showed that individuals on atypical antipsychotics gained an extra 2.1 kg compared with those on typical antipsychotics (P = 0.04, Fig. 4). Heterogeneity was present according to $\chi^2$ ($P < 0.001$). One of the trials\textsuperscript{27,37} reported body mass index (BMI) instead of weight. In order to include this outcome with the rest of the studies, participants’ BMIs were transformed to kilograms assuming that everyone’s height was 1.70 m (an assumption that probably decreased its variance). Excluding this study from the analysis had little effect on the results and only marginally decreased heterogeneity ($I^2$ decreased from 80 to 74%). Meta-regressions were performed using the following covariates: amount of time exposed, typical doses, and percentage of participants receiving olanzapine or clozapine. None of these factors reached statistical significance.

For an analysis of extrapyramidal side-effects, nine studies with 1341 participants were pooled. As described previously, most of the studies utilised the high-potency antipsychotic haloperidol and only two used zuclopenthixol and chlorpromazine. Rating scales reported varied, with five studies using the Simpson–Angus Scale (SAS),\textsuperscript{13,28,30,36,38} three studies the Extrapyramidal Symptom Rating Scale (ESRS),\textsuperscript{24,26,39} and one the St Hans Rating Scale for Extrapyramidal Syndrome (SHRS).\textsuperscript{22} There are differences between the rating scales, but all of them include an objective evaluation of parkinsonism. The SHRS and ESRS both rate dystonia and akathisia, and the latter also includes a...
any statistically significant results. Exclusion of the two studies
antipsychotics, amount of time exposed, and proportion of
to as in Kahn
the assigned antipsychotic than prescribed for a period of 2 weeks
adherence to a medication regime (e.g., taking lower doses of
definitions of discontinuation ranged from irregularities in the
seems an appealing concept reflecting both efficacy of a drug
Main findings
Discussion

Discussion
We did not find a significant difference between atypical and
typical antipsychotics in discontinuation rates. Discontinuation
seems an appealing concept reflecting both efficacy of a drug
and side-effects, but unfortunately there does not appear to be a
consensus defining what exactly discontinuing a drug is:
definitions of discontinuation ranged from irregularities in the
adherence to a medication regime (e.g., taking lower doses of
the assigned antipsychotic than prescribed for a period of 2 weeks
as in Kahn et al) to total discontinuation of the study drug (as in
Schooler et al) in the studies included in this meta-analysis. It is
possible that a number of factors underpin these variations in
what is defined as ‘discontinuation’ and this could be one of the
causes of the significant statistical heterogeneity present in that
comparison. Since only one study explicitly defined discontinua-
tion in the context of being the primary outcome, we were
not able to analyse whether variation in the definition of discon-
tinuation had an effect on the pooled outcome.

We found no significant difference between atypical and
typical antipsychotics in acute symptomatic effect. Individuals
with first-episode psychosis usually show a good symptomatic
response to antipsychotic treatment, and this may have
introduced a ceiling effect that complicated comparisons.
However, even if additional studies had been included such that
the power of the analysis was increased, the estimated effect size
of s.d. = 0.1 (equivalent to two points on the PANSS scale using
the variance found in the biggest study included) suggests that
even if a significant difference could be identified it may not be
clinically meaningful. A previously published study found that
one-step change in the Clinical Global Improvement scale
(allegedly a more ‘clinically meaningful’ scale) required a 15-point
change on the PANSS. A meta-analysis of treatment in chronic
schizophrenia found an advantage for atypicals only when
compared with high doses of typicals. In the present study,
although the doses of typical antipsychotics prescribed in the
studies we analysed were low, there was a similar trend for
atypicals to be superior when the comparison involved higher
doses of typicals. Although this observation was not significant,
it supports the notion that when using typical antipsychotics in
individuals with a first episode, lower doses of medication are
indicated compared with individuals with chronic schizophrenia.
Although there were no significant differences between
atypicals and typicals in discontinuation rates or symptom
control, we did find differences in their side-effect profile. In line
with previous studies our meta-analysis found that, on
average, participants prescribed an atypical antipsychotic would
gain 2 kg more than those on typicals, whereas those prescribed
a typical antipsychotic would rate 0.4 standard deviations higher
in the extrapyramidal scales (e.g. approximately one extra point
in the SAS if using the data from one of the studies included).
We did not find a correlation between these findings and the
use of specific atypical drugs that have been particularly
associated with weight gain or extrapyramidal side-effects. This
do not mean we can exclude any differences between
the atypicals in their side-effect profiles in first-episode participants
as this meta-analysis was not designed to look at within-class
differences, and our meta-regression analysis was probably
underpowered. As most of the studies we analysed included
haloperidol, there is a possibility that the difference in extra-
pyramidal side-effects between atypicals and low-potency typical
antipsychotics is less marked, as is the case in people with chronic
schizophrenia.

Future research
This meta-analysis leaves many questions unanswered. First, it
would have been interesting to look at differences in relapse rates
between atypicals and typicals. We decided not to pool this
outcome as there were too few studies reporting it. From the
long-term studies included in this meta-analysis, three reported
relapse rates in participants who achieved remission and
one reported readmissions to hospital in participants recruited
from an in-patient unit. Of these four, three reported no
significant differences. The other trial, which was the largest and
longest, reported significantly lower relapse rates with
risperidone compared with haloperidol (42.1% vs. 54.7% respectively),
even though no differences were found in remission and
medication adherence. As relapse is an important determinant
of long-term outcome, this should be a serious consideration in
the choice of antipsychotic. Further large long-term studies
would be needed to verify this study’s findings. Second, some of the most
important risks with antipsychotics such as diabetes (seen with
some atypicals) or tardive dyskinesia (commonly seen with

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardised mean difference</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Emmsley</td>
<td>-0.25 (±0.54 to 0.04)</td>
<td>14.6</td>
</tr>
<tr>
<td>Sanger</td>
<td>-0.97 (±1.47 to -0.47)</td>
<td>7.0</td>
</tr>
<tr>
<td>Glenthoj</td>
<td>-1.06 (±2.05 to -0.08)</td>
<td>2.1</td>
</tr>
<tr>
<td>Lieberman</td>
<td>-0.13 (±0.44 to 0.58)</td>
<td>13.6</td>
</tr>
<tr>
<td>HGDK</td>
<td>-0.41 (±0.65 to -0.17)</td>
<td>17.6</td>
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<tr>
<td>EPGN</td>
<td>-0.37 (±0.74 to 0.00)</td>
<td>10.7</td>
</tr>
<tr>
<td>Crespo-Facorrot</td>
<td>-0.53 (±0.85 to -0.20)</td>
<td>12.9</td>
</tr>
<tr>
<td>GRNS</td>
<td>-0.21 (±0.53 to 0.11)</td>
<td>13.1</td>
</tr>
<tr>
<td>EUFEST</td>
<td>-0.37 (±0.82 to 0.07)</td>
<td>8.4</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.38 (±0.53 to -0.24)</td>
<td>100.0</td>
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<table>
<thead>
<tr>
<th>Standardised mean difference (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>-0.25 (±0.54 to 0.04)</td>
<td>14.6</td>
</tr>
<tr>
<td>-0.97 (±1.47 to -0.47)</td>
<td>7.0</td>
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<td>-1.06 (±2.05 to -0.08)</td>
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Fig. 5 Extrapyramidal side-effects in both groups using standardised mean differences.
typicals) usually appear after years of exposure to these medications. This makes it exceedingly unlikely that this will ever be studied using randomised controlled trials. However, these serious long-term outcomes should also be considered when deciding upon maintenance medication. Changes in glucose and lipid levels with antipsychotic medication could be seen as an intermediate outcome in metabolic complications, but the small proportion of studies reporting this outcome from the included studies discouraged us to perform a meta-analysis.

Recent criticisms have been raised about the validity of atypical antipsychotics as a group.12,44 This is backed mostly by two recent meta-analyses by Leucht et al, who reported differences within the atypical antipsychotics45 and also when compared with typical antipsychotics.45 As already mentioned, our meta-analysis was not designed to look at differences within the atypical antipsychotics. Nevertheless, it should be noted that almost all the drugs included in this meta-analysis were those that were reported as more effective than their comparisons for chronic schizophrenia in the above mentioned studies (namely olanzapine, risperidone, clozapine and amisulpride).

Implications
This meta-analysis revealed no significant differences between typical and atypical antipsychotics in discontinuation rates or in short-term symptomatic response in individuals with first-episode psychosis. However, treatment with atypical antipsychotics was associated with relatively more weight gain, whereas treatment with typicals was associated with a greater incidence of extra-pyramidal side-effects. Choice of antipsychotic drug in the treatment of first-episode psychosis may thus be more influenced by side-effect profile than efficacy.

References
3 Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; 60: 553–64.
On therapy

Ramy Daoud

I worked in medicine for many years before I was drawn to psychiatry. My encounters with patients with physical ailments prefigured those encounters I would have as a psychiatrist. The cognition of pain. The search for meaning. The elucidation of a story. The laying of hands on where it hurts. The re-cognition of pain. Sometimes I would cut it out. Sometimes I would cover it up. Sometimes I could do neither. In these instances, I am reminded of Mural by the Palestinian poet of exile, Darwish. I find it quite a haunting piece, lingering in the back of my mind before, during, between sessions with patients. A patient knocks at the door of therapy. Therapy: ‘the dialogue of dreamers’ where the patient ‘shuns body and self . . . to finish that first journey towards meaning, which burnt me, and disappeared.’ Disappeared into absence and no space, where ‘nothing hurts at the door of doom’. In no space, and no time, that insistent voice says ‘one day I shall become . . .’. And they come, knocking at the door of therapy. Therapy is a space-time, an enclosure where dis-closure unfolds through language/thoughts (‘one day I shall become a thought’), that threatens to ‘split [the patient’s nascent sense of being like] a burgeoning blade of grass’. A battle-field, between ‘neither being nor nothingness’. Therapy, language, the act of re-telling one’s story turns to me like a sword ‘wresting being from non-being’, that promises an ‘epiphany’. That epiphany that comes on the wings of the words: ‘This is your name’. Darwish’s ‘epiphany’ reminds me of Heidegger’s Da-sein and the ecstasy of temporality. Being which temporalises itself yet unites past, present and future ‘selves’. I believe Darwish wishes to leave this activity of being open: ‘I know this epiphany, and know I’m on my way towards what I don’t know’.

Ramy Daoud is specialty registrar in general adult psychiatry, East Cornwall Community Mental Health Team.
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria (diagnosis; definition of early psychosis)</th>
<th>Duration of psychosis in treatment or % antipsychotic naive</th>
<th>Interventions and doses received (measured if otherwise not stated)</th>
<th>Recruited atypical/typical, n</th>
<th>Length of study</th>
<th>Quality (concealment of sequence of allocation, masking, loss to follow-up or number dropped out reported)</th>
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<tbody>
<tr>
<td>Risperidone Working Group (1999)</td>
<td>DSM-III schizophrenia or schizophreniform disorder aged 15-45 years, no previous antipsychotic treatment</td>
<td>No previous antipsychotic treatment (up to 3 days of emergency treatment allowed)</td>
<td>Risperidone 6.1 mg/haloperidol 5.6 mg</td>
<td>99/84</td>
<td>6 weeks</td>
<td>Unclear if allocation was concealed, described as 'double-blind' 25% reported as non-completers</td>
</tr>
<tr>
<td>Sanger (1999)</td>
<td>DSM-III-R schizophrenia, schizophreniform disorder, or schizoaffective disorder, with BPRS &gt; 18 or intolerance of current antipsychotic therapy and aged &gt; 18 years; first episode of psychosis with a duration of less than 5 years and before 45 years of age</td>
<td>Duration of treatment for psychosis of 13 months (mean)</td>
<td>Olanzapine 11.6 mg/haloperidol 10.8 mg</td>
<td>59/4</td>
<td>6 weeks</td>
<td>Subsample analysis of randomised controlled trial Unclear if allocation was concealed, described as 'double-blind' Original study reported 1.3% of sample was lost to follow-up 49</td>
</tr>
<tr>
<td>Mackeprang (2002–2007)</td>
<td>ICD–10 schizophrenia, antipsychotic-naive patients on their first admission to hospital</td>
<td>All antipsychotic naive</td>
<td>Risperidone 3.6 mg/zuclopenthixol 9.6 mg</td>
<td>15/10</td>
<td>13 weeks</td>
<td>Unclear if allocation was concealed, 'open labelled' LTF 19%</td>
</tr>
<tr>
<td>Lieberman (2003)</td>
<td>DSM-IV schizophrenia or schizophreniform disorder aged 16–40 years and current psychotic symptoms of moderate severity or greater measured by one of the five psychotic symptoms in BPRS, history of psychosis less than 60 months, no prior treatment with antipsychotic medication or a total lifetime usage of &lt; 14 days</td>
<td>All antipsychotic naive</td>
<td>Clozapine 12 mg/placebo 400 mg at 12 weeks, then 300 mg/chlorpromazine plus benzthiazine 200 mg at 12 weeks, then 400 mg (median)</td>
<td>80/80</td>
<td>52 weeks</td>
<td>Described as 'double-blind', and authors confirmed that allocation, masking and treatment was concealed 12% of the participants reported to have dropped out</td>
</tr>
<tr>
<td>De Haan (2003)</td>
<td>DSM-IV schizophrenia aged 17–28 years admitted to adolescent clinic specialising in recent-onset schizophrenia</td>
<td>Duration of illness of 16.5 months (mean), but unclear duration of treatment</td>
<td>Olanzapine 7.5 mg/haloperidol 2.5 mg (fixed doses)</td>
<td>12/12</td>
<td>6 weeks</td>
<td>Unclear if allocation was concealed, described as 'double-blind' 17% dropped out</td>
</tr>
<tr>
<td>HGDH Study Group (2003)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder aged 16–40 years (onset before 35 years), experienced psychotic symptoms for at least 1 month, scored ≥4 on at least two PANSS items or scored ≥5 on one psychosis item, had a CGI severity score ≥4 (moderately ill) and required treatment with antipsychotic drugs on a clinical basis; history of psychosis ≤ 40 months</td>
<td>74% receiving antipsychotic for mean time of 5.9 weeks Rest antipsychotic naive</td>
<td>Olanzapine 9.1 mg in acute phase, 10.2 mg in continuation phase/haloperidol 4.4 mg in acute phase, 4.8 mg in continuation phase</td>
<td>131/132</td>
<td>24 months</td>
<td>Described as 'double-blind', and authors confirmed that allocation, masking and treatment was concealed LTF of 6% reported at 24 months</td>
</tr>
<tr>
<td>Early Psychosis Global Network (EPGN) (2006)</td>
<td>DSM-IV schizophrenia, schizoaffective disorder aged 16–45 years requiring antipsychotic treatment upon enrolment; history of psychosis for &lt; 1 year, less than 12 weeks of cumulative exposure to antipsychotics and no more than two psychiatric hospitalisations for psychosis</td>
<td>31% antipsychotic naive</td>
<td>Risperidone 3.3 mg/haloperidol 2.9 mg</td>
<td>278/277</td>
<td>Follow-up continued until last participant enrolled had completed 2 years of treatment</td>
<td>Unclear if allocation was concealed, described as 'double-blind' LTF of 7% reported</td>
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<tr>
<td>Wu (2003)</td>
<td>DSM-IV schizophrenia aged 18–45 years; first episode of psychosis, no previous antipsychotic exposure</td>
<td>All antipsychotic naive</td>
<td>Clozapine 275.6 mg, olanzapine 13.7 mg, risperidone 4.2 mg/sulpiride 733 mg</td>
<td>83/29</td>
<td>8 weeks</td>
<td>Adequate concealment of allocation, unmasked 7% dropped out</td>
</tr>
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<tr>
<th>Study</th>
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<th>Interventions and doses received (means reported if otherwise not stated)</th>
<th>Recruited atypical/ typical, n</th>
<th>Length of study</th>
<th>Quality (concealment of sequence of allocation, masking, loss to follow-up or number dropped out reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crespo-Facorro (2006)</td>
<td>DSM-IV schizophreniform, schizophrenia, schizoaffective, brief reactive psychosis, schizotypal personality disorder, psychosis not otherwise specified aged 15-60 years, with SAPS psychotic symptoms moderate severity or greater; antipsychotic naive or total lifetime exposure of less than 6 weeks</td>
<td>All antipsychotic naive or with a total lifetime exposure of &lt;6 weeks</td>
<td>Risperidone 4 mg, olanzapine 15.3 mg and haloperidol 5.4 mg in acute phase Risperidone 3.6 mg, olanzapine 10.1 mg and haloperidol 2.9 mg at 1 year</td>
<td>116/56</td>
<td>12 months</td>
<td>Unclear if allocation was concealed, unmasked LTF 11%</td>
</tr>
<tr>
<td>Brewer 2007</td>
<td>First episode of psychosis defined as onset between 16 and 30 years of at least one of the following: (a) delusions; (b) hallucinations; (c) disorder of thinking/speech, other than simple acceleration or retardation; and (d) disorganised, bizarre, or markedly inappropriate behaviour, without previous antipsychotic treatment. Diagnosis of schizophrenia DSM-IV was confirmed at 6 months</td>
<td>All antipsychotic naive</td>
<td>Risperidone 2 mg/haloperidol 2 mg (fixed doses)</td>
<td>3/4</td>
<td>8 weeks</td>
<td>Unclear if allocation was concealed, described as ‘double-blind’ LTF 12.5%</td>
</tr>
<tr>
<td>German Research Network on Schizophrenia (GRNS) (2007)</td>
<td>ICD–10 schizophrenia aged 18-60 years; participants in their first in-patient treatment of psychotic symptoms</td>
<td>57% of the participants had an onset of psychosis less than 6 months before study entry, but unclear duration of treatment</td>
<td>Risperidone 3.8 and 4.2 mg/haloperidol 3.7 mg and 4.1 mg (both in the acute and continuation phase respectively)</td>
<td>146/143</td>
<td>2 years</td>
<td>Described as ‘double-blind’, and authors confirmed that allocation, masking and treatment was concealed 69% reported to have dropped out in the acute phase, 68.2% in continuation trial (including discontinuation of drug)</td>
</tr>
<tr>
<td>Lee (2007)</td>
<td>DSM-IV schizophrenia, antipsychotic naive</td>
<td>Antipsychotic naive</td>
<td>Risperidone 4.1 mg/haloperidol 7.6 mg</td>
<td>10/10</td>
<td>8 weeks</td>
<td>Unclear if allocation was concealed, described as ‘double-blind’</td>
</tr>
<tr>
<td>Saddichha (2008)</td>
<td>DSM-IV schizophrenia; antipsychotic naive</td>
<td>Antipsychotic naive</td>
<td>Risperidone 4.4 mg and olanzapine 16.5 mg/haloperidol 13.4 mg</td>
<td>68/31</td>
<td>6 weeks</td>
<td>Unclear if allocation was concealed, described as ‘double-blind’</td>
</tr>
<tr>
<td>Bustillo (2008)</td>
<td>DSM-IV schizophrenia, schizoaffective or schizophreniform disorder; less than 3 weeks lifetime exposure to antipsychotics.</td>
<td>47% antipsychotic naive</td>
<td>Quetiapine 100–600 mg/haloperidol 2–12 mg (range allowed)</td>
<td>17/15</td>
<td>2 years</td>
<td>Unclear if allocation was concealed, reported to be ‘double-blind’ LTF 28%</td>
</tr>
<tr>
<td>European First-Episode Schizophrenia Trial (EUFEST) (2008)</td>
<td>DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder aged 18-40 years; &lt;2 years of onset of positive symptoms and lifetime exposure of antipsychotics of less than 2 weeks in the last year or 6 weeks at any time</td>
<td>33% antipsychotic naive</td>
<td>Olanzapine 12.6 mg, ziprasidone 107.2 mg, quetiapine 498.6 mg, amisulpride 450.8 mg/haloperidol 3 mg</td>
<td>395/103</td>
<td>12 months</td>
<td>Adequate concealment of allocation sequence, unmasked LTF 31%</td>
</tr>
</tbody>
</table>

LTF, lost to follow-up; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; SAPS, Scale for the Assessment of Positive Symptoms.
a. All references from each selected trial are shown (additional references are cited below).49–59
Additional references


OR setous OR majorpin OR clozapine OR clozaril OR leponex) OR ("Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents"[Pharmacological Action] OR "Risperidone"[Mesh]) OR "olanzapine [Substance Name] OR "olanzapine-fluoxetine combination [Substance Name] OR "9-hydroxy-risperidone [Substance Name] OR "Dopamine Antagonists"[Mesh] OR "Molindone"[Mesh]) OR "typical antipsychotic*" OR "atypical antipsychotic*")) AND (("first episode" OR "first onset" OR "early onset" OR naive OR "never medicated")) AND ((("psychosis OR psychotic OR schizophreni* OR schizoaffective") AND "Schizophrenia and Disorders with Psychotic Features"[Mesh]) OR "Schizophrenia and Disorders with Psychotic Features"[Mesh])

EMBASE

(exp DEPRESSIVE PSYCHOSIS/ or exp MANIC DEPRESSIVE PSYCHOSIS/ or exp PARANOID PSYCHOSIS/ or exp SCHIZOAFFECTIVE PSYCHOSIS/ or exp MANIC PSYCHOSIS/ or exp AFFECTIVE PSYCHOSIS/ or exp ENDogenous PSYCHOSIS/ or exp ACUTE PSYCHOSIS/ or psychosis.mp. or exp PSYCHOSIS/ or schizophrenia.mp. or exp SIMPLE SCHIZOPHRENIA/ or exp PARANOID SCHIZOPHRENIA/ or exp SCHIZOPHRENIA/ or exp CATATONIC SCHIZOPHRENIA/ or exp RESIDUAL SCHIZOPHRENIA/ or exp LATENT SCHIZOPHRENIA/ or exp SCHIZOPHRENIFORM DISORDER/ or (schizophrenic or schizophrenics).mp. [mp=title, subject headings, heading word, original title, device manufacturer, drug manufacturer name]) AND (("first episode" or naive or "never medicated" or (never adj3 (antipsychoti$ or neurolepti$))).mp. [mp=title, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]) AND (exp Ziprasidone/ or exp Quetiapine/ or exp Olanzapine/ or exp Risperidone/ or exp ATYPICAL ANTIPSYCHOTIC AGENT/ or antipsychotics.mp. or exp Clozapine/ or (risperidon$ or quetiapin$ or clozapin$ or olanzapin$ or ziprasidon$).mp. [mp=title, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]) AND (Randomized Controlled Trial/ or random$).mp. [mp=title, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name])

PubMed

((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial*[tw]") OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]) OR (placebo[mh] OR placebo[mh] OR random*[tw] OR random* OR research design[mh] OR double-blind) OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT human[mh]))) AND ((amisulprid* OR amitrex OR demitan* OR disocyan* OR solian* OR sulamid* OR sulamid* OR zyprexa OR olanzapin* OR quetiapin* OR seroquel OR ICI-204636 OR (ICI and 204636) OR ICI204636 OR risperidone OR risperidone OR 9-OH-risperidone OR ziprasidone OR cp-88059 OR abilta OR championyl OR coolspan OR col-sulpir OR digton OR dixobon OR doben OR dogmatil OR domatil OR drownetas OR eglonyl OR equidil OR esusulpid OR guastil OR handad OR kapidire OR lavodina OR lebopride OR luesdan OR miradil OR mirbanil OR misulvan OR neuromyfar OR normum OR omerpan OR piscocon OR quirdnil OR sato OR sernevin OR sicoferol OR sulpiride OR sulpidan OR suprume OR sursumid OR tepavil OR tonofir OR ulpiz OR vipral OR zotepin OR lodopin OR nipolept OR zopite

PsychINFO

(exp DEPRESSIVE PSYCHOSIS/ or exp MANIC DEPRESSIVE PSYCHOSIS/ or exp PARANOID PSYCHOSIS/ or exp SCHIZOAFFECTIVE PSYCHOSIS/ or exp MANIC PSYCHOSIS/ or exp AFFECTIVE PSYCHOSIS/ or exp ENDogenous PSYCHOSIS/ or exp ACUTE PSYCHOSIS/ or psychosis.mp. or exp PSYCHOSIS/ or schizophrenia.mp. or exp SIMPLE SCHIZOPHRENIA/ or exp PARANOID SCHIZOPHRENIA/ or exp SCHIZOPHRENIA/ or exp CATATONIC SCHIZOPHRENIA/ or exp RESIDUAL SCHIZOPHRENIA/ or exp LATENT SCHIZOPHRENIA/ or exp SCHIZOPHRENIFORM DISORDER/ or (schizophrenic or schizophrenics).mp. [mp=title, abstract, heading word, table of contents, key concepts]) AND ("first episode" OR naive OR "never medicated" OR (never adj3 (antipsychoti$ or neurolepti$))).mp. [mp=title, abstract, heading word, table of contents, key concepts]) AND (exp Ziprasidone/ or exp Quetiapine/ or exp Olanzapine/ or exp Risperidone/ or exp ATYPICAL ANTIPSYCHOTIC AGENT/ or antipsychotics.mp. or exp Clozapine/ or (risperidon$ or quetiapin$ or clozapin$ or olanzapin$ or ziprasidon$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]) AND (Randomized Controlled Trial/ or random$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name])
COCHRANE

(MeSH descriptor Psychotic Disorders explode all trees OR (psychosis OR psychotic OR schizophrenia* OR schizoaffective)) AND ("first episode" OR "first onset" OR "early onset" OR naive OR "never medicated") AND (amisulprid OR amitrex OR deniban OR socian OR solian OR sulanid OR sulamid OR zyprex OR olanzapin OR quetiapine OR seroquel OR ICI-204636 OR (ICI and 204636) OR ICI204636 OR risperidone OR risperdal OR 9-OH-risperidone OR ziprasidone OR cp-88059 OR abilit OR championyl OR coolspan OR col-sulpir OR digton OR dixibon OR dober OR dogmatil OR dolmatil OR drominetas OR eglonyl OR equild OR eusulpid OR guastil OR isnamid OR kapiride OR lavodina OR lebopride OR lusedan OR miradol OR mirbanil OR misulvan OR neuromyfar OR normum OR omperan OR psicocen OR quiridil OR sato OR sernevin OR sico- frenol OR sulpiride OR sulpisedan OR suprium OR sursumid OR tepavil OR tonofit OR ulpir OR vpral OR zotepine OR lodopin OR nipolept OR zopite OR setous OR majorpin OR clozapine OR clozaril OR leponex OR "Antipsychotic Agents" OR "Antipsychotic Agents" OR "Risperidone" OR "olanzapine" OR "olanzapine-fluoxetine combination" OR "9-hydroxy-risperidone" OR "Dopamine Antagonists" OR "Molindone" OR "atypical antipsychotic" OR "atypical antipsychotic"
Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis
Nicolas A. Crossley, Miguel Constante, Philip McGuire and Paddy Power
Access the most recent version at DOI: 10.1192/bjp.bp.109.066217

Supplementary Material
Supplementary material can be found at:
http://bjp.rcpsych.org/content/suppl/2010/06/02/196.6.434.DC1

References
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