Health Technology Assessment 2003; Vol. 7: No. 13

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Health Technology Assessment
NHS R&D HTA Programme

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A systematic review of atypical antipsychotic drugs in schizophrenia

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Declared competing interests of the authors: none

Published June 2003

This report should be referenced as follows:

This report should be referenced as follows: Bagnall A-M, Jones L, Ginnelly L, Lewis R, Glanville J, Gilbody S, *et al*. A systematic review of atypical antipsychotic drugs in schizophrenia. *Health Technol Assess* 2003;**7**(13).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/20/01.

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ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Akathisia A movement disorder characterised by subjective feelings of inner restlessness, mental unease or dysphoria.

Anticholinergic Drugs that act to suppress side-effects of the antipsychotic drugs related to acetylcholine.

Antiparkinsonian Drugs that act to suppress the movement disorder or 'parkinsonian' side-effects of antipsychotic drugs, such as poverty of movement and tremor (these symptoms can be similar to those seen in Parkinson's disease).

Atypical antipsychotic Drugs that aim to treat the psychotic symptoms of schizophrenia and are considered to cause fewer movement disorder side-effects than typical antipsychotic drugs. Atypical antipsychotic drugs tend to be newer and therefore more expensive than their typical counterparts. The only definition of 'atypicality' relates to catalepsy in rats.

Cost–utility analysis Estimates of the additional cost per quality-adjusted life-year (QALY) saved or gained.

Dystonia A movement disorder side-effect characterised by unusual and involuntary movements or spasms.

Extrapyramidal syndrome/symptoms A type of movement disorder which can be a side-effect of antipsychotic drugs.

Funnel plot A method of assessing the probable extent of publication bias. The direction of effect found in each study is plotted against the number of participants. It can then be seen if there is an imbalance in the number of smaller studies that show positive or negative results. When publication bias exists fewer studies that are small and have a negative effect in the funnel plot would be expected.

Heterogeneity Differences between studies in terms of drugs or interventions used (either the drugs being investigated or the drugs with which they are compared or the doses used), participants, study setting or outcomes measured. When significant heterogeneity is present, studies should not be statistically combined in a meta-analysis.

Intention-to-treat (ITT) analysis The practice of reporting results for all trial participants who entered a study, rather than just those who remained at the end. Failure to use ITT analysis means that the trial findings may not be representative of all the individuals who entered the study.

Negative symptoms Symptoms of schizophrenia, such as such as poverty of speech, lack of motivation, apathy and inability to express emotions.

Neuroleptic An older name for typical antipsychotic drugs. It literally means 'to grasp the nerve'.

Neuroleptic malignant syndrome (NMS) A rare complication of antipsychotic (neuroleptic) drugs of which fever and muscle rigidity are characteristic when untreated. It can lead to death in about 21% of people.

Positive symptoms Symptoms of schizophrenia, such as hallucinations and delusions.

Publication bias The tendency for studies that show a positive effect for a particular intervention to be published more readily than those that show no effect.

continued

Glossary *contd*

Quality-adjusted life-years (QALYs) An index of survival that is weighted or adjusted by a patient's quality of life during the survival period.

Relative risk (RR) A measure of the likelihood of a certain event occurring in a group of people taking one intervention versus another. An RR > 1.00 means that a group is more at risk for a particular event and an RR < 1.00 means a group is less at risk (sometimes referred to as the risk ratio).

Schizoaffective disorder An illness characterised by both psychotic and mood symptoms in which patients do not clearly meet diagnostic criteria for either schizophrenia or a major mood disorder.

Schizophrenia An illness characterised by delusions and hallucinations, cognitive disturbances and negative symptoms (see above). Mood disturbances are also common. It has been suggested that schizophrenia is a blanket term used to cover several different illnesses that share some common features.

Schizophreniform disorder An illness in which patients manifest the symptoms of an acute episode of schizophrenia but make a complete recovery, with the whole episode lasting no more than 6 months.

Tardive dyskinesia Abnormal, repetitive and involuntary movements around the mouth, face and extremities.

Typical antipsychotic Drugs that aim to treat the psychotic symptoms of schizophrenia and which generally act on dopamine receptors in the brain. Typical antipsychotic drugs are considered to cause more movement disorder side-effects than atypical antipsychotic drugs. They tend to be older and less expensive than their atypical counterparts.

List of abbreviations

ACT	assertive community treatment
AIMS	Abnormal Involuntary Movement Scale
AMDP	Association for Methodology and Documentation [adverse events questionnaire]
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BAS	Barnes Akathisia Scale
b.d.	twice daily (*bis diem*)
BPRS	British Psychiatric Rating Scale
CGI-I/ -S	Clinical Global Impression–Improvement/–Severity
CI	confidence interval
CIPS	(app 3)
CONSORT	Consolidated Standards for Reporting of Trials
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms [dictionary]
CSF	cerebrospinal fluid
DAI	Drug Awareness Inventory
df	degrees of freedom
DOTES	Dosage Record and Treatment Emergent Symptom Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders [American Psychiatric Association]
EPS	extrapyramidal syndrome
ESRS	Extrapyramidal Syndrome Rating Scale
FSQ	Functional Status Questionnaire
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GCIS	General Cognitive Index Score
GP	general practitioner
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IRR	incidence rate ratio
ITT	intention-to-treat
MADRS	Montgomery–Asberg Depression Rating Scale
MD	mean difference
NICE	National Institute for Clinical Excellence
NMS	neuroleptic malignant syndrome
NOSIE	Nurses' Observation Scale for Inpatient Evaluation
OR	odds ratio
PAS	patient administration system
PANSS	Positive and Negative Symptoms Scale
PGI	Patient Global Impression
QALY	quality-adjusted life-year
QLS	Quality of Life Scale
RCT	randomised controlled trial
RR	relative risk/risk ratio
SANS	Scale for Assessment of Negative Symptoms
SAPS	Simplified Acute Physiology Score
SAS	Simpson–Angus Scale (or Index)
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-36	Short Form with 36 items

continued

List of abbreviations *contd*

SGPT/ALT	serum glutamate pyrovate transaminase/alanine aminotransferase
SMD	standardised mean difference
SMR	standardised mortality ratio
UKU	Udvalg fuer Kliniske Undersogelser
VAS	visual analogue scale
WAIS	Weschler Adult Intelligence Scale
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The clinical effectiveness, safety and cost-effectiveness of 'atypical' antipsychotic drugs in schizophrenia were compared with conventional antipsychotic drugs, placebo and other atypical antipsychotic drugs.

As secondary objectives, the response was investigated in those with 'treatment-resistant' schizophrenia, with predominantly negative symptoms or experiencing their first episode of schizophrenia.

Methods

Data sources

Existing Cochrane reviews were updated with relevant randomised controlled trials (RCTs) found from comprehensive literature searches. Search strategies focused on retrieving RCTs of atypical antipsychotic drugs and non-randomised studies of rare or long-term adverse events. In addition to extensive database searching, ongoing trial registers were searched and the reference lists of retrieved papers scanned.

A systematic review of cost-effectiveness was undertaken using the same sources. In addition, an economic model was constructed using data from the systematic review of clinical effectiveness.

Inclusion criteria

Effectiveness studies

- RCT
- Individuals with schizophrenia, however diagnosed.
- Use of 'atypical' antipsychotic medications.
- Reporting of clinical, economic or social/functional outcomes.

Safety (non-randomised) studies

- Case–control design or at least 2 years follow-up or at least 2000 participants.
- One of following outcomes reported: mortality, tardive dyskinesia, neuroleptic malignant syndrome, agranulocytosis, seizures, weight gain, hepatic dysfunction, cardiac problems.

Two reviewers independently assessed studies for inclusion, any discrepancies being resolved by discussion and, if necessary, a third reviewer.

The inclusion criteria for existing reviews were based on the criteria devised by the NHS Centre for Reviews and Dissemination (CRD) and used in the Database for Abstracts of Reviews of Effectiveness (DARE).

Data extraction

Two reviewers undertook data extraction independently, any discrepancies being discussed and resolved with reference to the original papers and, if necessary, a third reviewer.

Individuals who left studies early were considered to have had a negative outcome, except in the case of death. The impact of including studies with high attrition rates (25–50%) was analysed in a sensitivity analysis. For studies with greater than 50% attrition, all data were excluded other than the outcome 'leaving the study early'.

A validity assessment for RCTs was undertaken using the following criteria: adequacy of randomisation; adequacy of blinding; comparability of groups at baseline; attrition rate; adequacy of description of withdrawals; adequacy of intention-to-treat data analysis; appropriate dose of comparator drug; adequate washout period.

A validity assessment for non-randomised studies was performed using appropriate CRD checklists.

The validity of existing reviews was summarised using criteria for inclusion in the DARE database.

Data synthesis

For binary outcomes, the pooled relative risk and its 95% confidence interval were calculated for all included RCTs; a fixed-effects model was used.

To investigate the possibility of heterogeneity, a chi-squared test was used, together with visual inspection of graphs. A significance level of < 0.10 was interpreted as evidence of heterogeneity. The studies responsible for the heterogeneity were summated and presented separately, and the possible reasons for the heterogeneity explored.

Data from all included studies were entered, if possible, into a funnel plot (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias. If possible, reviewers entered data in such a way that the area to the left of the line of no effect in the resulting graph indicated a favourable outcome for an atypical antipsychotic drug.

For each non-randomised study, the main results and aspects of study design were summarised.

Results

Literature search

A total of 171 RCTs were included, of which 28 comprised wholly or partly commercial-in-confidence data from drug manufacturers.

Additional safety data were found in 52 non-randomised studies, of which seven (all relating to sertindole) were commercial-in-confidence. In addition to 31 published economic evaluations, six commercial-in-confidence evaluations were submitted.

Validity

Evidence for the effectiveness of new atypical antipsychotic drugs compared with older drugs was, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population with schizophrenia. Evidence for the effectiveness of new atypical antipsychotic drugs compared with each other was limited, as was evidence for their cost-effectiveness in the UK compared with each other and with older drugs. Thus the conclusions are based on limited evidence and should be treated with caution.

There was no evidence for the effectiveness of atypical versus typical antipsychotic drugs for individuals with concurrent substance abuse problems or comorbid mental illness, such as depression. There are few implications for those with related disorders such as schizoaffective and schizophreniform disorders, other than that ziprasidone, risperidone or olanzapine may be effective.

Effectiveness/safety

Atypical versus typical antipsychotic drugs

Effectiveness in controlling psychotic episodes

Risperidone, amisulpride, zotepine, olanzapine and clozapine were all more effective than typical comparators in relieving overall symptoms of schizophrenia. Quetiapine and sertindole were no more or less effective than typical antipsychotic drugs in alleviating overall symptoms of psychosis.

Attrition

In general, fewer individuals from atypical drugs groups left trials early than from typical drugs groups; the exceptions were ziprasidone and zotepine, which suggests that patients found atypical antipsychotic drugs more acceptable.

Side-effects

Movement disorders: all new antipsychotic drugs appeared to cause fewer movement disorder side-effects than typical antipsychotic treatments, although issues such as dose or definition and reporting of symptoms limited the confidence that can be placed in these results.

Sedation: clozapine increased daytime sleepiness (somnolence) or drowsiness compared with typical antipsychotic drugs. Treatment with olanzapine, amisulpride, sertindole and perhaps risperidone, caused less somnolence or drowsiness than typical comparator drugs; the other atypical antipsychotic drugs were no more or less sedating than their typical comparators.

Autonomic effects: side-effects, such as increased salivation, increased temperature and rhinitis (blocked nose), were seen in both clozapine- and sertindole-treated groups. For quetiapine, there was increased incidence of dry mouth. Olanzapine was associated with fewer autonomic effects than typical antipsychotic drugs. Other atypical antipsychotic drugs had similar numbers of autonomic side-effects to their typical comparators.

Gastrointestinal effects: atypical antipsychotic drugs were not significantly better or worse than typical drugs with regard to rates of nausea and vomiting, except for ziprasidone, which caused increased nausea and vomiting, and olanzapine, which caused less nausea and vomiting.

Weight gain: amisulpride, risperidone and sertindole caused weight gain. Ziprasidone, zotepine and, possibly, clozapine and olanzapine did not. It had been suggested that for those with schizophrenia, weight gain impacted negatively on their quality of life but this information was based on a telephone survey which was not rigorous in design.

Prolactin-related problems: for most atypical antipsychotic drugs, the problems related to hyperprolactinaemia, such as gynaecomastia, galactorrhoea, impotence and infertility, were not reported (the exceptions were amisulpride, risperidone and sertindole). This seems to reflect a lack of awareness or concern by those conducting

trials about the distressing nature of such side-effects. The adverse events related to hyperprolactinaemia reported for amisulpride, risperidone and sertindole showed no statistically significant differences from their typical comparators.

Cardiotoxic effects: at least two atypical antipsychotic drugs had potentially fatal effects on cardiac conductance. In the UK, sertindole was withdrawn from the market in 1999 (except for patients already stabilised on it) and, in a long-term follow-up study of clozapine, recipients reported cardiomyopathy or myocarditis at a rate of approximately 3 per 1,000 in physically healthy young adults. However, in non-randomised studies of mortality for both drugs compared with other antipsychotic treatments, an excess in the number of cardiac deaths was not reported.

Atypical versus atypical antipsychotic drugs

The following differences were observed.

- More people taking amisulpride, compared with risperidone, experienced 'agitation'.
- Fewer people treated with clozapine, compared with risperidone, suffered movement disorders, impotence, dry mouth or insomnia.
- Fewer individuals treated with olanzapine, compared with clozapine, suffered nausea and vomiting, orthostatic dizziness, hypersalivation and constipation.
- Compared with olanzapine or risperidone, clozapine caused more fatigue, nausea and vomiting, excess salivation, tachycardia, orthostatic dizziness, constipation and leucocytosis.
- Olanzapine caused more weight gain and dry mouth than risperidone but fewer movement disorders.
- Quetiapine may have been more likely to improve depression than risperidone.
- Zotepine was perhaps more likely to cause movement disorders than clozapine or risperidone.
- Amisulpride may be more effective than risperidone in terms of 'response'.

Treatment-resistant illness

Clozapine was more effective than typical antipsychotic drugs in treating those with treatment-resistant illness.

Negative symptoms

In most trials, the effect of new atypical antipsychotic drugs on negative symptoms was not addressed, which is surprising given the claims made by many manufacturers for their efficacy in treating these symptoms. Clozapine was found to be more effective than typical antipsychotic drugs in improving negative symptoms in those whose illnesses were resistant to conventional treatment. Zotepine also seemed to be more effective on negative symptoms.

First-episode schizophrenia

In one trial of risperidone in first-episode schizophrenia, participants responded similarly to all those with schizophrenia for all the major outcomes of interest. In a trial of olanzapine versus haloperidol, olanzapine was reported to be more effective than haloperidol in treating a subgroup with first-episode psychosis and caused fewer extrapyramidal symptoms; however, the quality of the report was poor. There was no evidence relating to other antipsychotic drugs in first-episode illness.

Schizoaffective disorder

In one trial of risperidone versus haloperidol for treatment of schizoaffective disorder, no differences were found between groups with regard to mental state but risperidone was associated with fewer movement disorder side-effects. In another trial, olanzapine was found to be significantly more effective than haloperidol in improving mental state in a subgroup with schizoaffective disorder.

Cost-effectiveness

Amisulpride was more effective than haloperidol and, if ziprasidone remains unlicensed, represents the most cost-effective atypical antipsychotic drug.

Clozapine was more cost-effective than haloperidol and appeared from the model to be cost-effective compared with other atypical antipsychotic drugs; however, the cost of weekly blood monitoring was not included and the total cost figure is likely to be significantly higher in practice.

Olanzapine was the cheapest atypical antipsychotic drug but may be less effective than the others (not statistically significant). Some side-effects, such as weight gain associated with olanzapine treatment, were not included in the estimation of quality-adjusted life-years (QALYs), hence the effectiveness of olanzapine may have been overestimated.

Quetiapine was not more cost-effective than haloperidol and, compared with other atypical drugs, it was not a cost-effective treatment option (differences are not, however, statistically significant).

Risperidone had the highest costs after amisulpride but was also associated with higher QALYs than other atypical antipsychotic drugs. It did not appear to be superior and was dominated by ziprasidone.

Sertindole was dominated by chlorpromazine (apart from in final-line therapy for which it has better outcomes). Its costs and QALYs were both lower than those for haloperidol. Sertindole did not seem to be superior to other atypical drugs and is dominated (higher costs and lower number of QALYs) by ziprasidone.

Zotepine was cheaper but less effective than haloperidol. It did not appear to be superior to other atypical antipsychotic drugs.

Conclusions

The evidence for the effectiveness of the new atypical antipsychotic drugs was, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population with schizophrenia. Thus all conclusions are based on limited evidence and should be treated with caution. Further research is needed.

However, individuals with schizophrenia may have found new atypical antipsychotic drugs (except for zotepine and ziprasidone) more acceptable than their typical comparators as, in general, fewer of them left trials early. Apart from clozapine for those with treatment-resistant illness, none of the new atypical antipsychotic drugs stands out as being more effective than the others. They all seemed to have slightly different side-effect profiles, which may have varying importance for those with schizophrenia and their carers.

Cost-effectiveness

Given the uncertainty about the validity of the clinical data for typical antipsychotic drugs and what is an acceptable cost/QALY, it was not possible to reach any definite conclusions as to whether the additional costs and benefits represent value for money.

Recommendations for research

1. More useful research is urgently needed: long-term trials involving large numbers of people, less rigid inclusion criteria, and outcomes relevant to those with schizophrenia and their carers should all be of primary concern. Less rigid, more pragmatic trial protocols may help to both decrease trial attrition rates and to increase the generalisability of the results. Outcomes related to prolactin problems and sexual side-effects are particularly poorly reported at present. Funding that is as free of conflicts of interest as possible is justified.
2. Large, long-term RCTs in which atypical antipsychotic drugs are compared with each other would be useful, particularly risperidone versus olanzapine and zotepine versus clozapine.
3. Trials of all atypical antipsychotic drugs, along with other aspects of care, should be undertaken in those with first-episode schizophrenia, treatment-resistant schizophrenia, schizoaffective disorder and predominantly negative symptoms. RCTs are also needed on effects in children and the elderly; on the effectiveness and safety of using more than one antipsychotic drug simultaneously; on whether differences in gender or ethnicity influence response to antipsychotic drugs; and on the impact of adjunctive psychosocial treatments on antipsychotic effectiveness.
4. Future systematic reviews of this topic should include trials in which clinician-determined switching of medication is allowed within the time frame of the study in reaction to poor response or serious side-effects.

Chapter 1
Introduction

How to use this document

This document was written in two stages. A complete systematic review was undertaken for the NHS Health Technology Assessment Programme but, before it could be published, the National Institute for Clinical Excellence (NICE) commissioned an update of the review. Consequently, the studies included in the original review have been incorporated into this publication. This two-step process and the sheer size of the review have resulted in a number of unusual features. The results of the effectiveness and safety data for each atypical antipsychotic drug (in alphabetical order) are reported in chapters 4–12, while the results of the cost-effectiveness analyses are reported in chapter 13. Within each of the separate drug reports, the numbers of 'new' and 'original' randomised controlled trials (RCTs) are reported separately because the data extraction sheets for the two reviews had slightly different formats. (Following details of the literature search strategy in appendix 1, the data extraction sheets for 'new' RCTs can be found in appendix 2 and for 'original' RCTs in appendix 3.) Data from new and original RCTs are then combined in chapters 5–12. The results of non-randomised safety studies are reported towards the end of each chapter. (The data extraction sheets for the non-randomised safety studies are presented in appendix 4, followed by a validity assessment of the systematic reviews in appendix 5. The data extraction sheets for the economic evaluations are presented in appendix 6.) The discussion of the results (chapter 14) begins with the main findings of the review being summarised on a drug-by-drug basis.

The aims of the review

The primary research objective was as follows.

- To evaluate the clinical effects, safety and cost-effectiveness of novel 'atypical' antipsychotic drugs compared with conventional drugs, placebo and other atypical drugs (note that placebo comparisons were not available for clozapine and risperidone, as these were not included in the Cochrane reviews on which the original report was based).

The secondary objectives were to investigate, where possible:

(i) whether people with schizophrenia that is described as 'treatment-resistant' differ in their response from those whose illness is not designated as such
(ii) whether people having predominantly positive or negative symptoms of schizophrenia are more responsive to 'atypical' antipsychotic drugs than those without this designation
(iii) whether people experiencing their first episode of schizophrenia differ in their response from those at later stages of their illness.

Chapter 2
Background

The underlying health problem and current service provision

Schizophrenia is one of the most common and serious mental illnesses. It is an extremely debilitating condition characterised by delusional and hallucinatory experiences, disordered thought processes and deteriorating social functioning. Its impact on the individual, their families or carers, and society as a whole is considerable. General population surveys[1] record a mean prevalence of about 0.5–1%, with a recent British survey from the Office of Population Censuses and Surveys[2] indicating a point prevalence for psychoses of four per 1000 in adults aged 16–64 years. Although the prognosis for the disorder shows a high degree of individual variation, the outcome for a large proportion of those with schizophrenia is poor, with about 52% suffering lasting impairment with little or no remission.[3]

Until recently, pharmacological therapy centred on the use of dopamine receptor blockers, such as chlorpromazine and haloperidol. These agents have been shown to be more effective than placebo in controlling the positive symptoms of schizophrenia (e.g. hallucinations, delusions) and in moderating acute episodes of schizophrenia in clinical trials.[4,5] However, they appear to have little effect on the negative symptoms (poverty of speech, lack of motivation, apathy and inability to express emotions[6]), which are very disabling and which may respond better to atypical antipsychotic drugs,[7] although this has not as yet been adequately established.[8] In addition, long-term use of conventional antipsychotic drugs is associated with a high risk of debilitating neurological side-effects, notably tardive dyskinesia, as well as shorter-term effects such as akathisia and dystonia. These distressing symptoms not only affect people with schizophrenia directly but are also likely to increase non-compliance with treatment regimens. Although representing a major step forward in the treatment of schizophrenia when initially introduced, the overall impact of conventional antipsychotic drugs is disappointing, given the risk and severity of the side-effects. About 30% of individuals complying with conventional antipsychotic treatment regimens derive little or no benefit in terms of symptom control or reduction, while another 30% gain only partial relief.[9]

In a systematic review of the effects of chlorpromazine versus placebo,[4] it was confirmed that chlorpromazine was effective in reducing relapse over a period of 6 months–2 years and in improving global state (although placebo response rate was 40%); however, the drug was associated with sedation, acute movement disorders, parkinsonism, hypotension and weight gain. A systematic review of haloperidol versus placebo[5] confirmed that haloperidol was also effective in improving global state but was associated with dystonia, akathisia and parkinsonism. The risk of movement disorders seemed to be higher with haloperidol than with risperidone but this was an indirect comparison – the two drugs have not been compared directly in a systematic review.

In response to the problems of conventional therapies outlined above, the pharmaceutical industry has put considerable effort into developing 'atypical' antipsychotic treatments with an improved clinical profile and reduced extrapyramidal side-effects. 'Atypical' is a widely used term to describe those antipsychotic drugs that have a low propensity to produce movement disorders, sedation and raised serum prolactin.[10] In particular, they are promoted as reducing both the negative and positive symptoms of schizophrenia, having a low risk of producing extrapyamidal side-effects and, in the case of clozapine, having the potential to improve the clinical outcome of those who do not respond to first-line treatment with conventional antipsychotic drugs. Early trials with clozapine provided support for this favourable profile of the novel atypical drugs; however, its use in the clinical setting was subsequently hampered by a heightened risk of agranulocytosis, which entailed the introduction of regular blood monitoring for those taking the drug. More recently, pharmaceutical companies have introduced a number of new atypical drugs (e.g. risperidone, olanzapine) that, it is claimed, show the benefits outlined above without the risk of agranulocytosis.

Atypical antipsychotic drugs are now widely used in the treatment of schizophrenia and, with the

introduction of additional atypical agents, this use is likely to increase. At present, there is widespread prescribing of atypical drugs that have not yet been conclusively shown to have clinical advantages over well-established treatment regimens and which, at face value, have substantially higher cost implications. Even assuming that novel atypical drugs have greater effectiveness (including fewer movement disorder side-effects) than conventional treatments, the lack of robust evaluative evidence suggests that clinicians presently lack the necessary information on which to base a rational choice between different atypical drugs.

Cost

Antipsychotic or neuroleptic therapy is the primary method of symptom control and management for the majority of people with schizophrenia. In 1992/93, the direct cost of health and social care for those with schizophrenia was approximately £810 million in England, or 3% of total health service spending. Of this, £32 million was spent on pharmaceuticals, mainly on antipsychotic drugs.[11,12]

The 1990s saw the introduction of new, so-called atypical antipsychotic drugs. Depending on dosage, the cost for clozapine is approximately £2500 per person per year and, for the other newer atypical drugs, risperidone, olanzapine and quetiapine, approximately £1400 per person per year. The cost of older, conventional antipsychotic treatments such as haloperidol or chlorpromazine is significantly lower, at less than £100 per person per year.

The potential impact of these new drugs on pharmacy budgets is substantial. If their use continues to expand, they will increase annual drug expenditure by between £86 million, if reserved for patients with treatment-resistant illness or who are treatment-intolerant, and £242 million, if used for all patients. However, their use may reduce the costs of other healthcare services, such as hospital inpatient care, and may lead to significant improvements in patient outcomes.

A number of economic evaluations have been published but most studies have been limited in both scale and methodology. Thus the results need to be treated with caution when extrapolating to alternative time frames, settings and patient populations. It has been suggested that the quantity and quality of clinical and economic evidence is not sufficient to enable clinical decision-makers to make treatment choices between different drugs with any certainty.[12–14]

Licensed indications, contraindications and warnings

The following information has been adapted from the *British National Formulary*.[15]

Typical antipsychotic drugs

Cautions and contraindications

Antipsychotic drugs should be used with caution in patients with hepatic impairment, renal impairment, cardiovascular disease, Parkinson's disease (which may be exacerbated by antipsychotic drugs), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a personal or family history of angle-closure glaucoma (chlorpromazine, pericyazine and prochlorperazine should be avoided in these conditions). Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (if unexplained infection or fever develops, blood counts should be undertaken). Antipsychotic drugs should be used with caution in the elderly, who are particularly susceptible to postural hypotension and to hyper- or hypothermia in very hot or cold weather. Serious consideration should be given before prescribing these drugs for elderly patients. As photosensitisation may occur at higher dosages, patients should avoid direct sunlight.

Antipsychotic drugs may be contraindicated in comatose states, CNS depression and phaeochromocytoma. Most antipsychotic drugs are best avoided during pregnancy, unless essential, and it is advisable to discontinue breast-feeding during treatment.

Driving: drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol may be enhanced

Withdrawal: withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

Side-effects: extrapyramidal symptoms are the most troublesome. These occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine and trifluoperazine), the butyrophenones (benperidol, and haloperidol), and the depot preparations. The symptoms are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug and

individual susceptibility. Extrapyramidal symptoms consist of:

- parkinsonian symptoms (including tremor), which may occur more commonly in adults or the elderly and may appear gradually
- dystonia (abnormal face and body movements) and dyskinesia, which occur more commonly in children or young adults and appear after only a few doses
- akathisia (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated
- tardive dyskinesia (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops during long-term therapy or at high doses but may develop during short-term treatment at low doses – short-lived tardive dyskinesia may occur after withdrawal of the drug.

Parkinsonian symptoms remit if the drug is withdrawn and may be suppressed by the administration of antimuscarinic drugs. However, routine administration of such drugs is not justified because not all patients are affected and because they may unmask or worsen tardive dyskinesia.

Tardive dyskinesia is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia – fine vermicular movements of the tongue – may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

Hypotension and interference with temperature regulation are dose-related side-effects that are liable to cause dangerous falls and hypo- or hyperthermia in the elderly.

Neuroleptic malignant syndrome (NMS) – hyperthermia, fluctuating level of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence – is a rare but potentially fatal side-effect of some drugs. Discontinuation of the antipsychotic drug is essential because there is no proven effective treatment; however, cooling, bromocriptine and dantrolene have been used. NMS usually lasts for 5–7 days after drug discontinuation, but may be unduly prolonged if depot preparations have been used.

Other side-effects include: drowsiness; apathy; agitation, excitement and insomnia; convulsions; dizziness; headache; confusion; gastrointestinal disturbances; nasal congestion; antimuscarinic symptoms (e.g. dry mouth, constipation, difficulty with micturition, blurred vision); cardiovascular symptoms (e.g. hypotension, tachycardia, arrhythmias); ECG changes (cases of sudden death have occurred); endocrine effects (e.g. menstrual disturbances, galactorrhoea, gynaecomastia, impotence, weight gain); blood dyscrasias (e.g. agranulocytosis, leucopenia); photosensitisation, contact sensitisation and rashes, and jaundice (including cholestatic); corneal and lens opacities; and purplish pigmentation of the skin, cornea, conjunctiva, and retina.

Chlorpromazine
Indications: schizophrenia and other psychoses, mania, short-term adjunctive management of severe anxiety, psychomotor agitation, excitement and violent or dangerously impulsive behaviour.

Cautions: see notes above; also patients should remain supine and the blood pressure should be monitored for 30 minutes after intramuscular injection.

Contraindications: see notes above.

Side-effects: see notes above; also intramuscular injection may be painful, cause hypotension and tachycardia, and give rise to nodule formation.

Haloperidol
Indications: schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour.

Cautions: see notes above; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia or hypomagnesaemia.

Contraindications: see notes above.

Side-effects: see notes above, but less sedating and fewer antimuscarinic or hypotensive symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms, particularly dystonic reactions and akathisia especially in thyrotoxic patients; rarely weight loss; hypoglycaemia; inappropriate antidiuretic hormone secretion.

Atypical antipsychotic drugs
Cautions: atypical antipsychotic drugs should be used with caution in patients with cardiovascular disease, history of epilepsy and Parkinson's disease.

Driving: atypical antipsychotic drugs may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Side-effects: side-effects of atypical antipsychotic drugs include weight gain, dizziness, postural hypotension (especially during initial dose titration) that may be associated with syncope or reflex tachycardia in some patients, extra-pyramidal symptoms (these are usually mild and transient, and respond to dose reduction or to antimuscarinic drugs), occasionally tardive dyskinesia on long-term administration; NMS has been reported rarely.

Amisulpride
Amisulpride is indicated for both positive and negative symptoms of schizophrenia.

Cautions: renal impairment, being elderly (risk of hypotension or sedation).

Contraindications: pregnancy and breast-feeding, phaeochromocytoma, prolactin-dependent tumours.

Clozapine
Clozapine is indicated for the treatment of schizophrenia only in patients unresponsive to, or intolerant of, conventional antipsychotic drugs. It can cause agranulocytosis and its use is restricted to those registered with the Clozaril® Patient Monitoring Service (Novartis).

Cautions: see notes above; initiation must be in hospital inpatients; leucocyte and differential blood counts must be normal before starting treatment and must be monitored weekly for first 18 weeks then at least fortnightly – patients who have received clozapine for at least 1 year and have stable blood counts may have their blood monitoring reduced to every 4 weeks (with monitoring continued for 4 weeks after discontinuation); drugs which depress leucopoiesis and taper off conventional neuroleptic drugs before starting should be avoided; treatment should be withdrawn permanently if leucocyte count falls below $3000/mm^3$ or absolute neutrophil count falls below $1500/mm^3$; patients should report any symptoms of infection immediately; mild-to-moderate renal impairment; prostatic hypertrophy, angle-closure glaucoma.

Contraindications: severe cardiac failure; hepatic impairment, severe renal impairment; history of drug-induced neutropenia or agranulocytosis; bone marrow disorders; alcoholic and toxic psychoses; history of circulatory collapse or paralytic ileus; drug intoxication; coma or severe CNS depression; uncontrolled epilepsy; pregnancy and breast-feeding.

Olanzapine
Olanzapine is licensed for use in 'schizophrenia' and is effective in maintaining clinical improvement in those patients who have responded to initial treatment.

Cautions: see notes above; pregnancy, prostatic hypertrophy, paralytic ileus, hepatic impairment, renal impairment, diabetes mellitus, low leucocyte or neutrophil count, bone marrow depression, hypereosinophilic disorders, myeloproliferative disease; concomitant administration of drugs that prolong Q-T intervals (especially in the elderly). (The Q-T interval, measured by ECG, is the time between ventricular depolarisation and repolarisation, and varies inversely with heart rate.)

Contraindications: angle-closure glaucoma; breast-feeding.

Quetiapine
Quetiapine is indicated for the treatment of both positive and negative symptoms. It should be used with caution in cardiovascular disease because it may prolong the Q-T interval; it is occasionally associated with neutropenia.

Cautions: see notes above; pregnancy, hepatic impairment, renal impairment, elderly, concomitant administration of drugs that prolong the Q-T interval (especially in the elderly), cerebrovascular disease.

Contraindications: breast-feeding.

Risperidone
Risperidone is indicated for psychoses in which both positive and negative symptoms are prominent.

Cautions: see notes above; pregnancy, breast-feeding; hepatic impairment, renal impairment, concomitant administration of drugs that prolong the Q-T interval.

Sertindole
Sertindole has been suspended following reports of arrhythmias and sudden cardiac death. The entry for sertindole has been removed from the British National Formulary; however, it remains available from the manufacturer on a named-patient-only basis for those who are already stabilised on it and

for whom other antipsychotic drugs are inappropriate.

Ziprasidone
Ziprasidone is not presently licensed in the UK.

Zotepine
Indications: schizophrenia.

Cautions: see notes above; personal or close family history of epilepsy; withdrawal of concomitantly prescribed CNS depressants; Q-T interval prolongation (ECG required before treatment); concomitant administration of drugs that prolong the Q-T interval or cause hypokalaemia; hepatic impairment; renal impairment; prostatic hypertrophy, urinary retention, angle-closure glaucoma, paralytic ileus, pregnancy.

Contraindications: acute intoxication with CNS depressants; high doses of concomitantly prescribed antipsychotics; acute gout (avoid use of zotepine for 3 weeks after resolution of episode), history of nephrolithiasis; breast-feeding.

Chapter 3
Methods

Methods of reviewing effectiveness

Search strategy

Full details of the search process, including full strategies for each search, are presented in appendix 1.

The National Research Register and the meta Register of Controlled Trials (see appendix 1 for details) were searched for any projects involving the named drugs. The proceedings of major conferences were handsearched for relevant papers. Searches of major bibliographic databases were then undertaken in three tranches – for RCTs, for economic evaluations and for studies of long-term side-effects. The first two were updating searches from 1998 onwards. The search for studies of side-effects was not date limited as no such search was undertaken as part of the original review.

The databases searched are listed in *Table 1*.

Inclusion and exclusion criteria

Participants

These were individuals diagnosed with schizophrenia, by whatever method of diagnosis. Those with schizoaffective disorder, schizophreniform disorder or 'psychotic illness'

TABLE 1 *Databases searched*

Database (supplier)	Searched for RCTs	Searched for economic evaluations	Searched for studies of side-effects
MEDLINE (ARC WinSPIRS)	Yes	Yes	Yes
Cochrane Controlled Trials Register (Cochrane Library CD-ROM issue 2001/1)	Yes		
Biological Abstracts (EDINA telnet service)	Yes		
EMBASE (ARC WinSPIRS)	Yes	Yes	Yes
PsycINFO (BIDS WebSPIRS)	Yes	Yes	Yes
Mental Health Abstracts (Dialog service)	Yes	Yes	
ExtraMED™ (Dialog service)	Yes	Yes	
Pascal (Dialog service)	Yes	Yes	
CAB HEALTH (Dialog service)	Yes	Yes	
Conference Papers Index (Dialog Service)	Yes	Yes	
International Pharmaceutical Abstracts (Dialog Service)	Yes	Yes	
JICST-EPlus (Dialog Service)	Yes	Yes	
NTIS (Dialog Service)	Yes	Yes	
Derwent Drug File (Dialog Service)	Yes	Yes	
IDIS Drug file (Datastar Service)	Yes	Yes	
ADIS Inpharma	Yes		
ADIS LMS DRUG ALERTS	Yes		
Pharmline (Datastar service)	Yes		
Pharma marketing (Datastar service)	Yes		
British Library Inside Conferences (Datastar service)	Yes		
HEED (CD-ROM)		Yes	
NHS EED administration database (CRD)		Yes	
Toxline (Internet)			Yes
SEDBASE (Datastar service)			Yes

were also included. If possible, those with dementing illnesses, bipolar disorder, depression and primary problems associated with substance abuse were excluded.

Interventions

Atypical antipsychotic drugs (amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine) used in accordance with their UK product licenses (in the case of ziprasidone, in accordance with its license in Sweden, and for sertindole, all indications were considered).

Study design

Generally only RCTs or systematic reviews were included. However, for long-term or rare adverse events and suicide or other mortality, all study designs were included. Large numbers of such studies with differing designs were found and, hence, only studies with either a case–control design, a follow-up of more than 2 years, or more than 2000 participants were included.

Outcomes

Outcomes were categorised as follows:

- death
  - suicide
  - sudden cardiac death
  - other toxicity
  - other causes
- morbidity
  - symptoms
    - global state
    - mental state
    - positive symptoms
    - negative symptoms
    - clinically significant response, as defined by included studies and/or average or change in score
  - adverse effects
    - extrapyramidal side-effects – clinically significant, as defined by included studies, and/or average or change in score
    - use of antiparkinsonian drugs
    - other adverse effects, general and specific, reported in RCTs
    - long-term and/or rare adverse events reported in non-RCT studies, such as NMS, cardiac and hepatic problems, tardive dyskinesia, neurological toxicity, neutropenia or agranulocytosis, weight gain
  - relapse
    - hospital admission; days in hospital; change in hospital status
- quality of life
  - satisfaction with care for either recipients or carers as measured by directly asking participants (significant change as defined by each of the studies and/or average score or change in score)
- social outcomes, for example, employment, 'trouble with the police', housing
- economic outcomes
- leaving study early.

Two reviewers independently assessed all retrieved studies for inclusion. Any discrepancies were resolved by discussion with reference to the original papers and, if necessary, a third reviewer was involved. The reference lists of all retrieved papers were checked for additional studies. Excluded studies and reasons for exclusion are reported in appendix 10.

Data extraction strategy

One reviewer undertook data extraction, which was checked by a second reviewer, on to a Microsoft ACCESS© database (in the original phase of the review, data were extracted by two reviewers independently but time constraints precluded this for the update). Any discrepancies were discussed and resolved with reference to the original papers and, if necessary, a third reviewer. Time constraints again precluded contacting authors of recent trials for further data in the second phase of the review. Outcomes are reported separately for the short to medium term (up to 26 weeks) and long term (over 26 weeks). Data on outcomes are not presented for studies in which more than 50% of participants were lost to follow-up. In studies with less than 50% loss to follow-up, patients leaving the study early are considered as having a negative outcome, except in the event of death. The impact of including studies with high losses to follow-up (over 25%) is analysed in sensitivity analyses.

Quality assessment strategy

A validity assessment of RCTs (see appendix 7) was undertaken in both phases of the review using the following criteria: adequacy of randomisation sequence generation, adequacy of allocation concealment, identification of co-interventions, reporting of eligibility criteria, adequacy of blinding, comparability of groups at baseline, attrition rate, adequacy of description of withdrawals, adequacy of intention-to-treat (ITT) analysis, appropriate dose of comparator drug, adequate washout period (defined as 7 days or more). RCTs were not given a quality grading but the results of the validity assessment are discussed in the text.

Studies of other designs were quality assessed using standard critical appraisal checklists as appropriate (see appendix 8).[16]

Methods of analysis/synthesis

For binary outcomes a standard estimation of the relative risk (RR) and its 95% confidence interval (CI) was calculated, using the fixed-effects model. Data were pooled to create a pooled RR and 95% CI when the trials were sufficiently homogeneous.

For continuous outcomes a weighted mean difference (WMD) between groups was estimated, with its 95% CI. If different scales were combined, a standardised mean difference (SMD) estimate and 95% CI was used instead. Where possible, endpoint data are presented; if both endpoint and change data were available for the same outcomes then only endpoint data are reported. Continuous outcomes are presented in appendix 9 only, as feedback from referees of the original review indicated that the dichotomous outcomes of 'improved' or 'not improved' were much more useful to clinicians than any of the efficacy scale data.

Visual inspection and a chi-squared test were used to investigate heterogeneity. If identified, studies responsible for the heterogeneity are summarised and presented separately, with possible reasons for the heterogeneity being explored.

To investigate the possibility of publication bias, data from all included studies were entered into a funnel plot (when sufficient data were available on the same outcomes).

When the data permitted, sensitivity analyses were used to investigate whether there were differences between: individuals with schizophrenia described as 'treatment-resistant' and those whose illness was not so designated; between individuals with predominantly positive or negative symptoms of schizophrenia and those without this designation; and between those experiencing their first episode of schizophrenia and those at later stages of the illness.

Sensitivity analyses were also conducted to assess the impact of including studies with > 25% loss to follow-up, and to assess the effect of using haloperidol as a comparator drug.

Cost-effectiveness

A large percentage of economic evaluations of schizophrenia therapy used a modelling framework that often involved the collection of data from a number of sources to populate the model. Conflicting evidence on the effects of drugs, in addition to the lack of cost data available for the UK population with schizophrenia, often meant that a large number of assumptions had to be made in the model, which, of course, increased the uncertainty surrounding the results.

There were three ways of assessing the economic evidence relating to this review. First, the published economic literature could be reviewed critically. This would have the advantage of being relatively rapid to undertake. On the other hand, there is a substantial disadvantage in that some pertinent economic analyses may not have been undertaken either because the correct question had not been addressed or because an economic evaluation might be unfavourable to a given drug (that is, publication bias). Then, different analyses might use different models and data assumptions, which would lead to difficulties in comparing studies. To address these shortcomings, an analysis should, ideally, be undertaken of all the drugs using a similar model with similar data inputs (for example, using costs in the same currency and price year). This approach is clearly more time consuming and complex because of the need not only to develop an economic model but also to identify relevant data with which to populate such a model. Finally, in relation to both the model and reviewing methods, some relevant and important data might not yet be in the public domain (publication might, for example, be pending); hence, economic analyses undertaken by the manufacturers of a drug might differ simply because they had access to more current data. Thus, in this review, all three approaches to evaluating drugs for schizophrenia have been adopted.

Aims

The overall aim of the review was to establish whether the newer atypical antipsychotic drugs offered any economic advantage for the treatment of schizophrenia over and above that of the older typical antipsychotic medications. Consequently, it was inappropriate to undertake an economic comparison of 'no treatment'. Thus, the cost-effectiveness review had two aims.

1. What were the costs of the health and social care service utilisation associated with the various antipsychotic drugs?
2. What were the patient outcomes or benefits associated with the use of the various antipsychotic drugs?

Search strategies and study selection

The searches employed to identify relevant economic literature are presented in appendix 1. Searches carried out for the economic component of the original review were updated to March 2001. Potentially relevant titles and/or abstracts were retrieved.

Evaluations were included if they met the following criteria.

1. Two or more antipsychotic drugs were compared and the antipsychotic regimen was clearly defined.
2. Data for the direct costs of providing health and social care and the outcomes of care were reported for each comparator.
3. Sources of resource use, cost and patient outcome data were clearly specified, and the estimates of costs and outcomes were calculated from observed data; economic studies that used expert opinion to derive estimates of resource use or patient outcome were excluded.
4. Antipsychotic regimens were clearly defined so that it was clear which antipsychotic drugs were being compared, the dose and route of administration used, and the duration of treatment. In particular, evaluations in which two or more antipsychotic drugs were treated as a class, and in which clear comparisons between individual drugs were not given, were excluded as, to date, there is insufficient evidence to support the assumption that antipsychotic drugs can be categorised into classes (for example, conventional or typical antipsychotic drugs versus atypical antipsychotic drugs) that are equivalent in terms of pharmacological action or efficacy and side-effect profile.

Original analyses that did not meet these criteria, reviews and overviews of published and unpublished analyses, and multiple reports of single studies were excluded.

Study validity

The validity of studies were assessed in terms of their sources for resource use, effectiveness, quality-of-life data, valuation methods used to cost resource use and estimate patient benefits, methods of analysis and generalisability of results. A checklist derived from the Drummond checklist[17] (see appendix 12) was used to conduct this in a systematic fashion. Using the Drummond criteria data on study validity, resource use, costs per item of resource or service use, total costs and the primary measure of outcome for the economic evaluation were extracted for each of the included drugs.

The studies were divided into two groups – those that were economic evaluations using largely primary data (that is, part of a clinical trial) and those that were mainly modelling studies. Studies based on clinical trials were then classified into groups as indicated in *Table 2*.

Economic model of alternative antipsychotic drugs

Introduction to the decision problem

As is shown later in chapter 13, both trial-based and model-based studies used a variety of methods to assess the cost-effectiveness of atypical antipsychotic drugs. In order to check the validity of the economic studies identified by the review and, also, to undertake comparisons between drugs for which, as yet, no review existed, an economic modelling exercise was undertaken. A model was constructed to assess the incremental costs and outcomes associated with atypical antipsychotic treatment in patients with schizophrenia. The model also addressed the issue of uncertainty surrounding key data.

Aims and objectives

The overall aim of the economic analysis was to inform healthcare decision-makers concerned with the provision and funding of antipsychotic therapy for those with schizophrenia about the relative costs and effectiveness of the drugs and the requirements for primary research. There were two main objectives. First, to compare the

TABLE 2 *Classification of trial-based evaluations*

	Prospective resource use and patient outcome data	Mixed prospective and retrospective data	Retrospective data
RCT	IA	IIA	IIIA
Controlled trial	IB	IIB	IIIB
Cohort with concurrent controls	IC	IIC	IIIC
Cohort study with historical controls	ID	IID	IIID

potential economic impact of alternative antipsychotic therapies in terms of direct healthcare and social care costs and patient outcomes. Second, to assess the level of uncertainty around the key variables of clinical efficacy and adverse events, measured by remaining on initial therapy for 12 months, and patient benefit and costs. This would give an indication of the robustness of the analysis and current data, and isolate those variables with the greatest potential to alter the results.

Approach

The economic analysis was based on a model that described the paths of management and events associated with antipsychotic therapies. The study used the framework of economic evaluation to estimate the expected costs and patient outcomes from the use of the alternative antipsychotic drugs included in the review. The analysis was conducted from the perspective of the NHS and local authority social services departments. Ideally, this would have been extended to a societal perspective, given the likely impact on the families of schizophrenia sufferers over a year of treatment. However, there are few data relating to these types of costs in the UK.

Population

The patient population for the analysis was defined as the patient population enrolled in the clinical trials included in the systematic review of effectiveness. Patients did not differ significantly between different trials.

Comparators

The atypical antipsychotic drugs included in the analysis were olanzapine, quetiapine, risperidone, zotepine, clozapine, ziprasidone, sertindole and amisulpride. Haloperidol and chlorpromazine were also included as reference or baseline comparators; data for these were derived from studies in which their use was compared with atypical drugs – systematic searching of trial data for chlorpromazine and haloperidol was not undertaken. Given that 'no treatment' was not considered as an option in the evaluation, the search strategy did not include trials of inactive placebos. This may have led to the exclusion of clinical and economic studies of treatment with typical antipsychotic drugs alone. No treatment strategies were presumed in the analysis and, hence, each antipsychotic drug was compared with all other possible comparators. As none of the trials covered all the included drugs, the comparisons are indirect.

Defining economic efficiency

There are a number of ways of assessing economic efficiency. First, if an intervention is cheaper and more effective or of the same effectiveness, then it is said to dominate the alternative. Clearly, in this instance, the cheaper, more effective alternative should be chosen. Second, there is a situation when an intervention is more effective and more costly. Whether the treatment in this instance is worthwhile or efficient will depend upon society's willingness to pay for the extra or incremental benefit. Finally, there is a similar situation, and one that can be confusing, when a treatment is less effective than the alternative but is substantially cheaper. The less effective treatment may be more efficient if the extra costs incurred by using the more effective therapy is greater than society's willingness to pay for the added benefit of that therapy. Hence, both the costs and effects of paired comparisons were compared simultaneously.

Time frame of analysis

A 1-year time frame was used for the analysis. Ideally, a longer time frame would have been used in the analysis over which costs and outcomes could be assessed. However, as the majority of clinical trials included a follow-up period of less than 1 year, an extrapolation of the data to 2 years or more would undoubtedly impact on the reliability of the results.[14,18] A 1-year time frame would reflect the minimum time required to detect and incorporate the majority of the effects relating to symptom control from acute and maintenance therapy, adverse events and relapse rates.

Decision-analytic model

The decision path presented in *Figure 1*, illustrates the potential consequences associated with the initial decision to prescribe an antipsychotic medication for individuals with an episode of schizophrenia. The model starts at the point at which an individual presents with an episode of schizophrenia. The clinician and patient then have a choice of antipsychotic drug therapies for the treatment of the acute episode. It is assumed that the option of no drug therapy is not applicable in this case.[19] Whichever therapy is chosen, the range of possible events is assumed to be the same. However, the probability of an event occurring may vary between the antipsychotic drugs.

The model makes a number of assumptions about the treatment of schizophrenic patients receiving antipsychotic drugs:

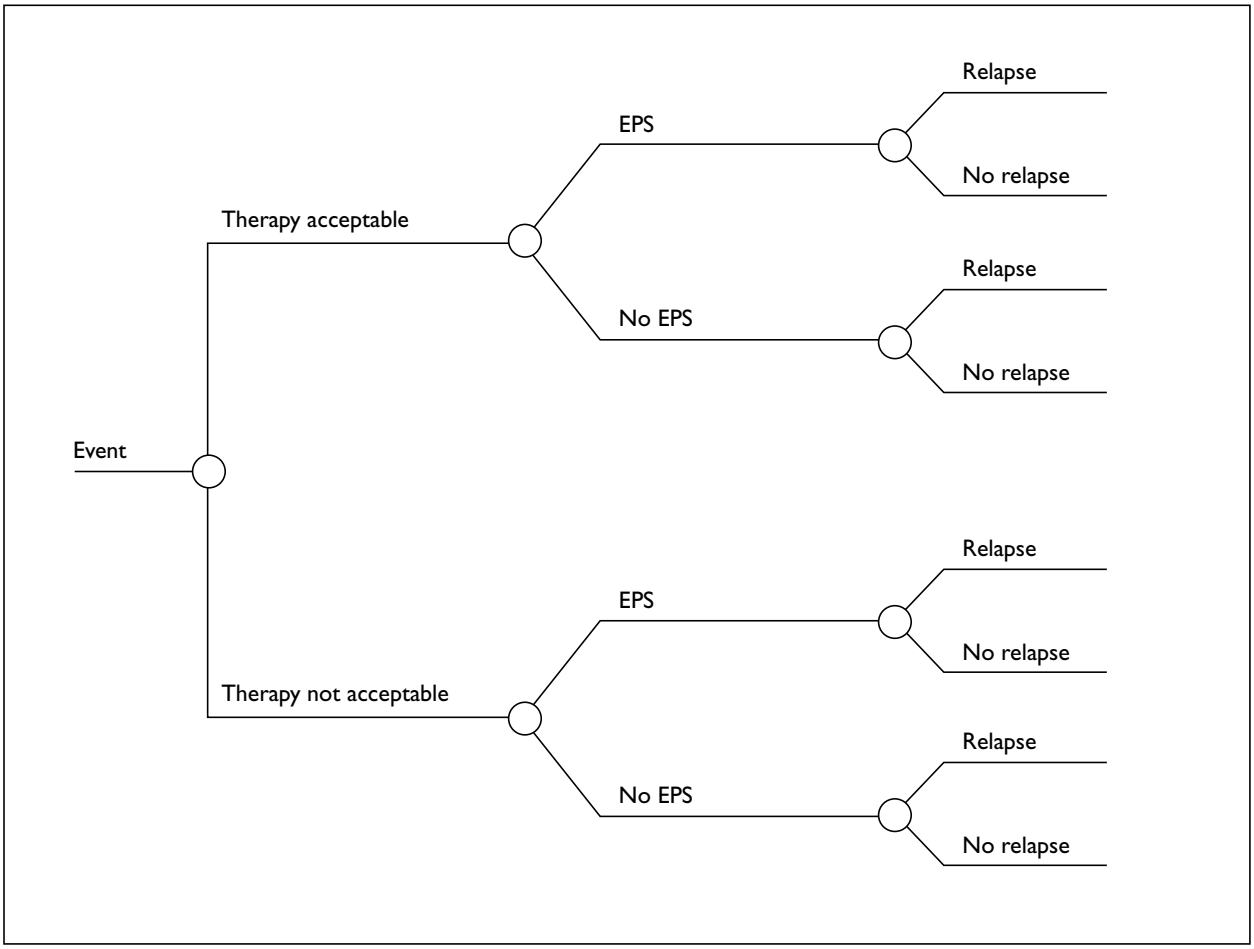

FIGURE 1 *Decision path used in the decision-analytical model (EPS, extrapyramidal syndrome)*

(i) the 'no drug' option is not available
(ii) the range of events that can occur is the same for all drugs but the probabilities of these occurring may differ
(iii) if a patient relapses during acceptable treatment, they will be treated again with the same drug
(iv) patients with an adequate response have mild symptoms
(v) patients with an inadequate response have moderate symptoms
(vi) if a patient does not relapse on therapy, the antipsychotic drug will not be changed.

The use of long-stay residential or institutional care for patients is determined by their socio-demographic characteristics and severity of disease rather than by the choice of anti-psychotic drug.

Following initiation of antipsychotic therapy to treat an acute episode of schizophrenia, there is a chance that the treatment will be acceptable or not acceptable to both patient and clinician. For those patients who find treatment acceptable, there may be associated adverse events. If patients have no adverse events or treatable adverse events, they are transferred to maintenance therapy. While on maintenance therapy, a patient may relapse within the 1-year time frame. If patients relapse following acceptable treatment, it is assumed that they will be treated for an acute episode with the same antipsychotic drug. Following each relapse there will be a chance that therapy is either acceptable or not acceptable. For those patients continuing on maintenance therapy, there is a chance that they will have an adequate response to therapy or not. Those with an adequate response are assumed to have mild symptoms and those with an inadequate response to have moderate symptoms.

If a patient does not comply with therapy, for whatever reason, there is a chance of relapse. If a patient relapses, the antipsychotic drug will be changed. Following each change in therapy there is a chance that the new treatment will be acceptable or not. If a patient does not relapse, it is assumed that there will be no change in treatment strategy.

Estimating the probabilities of events in the model

The systematic reviews of clinical trials were used as the principal source of probability data for the model. Data on event rates were, however, not consistent or directly comparable across studies, as such a number of composite variables were defined in order to reduce variation in the outcome measures reported. These were clinical improvement, acceptability of treatment, intolerance, compliance and inadequate response.

The definition of inadequate response was taken to be that used by the trial investigators. Adequate response or clinical improvement was estimated as (1 – the probability of inadequate response).

Acceptability of treatment was defined as the proportion of people able and willing to continue with a prescribed antipsychotic drug as maintenance therapy. These individuals may have no adverse events associated with therapy, or adverse events that are tolerable or treatable. They may also have an inadequate response but prefer to remain on the allocated treatment. Acceptability of treatment was estimated from systematic review or clinical trial data, based on the number of people who remained in allocated therapy. Unacceptable treatment was estimated as (1 – the probability that treatment was acceptable).

Intolerance, inadequate response and non-compliance were then defined as unacceptable levels of these events that led to discontinuation of allocated therapy. Intolerance was defined as events that mandated a switch in therapy owing to:

- irreversible or life-threatening consequences that could not be adequately treated (for instance, NMS, tardive dyskinesia, agranulocytosis and hepatic dysfunction)
- a level of severity of adverse events that could not be adequately resolved with additional treatment.

The conditional probability of intolerance, given unacceptable treatment, was estimated as:

$$(P_{ae} - (P_{ae} \times P_{at}) + P_{td} + P_{nms} + P_{ag} + P_{hd})/P_{at}$$

where:

P_{ae} = the probability of adverse events which are not irreversible or life threatening
P_{at} = the probability that treatment is acceptable
P_{td} = the probability of tardive dyskinesia
P_{nms} = the probability of NMS
P_{ag} = the probability of agranulocytosis
P_{hd} = the probability of hepatic dysfunction.

This calculation ensures that adverse events that are not irreversible or life threatening are weighted by the acceptability of treatment and that there is no double counting. It also ensures that events which are irreversible or life threatening are only represented in the intolerance branch of the model and are not underestimated.

Non-compliance was defined as refusal to adhere to a treatment regime that had adequate symptom control. In addition, depot therapy had either failed or was not an appropriate option. The probability of non-compliance was estimated from the literature review. The conditional probability of non-compliance, given unacceptable treatment, was estimated as the probability of non-compliance divided by the probability of unacceptable treatment.

The definition of adequate and inadequate response to therapy varied considerably between clinical trials. Hence, inadequate response requiring a change in therapy was defined as a default variable. The conditional probability of an inadequate response, given unacceptability of treatment, was defined as (1 – the conditional probability of intolerance – the conditional probability of non-compliance).

When more than one source of data was available, the base-case probability values for the model were estimated as the weighted average of all included trials. As not all trials reported on all events, pooling was undertaken for those trials that did report an event. Probability data obtained from a single study was used only if the study length was greater than 6 weeks.

Probability estimates that were not available from the included reviews were obtained from the economic review or other published clinical literature, if necessary. Sources of these data are described in appendix 11.

Estimating the costs of events

The costs of events were estimated from measures of the healthcare and social care service use associated with the events, multiplied by the unit costs or prices of those events. It was assumed that the use of long-stay residential or institutional care for patients would be determined by the socio-demographic characteristics of the patients and the severity of their disease, rather than by the

choice of antipsychotic drug. This meant that the choice of antipsychotic treatment would affect only the need for acute inpatient services for initiation of therapy, the switching of antipsychotic treatment and the acute management of relapses. In particular, for the principal analysis, the costs of long-term maintenance therapy excluded the costs of long-stay nursing home or residential care. There was no evidence that these would be directly affected by the choice of drug in the patient population considered.

Estimating QALYs for the model

Effectiveness was determined in the model using quality-adjusted life-years (QALYs). It was assumed that all patients would survive for the full period of analysis but that health status and health-related quality of life would vary according to symptoms and adverse events. These events were defined as mild or moderate/severe symptoms and utility values were attached to these states accordingly. A disutility was also associated with the occurrence of extrapyramidal syndrome (EPS) and admission to hospital.[18,20]

Data

Data on the rates of clinical events such as control of symptoms, adverse events and relapse were taken from the results of the clinical component of the review. Data on patient-specific outcomes were based on the results of a review of published literature specific to schizophrenia. Patient valuations of utility or preferences were used rather than proxy valuations. Use of resources and services and the costs of those services were based on available estimates from UK specific national statistics and databases. These were supplemented where necessary by the broad clinical and economic literature relating to the care and management of those with schizophrenia.

Analysis of data

Probabilistic simulations were used to estimate the expected costs and outcomes associated with each of the antipsychotic drugs and alternative guidelines or treatment protocols. To conduct the simulations, key variables were each assigned a central value (for example, mean, best guess) and a distribution or spread around that measure (for example, standard deviation (SD), minimum or maximum). The simulation recalculated the results over a number of iterations. For each iteration, the value of the key variables was sampled at random from the distributions specified. By repeating the calculations of expected costs and outcomes in this way, a spread of estimates was obtained, which allowed the estimation of the mean expected costs and QALYs and associated 95% CIs.

Three analyses were conducted using the distributional form that best replicated the data. This was determined by the simulation package used. In addition, the inputs to the simulations were checked to ensure that key measures (such as medians, means and ranges) were replicated. A truncated distribution was specified for the probability parameters, which were constrained to values between 0 and 1. Resource use and unit cost variables were also constrained to values between the minimum and maximum possible for each item. For example, inpatient stay per year must be constrained to be equal to or greater than 0 days but less than 366 days. When national statistics gave minimum and maximum values for variables, these were used in preference to logical minimum and maximum constraints.

A Monte Carlo, true expected value sampling method was used. The simulation software used was @RISK, as an add-on to Microsoft Excel v. 7.0. Every simulation required sufficient iterations to ensure that each variable is sampled over the full distribution of values specified and the statistics generated are reliable. As the number of iterations increases, the distribution for the outcomes is described in more detail and becomes more stable. The amount of change in the percentile value, mean and SD decreases with each subsequent iteration. The numbers of iterations for each simulation were determined by the software, which halted the simulation when convergence was achieved at less than 1.5% for percentile value, mean and SD.

Simulated expected costs and QALYs

The analysis of expected costs and QALYs associated with each of the antipsychotic drugs was conducted in three stages. It was assumed for this analysis that the choice of first-, second-, third- and final-line therapies was not governed by predetermined decision rules. The expected costs and QALYs of follow-on therapy were estimated using a triangular distribution. This required three values – minimum, best guess and maximum. The minimum and maximum were determined from the range of expected costs and QALYs estimated by the model. The best guess estimate was set as the median value of these variables.

The first stage was to determine the costs of failure of final-line therapy. This was imputed by estimating the expected costs and QALYs associated with each of the antipsychotic drugs when used as final-

line therapy, excluding follow-on medication for those who found final-line therapy unacceptable. The median expected costs and QALYs were used as proxies for the expected costs and QALYs of final-line therapy. A triangular distribution was used, based on the minimum and maximum values found, with the median values used as the measure of central tendency.

In the second stage, the imputed total expected costs and QALYs for follow-on medication for patients who failed third-line therapy were estimated. These were calculated as the expected costs and QALYs of second-line therapy (including the expected costs and QALYs of final-line follow-on medication and care). The imputed costs and benefits of final-line medication for those patients who found the third-line antipsychotic drugs unacceptable were estimated from the median values using a triangular distribution.

The third stage was to calculate the expected costs and QALYs of follow-on therapy for those patients who found the first-line antipsychotic drugs unacceptable; these were calculated as for second-line therapy.

Sensitivity analysis

Uncertainty within an economic analysis is dealt with by using sensitivity analysis. Traditional sensitivity analyses have a number of drawbacks. Usually variables that impact on the results can only be changed one at a time. This results in a number of 'point' estimates of costs and effects, when in fact there is uncertainty simultaneously over a wide number of variables. Furthermore, the choice of which variable to change and by what quantity is frequently an arbitrary decision. More recently, probabilistic methods have become available that allow the analyst to represent all the uncertainties surrounding key variables within the economic model. For instance, the distribution of benefits, side-effects and costs parameters derived from a meta-analysis or other data source can be simultaneously included in the analysis.

Thus, probabilistic simulations using the Monte Carlo method were used to estimate the expected costs and outcomes associated with each of the antipsychotic drugs. The simulation software used was Crystal Ball (2000), as an add-on to Microsoft Excel v. 7.0. Key variables in the model were assigned a distribution and the model then re-sampled from this distribution to produce a range of estimates of cost and outcomes. The results from the Monte Carlo simulation were used to define a mean and its quasi-95% CI.

Confidentiality

Some manufacturers of the atypical antipsychotic drugs have requested that NICE remove all the commercial-in-confidence information that they submitted from this report. The relevant information has been removed and the text clearly annotated accordingly. When possible, such information has been replaced by trial details that are in the public domain.

The NICE Appraisal Committee had access to the full text when drawing up their recommendations relating to the use of atypical antipsychotic drugs for schizophrenia.

Chapter 4

Results of the literature search: effectiveness

In all, 6477 records of publications were found; 924 were ordered as full papers and, of these, 260 publications were included in the review.

The total number of RCTs included was 171. Of these, 28 were provided wholly or partly as commercial-in-confidence data by the drug manufacturers. In *Table 3,* the numbers in parentheses represent the number of trials of each drug that were commercial-in-confidence.

For additional safety data, 52 non-randomised studies were also included. Of these, data from seven were commercial-in-confidence (all relating to sertindole). A total of 31 published economic evaluations were included together with six economic evaluations submitted by drug manufacturers (all of which contained commercial-in-confidence data).

Further details of included and ongoing effectiveness and safety studies can be found under the individual drug headings. Further details of the economic evaluations can be found in chapter 13.

Excluded studies

A total of 642 publications were excluded from the report once the full papers had been seen. Of these, 197 did not meet the initial inclusion criteria because the participants did not have schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis and/or the effectiveness, cost-effectiveness or safety of an atypical antipsychotic drug was not reported.

In all, 48 reports of RCTs were excluded because: the study outcome was outside the scope of this review; a comparator drug was not included or no usable results were reported; or they were new reports of RCTs already included and did not contain any additional data.

Of the studies relating to side-effects or long-term safety data, 94 were excluded. Of these, 60 studies did not meet the inclusion criteria because the study design was not considered appropriate for this review or they were non-systematic reviews; 28 did not clearly describe the use of antipsychotic

TABLE 3 *Numbers of included RCTs*

Atypical antipsychotic drug	Numbers of RCTs versus comparator[a]										
	Total[a]	Amisulpride	Clozapine	Olanzapine	Quetiapine	Risperidone	Sertindole	Ziprasidone	Zotepine	Typical antipsychotic drug	Placebo
Amisulpride	22 (1)	–	0	1	0	2	0	1 (1)	0	13	4
Clozapine	47 (1)	0	–	5 (1)	0	6*	0	0	1*	36	0
Olanzapine	39 (2)	1	5 (1)	–	0	7	0	1 (1)	0	24	1
Quetiapine	13 (1)	0	0	0	–	1 (1)	0	0	0	9	3
Risperidone	45 (3)	2	6*	7	1 (1)	–	0	2 (2)	1*	27	0
Sertindole	3 (0)	0	0	0	0	0	–	0	0	2	1
Ziprasidone	17 (9)	1 (1)	0	1 (1)	0	2 (1)	0	–	0	9 (4)*	5
Zotepine	13 (2)	0	2*	0	0	1*	0	0	–	8 (1)	3 (1)

[a] *Numbers of commercial-in-confidence trials given in parentheses*

* *Study with more than one comparator*

drugs, reported outcomes or included diagnoses that were not within the scope of this review or presented no usable data; and six were foreign language papers.

Twenty cost-effectiveness studies were excluded. Seven were cost analyses only (no effectiveness data),[21–27] three were reviews,[28–30] one was in Spanish,[31] three reported costs only in terms of hospitalisations,[32–34] and six lacked data on costs or outcomes.[35–40]

Of the 305 unclassified studies excluded, most were because they were non-systematic reviews, had inappropriate study designs or were published comments, letters or editorials.

Details of excluded studies, with the reasons for exclusion, can be found in appendix 10.

Studies awaiting assessment

Nine studies are awaiting assessment, having been ordered but not having arrived at the time of writing. Two RCTs were not assessed because they were in a foreign language (one Chinese, one Spanish). Bibliographic details of these studies can be found in appendix 11.

Chapter 5

Amisulpride: effectiveness

Numbers and characteristics of included RCTs

New RCTs

Seven new RCTs were found in this update review: Muller 1998,[41] Lecrubier 1999,[42] Lecrubier 2000,[43] Ziegler 1989,[44] Wetzel 1998,[45] Study 128-305 (Pfizer, commercial-in confidence)[46] and Carriere 2000.[47] A further report of Colonna 1998[48,49] was found[50] which contained some additional information. Appendix 2 contains the data extraction sheets for these trials.

Old RCTs

The original review included 15 studies: Boyer 1995,[51] Martinot 1995,[52] Delcker 1990,[53] Hillert 1994,[54] Turjanski 1998 (1),[55] Turjanski 1998 (2),[55] Puech 1998,[56] Moeller 1997,[57] Klein 1985,[58] Colonna 1998,[48,49] Speller 1997,[59] Danion 1998,[60] Boyer 1990,[61] Fleurot 1997,[62] Loo 1997.[63] Appendix 3 contains the data extraction sheets for these studies.

Total RCTs

Most of the 22 RCTs included were carried out in mainland Europe (France and Germany). At least nine trials (Colonna 1998,[64] Danion 1998,[60] Loo 1997,[63] Moeller 1997,[65] Martinot 1995,[52] Puech 1998,[56] Speller 1997,[59] Fleurot 1997,[62] Carriere 2000[47]) were carried out or sponsored by Synthelabo, the manufacturers of amisulpride. Nine studies were published only as conference abstracts (including the amisulpride versus risperidone and olanzapine studies) and many methodological details are missing from these reports. The report of one study (Ziegler 1989[44]) was unobtainable and details were taken from the manufacturer's submission.

Interventions

In four studies, amisulpride was compared with placebo and in 13 studies the comparator drug was either haloperidol (ten), fluphenazine (one) or flupentixol (two). In one study amisulpride was compared with olanzapine, in two with risperidone, and in one with ziprasidone.

Duration of studies

The trials were mainly of short duration, 12 being 4–8 weeks long and two (both reported by Turjanski[55]) lasted only 2 weeks. Two trials (Danion 1998,[60] Carriere 2000[47]) were of medium duration – 3–4 months, two trials lasted for 6 months (Lecrubier 1999,[42] Lecrubier 2000[43]), with the remaining three trials (Colonna 1998,[49] Loo 1997,[63] Speller 1997[59]) being of 1 year's duration (Loo 1997 was run initially for 6 months with 141 participants, then extended to 12 months for those patients who responded to treatment).

Ziprasidone commercial-in-confidence data removed from this section.

Participants

The participants were all adults and all fulfilled either the American Psychiatric Association Diagnostic and Statistical Manual (DSM)-IV, -III, -III-R[66] or the International Classification of Diseases (ICD) diagnostic criteria for schizophrenia and, in one study (Martinot 1995[52]), for schizotypal personality disorder and, in another (Carriere 2000[47]), for schizophreniform disorder as well. Participants had predominantly negative symptoms in seven studies, three of which were long term (Speller 1997,[59] Lecrubier 1999,[42] Loo 1997[63]).

Interventions

Doses of amisulpride ranged from 50 mg/day (in those without acute exacerbation of their illness) to 1200 mg/day (in those experiencing acute exacerbations). In one study in which the participants were acutely ill, amisulpride was given at a low dose (100 mg/day) but the trial authors described this as ineffective, equivalent to placebo. Haloperidol was given in doses ranging from 3 mg/day to 40 mg/day, fluphenazine at 2–12 mg/day and flupentixol at 15–25 mg/day. Risperidone was given at 8 mg/day (a high dose) in one trial and at 6 mg/day (range 4–10 mg/day, the recommended dose) in a more recent study.

Outcomes

The outcomes reported included: attrition; some measures of global state; many measures of mental state including most of the negative subscales and the Scale for Assessment of Negative Symptoms (SANS) subscores (N.B. continuous data is reported only in appendix 9); side-effects, including measures of extrapyramidal dysfunction. Most notable was the inclusion of

death as an outcome for one participant in one study – an outcome that is not reported in most RCTs of atypical antipsychotic drugs (except for clozapine).

Quality of included studies

Details of randomisation and allocation concealment procedures were poorly reported – in only one study were more details reported beyond that participants were randomised to treatment, and in two studies (those reported by Turjanski[55]) there was no clear statement that randomisation took place. After some discussion it was decided to include these two studies in the review provisionally. Of the 22 studies, 20 were reported as double-blind, the other two (Boyer 1990,[61] Colonna 1998[48–50]) being of open randomised design. Blinding of patients and staff to treatment allocation was described in only one study and blinding of outcome assessments was described in none.

As well as poor reporting of randomisation and blinding procedures, in 18 of the 22 studies either it was not clear whether or how ITT analysis was undertaken, or the ITT analysis was inadequate (the exception was Carriere 2000[47]). Reasons for withdrawal from the trial were not described in seven studies. In four studies (Moeller 1997,[57] Delcker 1990,[53] Hillert 1994,[54] Fleurot 1997[62]) an inappropriately high dose of comparator drug was used and in three (Moeller 1997,[57] Carriere 2000,[47] Klein 1985[58]) an inadequate washout period.

Ziprasidone commercial-in-confidence data removed from this section.

Amisulpride versus placebo

The RRs with 95% CIs for amisulpride versus placebo are presented in *Table 4* (short to medium term) and *Table 5* (long term). The greatest number of studies included in any outcome assessment was three and most involved only one study; hence, limited weight can be given to these results.

Leaving the study early

Leaving the study early for any reason was higher in the placebo group than the amisulpride group in the short to medium term (RR, 0.48; 95% CI, 0.33 to 0.69) and in the long term (RR, 0.66; 95% CI, 0.49 to 0.90), and leaving the study owing to lack of efficacy was also higher in the placebo group in the long term (RR, 0.58; 95% CI, 0.37 to 0.92).

There were no significant differences in attrition rate because of worsening of either positive or negative symptoms between amisulpride and placebo groups in either the short to medium or the long term.

Mental state

Mental state outcomes were given only in the Loo 1997 trial[63] and, as the attrition rate was > 50%, these outcomes had to be excluded from the review (as specified in the protocol). Information based on a study with more than half the participants missing would be unreliable and misleading.

Side-effects

There were no statistically significant differences between amisulpride- and placebo-treated groups

TABLE 4 *Amisulpride versus placebo – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
Leaving study early				
Any reason	Boyer 1995 (104) Danion 1998 (242)	10/70 29/159	9/34 33/83	0.48 (0.33 to 0.69)
Worsening of positive symptoms	Boyer 1995 (104)	2/70	4/34	0.24 (0.05 to 1.06)
Worsening of negative symptoms	Boyer 1995 (104)	2/70	2/34	0.49 (0.07 to 3.30)
Side-effects				
Any adverse event	Boyer 1995 (104)	22/70	7/34	1.25 (0.83 to 1.87)
Received antiparkinsonian drugs	Boyer 1995 (104)	1/70	1/34	0.49 (0.03 to 7.53)
Anticholinergic effects	Boyer 1995 (104)	8/70	2/34	1.94 (0.44 to 8.66)
Various somatic complaints	Boyer 1995 (104)	10/70	4/34	1.21 (0.41 to 3.59)
Sleep disorders and agitation	Boyer 1995 (104)	10/70	2/34	2.43 (0.56 to 10.48)

n, *number of events;* N, *number of participants in group*

TABLE 5 *Amisulpride versus placebo – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
No response (SANS < 20%; PANSS < 10%)	Lecrubier 1999 (104)	30/70	18/34	0.81 (0.53 to 1.23)
Leaving study early				
Any reason	Loo 1997 (141)	31/69	49/72	0.66 (0.49 to 0.90)
Worsening of positive symptoms	Loo 1997 (27)	3/14	1/13	2.79 (0.33 to 23.53)
Worsening of negative symptoms	Loo 1997 (27)	1/14	2/13	0.46 (0.05 to 4.53)
Adverse events	Loo 1997 (27)	0/14	2/13	0.19 (0.01 to 3.56)
Lack of efficacy	Loo 1997 (141)	19/69	34/72	0.58 (0.37 to 0.92)

n, *number of events;* N, *number of participants in group*

for any side-effects, except for extrapyramidal symptoms, which were greater in the amisulpride than in the placebo group in the long term (results not presented because attrition rate > 50%). The absolute RR (risk difference) of receiving anti-parkinsonian drugs in the short to medium term was –0.02 (95% CI, –0.08 to 0.05; not significant).

Amisulpride versus typical antipsychotic drugs

For amisulpride versus typical antipsychotic drugs, RRs with 95% CIs are reported in *Tables 6* and *7*.

There were no differences in attrition rates between those treated with amisulpride and those treated with typical antipsychotic drugs except for the short-term outcomes 'leaving study early – any reason' and 'leaving study early – adverse events/intolerance', which both favoured amisulpride over typical antipsychotic treatments (RR, 0.63 (95% CI, 0.52 to 0.78) and RR, 0.33 (95% CI, 0.19 to 0.57)). In one study, one death resulted from suicide in the group treated with typical antipsychotic drugs compared with no deaths in the amisulpride group, but this difference was not significant.

Global state

Amisulpride was favoured over typical antipsychotic drugs for the global state outcomes 'no response (Clinical Global Impression (CGI) – Improvement (I))' – RR, 0.62; 95% CI, 0.49 to 0.80; risk difference, –0.18; 95% CI, –0.28 to –0.09 – and 'no response (CGI – Severity (S))' – RR, 0.79; 95% CI, 0.67 to 0.93; risk difference, –0.13, 95% CI, –0.21 to –0.04 – in the short term. There were no significant differences between groups treated with amisulpride and typical antipsychotic drugs for any of the other measured global outcomes in the short term.

Amisulpride was favoured over typical antipsychotic treatments for the outcome 'efficacy not maintained (CGI-I)' (RR, 0.79; 95% CI, 0.68 to 0.93) in the long term. There were no significant differences between the groups for any of the other measured global outcomes, although 'psychotic exacerbation' showed a borderline result in the long term (RR, 0.46; 95% CI, 0.20 to 1.03); this may reflect a real difference but sample sizes were too small to show significance.

Mental state

A borderline significant result (that may reflect real differences but did not achieve significance owing to the small sample size) was found for the mental state outcome 'psychiatric adverse events' in the short term (RR, 0.68; 95% CI, 0.45 to 1.04).

Amisulpride-treated participants were less likely to experience depression in the short term than those treated with typical antipsychotic drugs (RR, 0.10; 95% CI, 0.01 to 0.77), and more likely to respond to treatment in the long term, as measured by the British Psychiatric Rating Scale (BPRS) scores (RR, 0.52; 95% CI, 0.38 to 0.70; risk difference, –0.03; 95% CI, –0.10 to 0.03).

Side-effects

For the outcome, 'side-effects: any (at least one Udvalg fuer Kliniske Undersogelser (UKU) symptom), short term', amisulpride was favoured over typical antipsychotic treatments (RR, 0.92; 95% CI, 0.84 to 0.99); however, statistical heterogeneity was seen in this result (chi-squared = 8.01; $p = 0.018$). On closer inspection, the three studies

TABLE 6 *Amisulpride versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
Death (suicide)	Moller 1997 (191)	0/95	1/96	0.34 (0.01 to 8.17)
Leaving study early				
Any reason	Boyer 1990 (62)	10/34	10/28	0.63 (0.52 to 0.78)
	Carriere 2000 (199)	24/94	46/105	
	Delcker 1990 (41)	1/21	3/20	
	Hillert 1994 (132)	19/70	25/62	
	Klein 1985 (19)	0/9	5/10	
	Moller 1997 (191)	25/95	39/96	
	Puech 1998 (258)	45/194	21/64	
Adverse events/intolerance	Boyer 1990 (62)	1/34	1/28	0.33 (0.19 to 0.57)
	Carriere 2000 (199)	4/94	22/105	
	Hillert 1994 (132)	4/70	11/62	
	Moller 1997 (191)	3/95	10/96	
	Puech 1998 (258)	8/194	3/64	
Global state				
No response (CGI-I)	Carriere 2000 (199)	29/94	56/105	0.62 (0.49 to 0.80)
	Puech 1998 (258)	58/194	28/64	
No response (CGI-S)	Carriere 2000 (199)	58/94	79/105	0.79 (0.67 to 0.93)
	Hillert 1994 (132)	27/70	24/62	
	Moller 1997 (188)	36/94	55/94	
Mental state				
No response (BPRS 40–50%)	Hillert 1994 (132)	43/70	24/62	0.95 (0.87 to 1.05)
	Turjanski 1998 – 1 (186)	103/125	58/61	
	Turjanski 1998 – 2 (188)	68/94	81/94	
No response (PANSS positive)	Moller 1997 (188)	56/94	54/94	1.04 (0.82 to 1.32)
No response (PANSS negative)	Moller 1997 (188)	42/94	49/94	0.86 (0.64 to 1.15)
Depression	Carriere 2000 (199)	1/94	11/105	0.10 (0.01 to 0.77)
Psychiatric adverse events	Moeller 1997 (191)	25/95	37/96	0.68 (0.45 to 1.04)
Side-effects				
At least one UKU symptom	Hillert 1994 (132)	61/70	57/62	0.92 (0.84 to 0.99)
	Puech 1998 (158)	174/194	56/64	
	Moeller 1997 (191)	54/95	72/96	
Use of antiparkinsonian drugs	Delcker 1990 (41)	11/21	13/20	0.59 (0.49 to 0.72)
	Hillert 1994 (132)	30/70	38/62	
	Klein 1985 (19)	1/9	6/10	
	Moller 1997 (191)	28/95	54/96	
	Puech 1998 (258)	45/194	26/64	
At least one extrapyramidal symptom	Carriere 2000 (199)	22/94	49/105	0.72 (0.62 to 0.84)
	Hillert 1994 (132)	49/70	49/62	
	Puech 1998 (258)	92/194	37/64	
	Ziegler 1989 (40)	4/20	11/20	
Neurological adverse events	Moller 1997 (191)	34/95	59/96	0.58 (0.43 to 0.80)
Dyskinesia	Carriere 2000 (199)	0/94	6/105	0.37 (0.09 to 1.50)
	Moller 1997 (19)	2/9	1/10	
Akathisia	Moller 1997 (19)	2/9	2/10	1.11 (0.19 to 6.34)
Hypertonia	Carriere 2000 (199)	6/94	10/105	0.67 (0.25 to 1.77)
Tremor	Carriere 2000 (197)	2/92	8/105	0.29 (0.06 to 1.31)
Hyperkinesia	Carriere 2000 (199)	2/94	5/105	0.45 (0.09 to 2.25)
Akinesia	Moller 1997 (19)	4/9	8/10	0.56 (0.25 to 1.23)

continued

***TABLE 6* contd** *Amisulpride versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
***Side-effects* contd**				
Use of sedatives	Delcker 1990 (41) Hillert 1994 (132)	5/21 49/70	7/20 41/62	1.00 (0.79 to 1.27)
Insomnia	Moller 1997 (191)	6/95	10/96	0.61 (0.23 to 1.60)
Somnolence	Carriere 2000 (199) Moller 1997 (191)	1/94 1/95	6/105 5/96	0.19 (0.04 to 0.86)
Increased duration of sleep	Hillert 1994 (132)	16/70	24/62	0.59 (0.35 to 1.01)
Asymptomatic high blood pressure	Moller 1997 (191)	1/95	0/96	3.03 (0.13 to 73.49)
Orthostatic dizziness	Hillert 1994 (132)	9/70	11/62	0.72 (0.32 to 1.63)
Constipation	Hillert 1994 (132)	12/70	6/62	1.77 (0.71 to 4.44)
Agitation	Moller 1997 (191)	8/95	6/96	1.35 (0.49 to 3.74)
Anxiety	Moller 1997 (191)	3/95	6/96	0.51 (0.13 to 1.96)
Impotence	Moller 1997 (191)	0/95	1/96	0.34 (0.01 to 8.17)
At least one endocrine symptom	Puech 1998 (258)	21/194	9/64	0.77 (0.37 to 1.59)
Sedation	Hillert 1994 (132)	32/70	34/62	0.83 (0.59 to 1.17)
Inner unrest	Hillert 1994 (132)	19/70	18/62	0.93 (0.54 to 1.61)
Headache	Hillert 1994 (132)	14/70	5/62	2.48 (0.95 to 6.49)
Accommodation disturbance	Hillert 1994 (132)	13/70	17/62	0.68 (0.36 to 1.28)
Increased salivation	Hillert 1994 (132)	12/70	14/62	0.76 (0.38 to 1.52)
Sweating	Hillert 1994 (132)	10/70	6/62	1.48 (0.57 to 3.83)
Menorrhagia	Hillert 1994 (132)	5/34	3/24	1.18 (0.31 to 4.46)
Galactorrhoea	Hillert 1994 (132)	4/70	3/62	1.18 (0.27 to 5.07)
Dry mouth	Carriere 2000 (199)	1/94	6/105	0.19 (0.02 to 1.52)
Suicide attempt	Carriere 2000 (199)	0/94	5/105	0.10 (0.01 to 1.81)
Gynaecomastia	Hillert 1994 (132)	2/70	2/62	0.89 (0.13 to 6.10)
Ejaculatory dysfunction	Hillert 1994 (74)	2/36	2/38	1.06 (0.16 to 7.10)
Erectile dysfunction	Hillert 1994 (74)	1/36	5/38	0.21 (0.03 to 1.72)
Weight gain	Carriere 2000 (199) Hillert 1994 (132)	7/94 15/70	0/105 14/62	1.44 (0.80 to 2.59)

n, *number of events;* N, *number of participants in group*

that reported this outcome (Hillert 1994,[54] Moeller 1997,[57] Puech 1998[56]) were quite similar, all lasting between 4 and 6 weeks, using similar doses of amisulpride and treating patients with acute exacerbations of chronic illness (that is, not patients with predominantly negative symptoms). One of the inclusion criteria for Moeller 1997 was patients with first-episode illness so, for this reason, this study may be different from the others; however, no details are given of the number of patients with first-episode illness, so the reviewers cannot be sure that it is different from the other two studies. Removing Moeller 1997 from the analysis gave no significant difference between groups (RR, 0.99; 95% CI, 0.92 to 1.07).

In short-term studies, significant differences in favour of amisulpride were seen in: use of antiparkinsonian drugs (RR, 0.59; 95% CI, 0.49 to 0.72), 'neurological' adverse events (RR, 0.58; 95% CI, 0.43 to 0.80), somnolence (RR, 0.19; 95% CI, 0.04 to 0.86) and 'at least one extra-pyramidal symptom' (RR, 0.72; 95% CI, 0.62 to 0.84; risk difference, –0.16, 95% CI, –0.24 to –0.09). Significant heterogeneity was seen in this last result (chi-squared = 9.87, $p = 0.02$). The removal of Carriere 2000[47] and Ziegler 1989[44] from the analysis (leaving Hillert 1994[54] and Puech 1998[56]) removed the heterogeneity and gave a result of borderline significance (RR, 0.85; 95% CI, 0.72 to 1.00) but it is

TABLE 7 *Amisulpride versus typical antipsychotics – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any reason	Speller 1997 (60)	5/29	7/31	0.86 (0.70 to 1.06)
	Colonna 1998 (440)	145/322	61/118	
Global state				
Efficacy not maintained (survival analysis)	Colonna 1998 (440)	173/322	80/118	0.79 (0.68 to 0.93)
No response (CGI)	Colonna 1998 (488)	170/370	66/118	0.82 (0.68 to 1.00)
Psychotic exacerbation	Speller 1997 (60)	6/29	14/31	0.46 (0.20 to 1.03)
Mental state				
No response (MS negative subscale)	Speller 1997 (60)	23/29	26/31	0.95 (0.74 to 1.20)
No response (BPRS)	Colonna 1998 (440)	69/322	49/118	0.52 (0.38 to 0.70)
Side-effects				
Patients suffering at least one side-effect	Speller 1997 (60)	15/29	21/31	0.76 (0.50 to 1.17)
Received anticholinergic medication	Speller 1997 (60)	10/29	25/31	0.43 (0.25 to 0.73)
Parkinsonian side-effects	Colonna 1998 (440)	83/322	48/118	0.65 (0.52 to 0.83)
	Speller 1997 (60)	16/29	24/31	
Akathisia	Speller 1997 (60)	2/29	8/31	0.27 (0.06 to 1.16)
Drowsiness	Speller 1997 (60)	12/29	7/31	1.83 (0.84 to 4.01)
Insomnia	Speller 1997 (60)	1/29	5/31	0.21 (0.03 to 1.72)
Tachycardia/palpitations	Speller 1997 (60)	3/29	7/31	0.46 (0.13 to 1.61)
Dizziness	Speller 1997 (60)	3/29	6/31	0.53 (0.15 to 1.94)
Constipation	Speller 1997 (60)	3/29	6/31	0.53 (0.15 to 1.94)
Dry mouth	Speller 1997 (60)	6/29	12/31	0.53 (0.23 to 1.24)
Blurred vision	Speller 1997 (60)	4/29	6/31	0.71 (0.22 to 2.27)
Sweating	Speller 1997 (60)	4/29	5/31	0.86 (0.25 to 2.88)
Nasal stuffiness	Speller 1997 (60)	3/29	7/31	0.46 (0.13 to 1.61)
Urinary retention	Speller 1997 (60)	2/29	2/31	1.07 (0.16 to 7.10)
Galactorrhoea/menstrual disturbance	Speller 1997 (60)	0/29	1/31	0.36 (0.02 to 8.39)
Endocrine events	Colonna 1998 (440)	13/322	3/118	1.59 (0.46 to 5.47)
Increase of 5% from baseline weight	Colonna 1998 (440)	103/322	21/118	1.80 (1.18 to 2.73)

n, *number of events;* N, *number of participants in group*

not clear how these four studies differed in design and whether the two removed studies were the appropriate ones to remove.

No significant difference was seen between groups for the outcome 'dyskinesia'; however, significant heterogeneity was seen in this result (chi-squared = 3.49, $p = 0.062$). The pooled result was taken from only two studies and when these were analysed separately there was still no significant difference between the groups (Carriere 2000:[47] RR, 0.09; 95% CI, 0.00 to 1.50; Moeller 1997:[57] RR, 2.22; 95% CI, 0.24 to 20.57).

No differences were observed between amisulpride-treated and typical antipsychotic-treated participants for cardiovascular problems, gastrointestinal problems, endocrine events or any of the other commonly listed side-effects for antipsychotic drugs.

In long-term studies, the following outcomes showed significant differences in favour of amisulpride: use of anticholinergic drugs (RR, 0.43; 95% CI, 0.25 to 0.73; risk difference, –0.22; 95% CI, –0.46 to 0.01) and parkinsonian side-effects (RR, 0.65; 95% CI, 0.52 to 0.83). In one long-term study

TABLE 8 *Amisulpride versus atypical antipsychotic drugs (olanzapine) – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early	Lecrubier 1999 (210)	36/70	75/140	0.96 (0.73 to 1.26)
Not improved (SANS < 20%; PANSS < 10%)	Lecrubier 1999 (210)	30/70	53/140	1.13 (0.80 to 1.60)

n, *number of events;* N, *number of participants in group*

(Colonna 1998[48–50]), patients taking amisulpride were significantly more likely to gain weight than those taking typical antipsychotic drugs (RR, 1.80; 95% CI, 1.18 to 2.73), although no difference between groups was seen in the short term. Heterogeneity was seen in the short-term result (chi-squared = 4.45, $p = 0.035$); however, the pooled result was from only two studies. When these were analysed separately, there was still no significant difference between groups (Carriere 2000:[47] RR, 16.74; 95% CI, 0.97 to 289; Hillert 1994:[54] RR, 0.95; 95% CI, 0.50 to 1.81).

No differences were seen between patients treated with amisulpride and typical antipsychotic drugs for sleep problems, cardiovascular problems, gastrointestinal problems, endocrine events or any of the other commonly listed side-effects for antipsychotic drugs.

Sensitivity analysis

When only those studies in which amisulpride was compared with haloperidol were included (that is, Hillert 1994,[54] Boyer 1990,[51] Muller 1998[41] and Wetzel 1998[45] were excluded from the analysis), the following changes were seen: mental state response (BPRS) was significantly better in patients receiving amisulpride than in those receiving haloperidol (RR, 0.85; 95% CI, 0.78 to 0.93) and the result for 'any side-effect' changed from being significantly in favour of amisulpride to borderline significance (RR, 0.90; 95% CI, 0.81 to 1.00).

Amisulpride versus atypical antipsychotic drugs

In one study, Lecrubier 1999,[43] the effect of amisulpride versus olanzapine was evaluated. Improvement and attrition were the only outcomes reported (*Table 8*) and these favoured neither drug (improvement: risk difference, 0.05; 95% CI, –0.09 to 0.19). SANS summary scores were also reported and are presented in appendix 9.

The effect of amisulpride versus risperidone was evaluated in two studies (Fleurot 1997,[62] Lecrubier 2000[43]). The RRs and 95% CIs are presented in *Tables 9* and *10*. The studies were of patients who were acutely ill, with predominantly positive schizophrenic symptoms and one (Fleurot 1997) was of short duration, lasting for 8 weeks, while the other (Lecrubier 2000) was of medium to long duration, lasting for 6 months. No significant differences were seen between amisulpride and risperidone-treated groups apart from on some measures of 'response', which were in favour of risperidone (CGI risk difference, 0.08; 95% CI, 0.00 to 0.16) and amisulpride (Positive and Negative Symptom Scale (PANSS) risk difference, –0.13; 95% CI, –0.24 to –0.02; BPRS risk difference, –0.13; 95% CI, –0.24 to –0.03), the subjective measure of 'response', which was in favour of risperidone, and 'agitation', which was also in favour of risperidone (RR, 3.44; 95% CI, 1.17 to 10.13).

Ziprasidone versus amisulpride: commercial-in-confidence data, including table, removed from this section.

Sensitivity analysis

Exclusion of studies with overall attrition rates of more than 25% from the analysis led to the following changes in the results.

Versus placebo

No outcomes included studies with both high and low attrition, so no sensitivity analysis was performed.

Versus typical antipsychotic drugs

The only study with less than 25% attrition was Delcker 1990.[53] Removal of other studies from relevant outcomes led to one change in the results – there was no longer any difference between groups for the outcome 'use of anti-parkinsonian drugs' (RR, 0.81; 95% CI, 0.48 to 1.35). All other outcomes were either

TABLE 9 *Amisulpride versus atypical antipsychotic drugs (risperidone) – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any reason	Fleurot 1997 (228)	37/115	32/113	1.14 (0.76 to 1.69)
Lack of efficacy	Fleurot 1997 (228)	8/115	10/113	0.79 (0.32 to 1.92)
Adverse events	Fleurot 1997 (228)	15/115	14/113	1.05 (0.53 to 2.08)
Side-effects				
At least one endocrine symptom	Fleurot 1997 (228)	7/115	7/113	0.98 (0.36 to 2.71)
Constipation	Fleurot 1997 (228)	8/115	1/113	7.86 (1.00 to 61.84)
Saliva – increased	Fleurot 1997 (228)	9/115	5/113	1.77 (0.61 to 5.12)
Vomiting	Fleurot 1997 (228)	7/115	4/113	1.72 (0.52 to 5.71)
Any extrapyramidal	Fleurot 1997 (228)	17/115	13/113	1.28 (0.65 to 2.52)
Hyperkinesia	Fleurot 1997 (228)	15/115	11/113	1.34 (0.64 to 2.79)
Hypertonia	Fleurot 1997 (228)	9/115	6/113	1.47 (0.54 to 4.01)
Tremor	Fleurot 1997 (228)	5/115	8/113	0.61 (0.21 to 1.82)
Used antiparkinsonian medication	Fleurot 1997 (228)	35/115	26/113	1.32 (0.86 to 2.05)
Agitation	Fleurot 1997 (228)	14/115	4/113	3.44 (1.17 to 10.13)
Anxiety	Fleurot 1997 (228)	10/115	7/113	1.40 (0.55 to 3.56)
Insomnia	Fleurot 1997 (228)	10/115	8/113	1.23 (0.50 to 3.00)
Weight gain	Fleurot 1997 (228)	4/115	6/113	0.66 (0.19 to 2.26)

n, *number of events;* N, *number of participants in group*

TABLE 10 *Amisulpride versus atypical antipsychotic drugs (risperidone) – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state				
Response (CGI)	Lecrubier 2000 (310)	117/152	103/158	1.18 (1.02 to 1.36)
No response – social functioning (SOFA)	Lecrubier 2000 (310)	102/152	122/158	0.87 (0.76 to 1.00)
No response – subjective Van Putten scale	Lecrubier 2000 (310)	141/152	131/158	1.12 (1.03 to 1.22)
Mental state				
No response (PANSS)	Lecrubier 2000 (310)	53/152	76/158	0.72 (0.55 to 0.95)
No response (BPRS)	Lecrubier 2000 (310)	43/152	66/158	0.68 (0.50 to 0.93)

n, *number of events;* N, *number of participants in group*

reported by only one study or all studies reporting an outcome fell into the excluded group (that is, the outcome was not reported by Delcker 1990). Outcomes reported by Delcker 1990 were: leaving study early, use of anti-parkinsonian drugs and use of sedatives. The results for other outcomes may not be robust.

Versus atypical antipsychotic drugs

Versus risperidone, the removal of Fleurot 1997[62] (30% attrition) made no substantial difference to the results. Versus olanzapine and ziprasidone, only one study was included in each case, so no sensitivity analyses were possible.

Subgroup analyses

If only those studies that included participants who had predominantly negative symptoms were considered (Boyer 1990,[61] Boyer 1995,[51] Danion 1998,[60] Klein 1985,[58] Martinot 1995,[52] Speller 1997[59]), the following differences were noted.

Versus placebo

Inclusion of only those studies of participants with predominantly negative symptoms made no difference to the significance of the results.

Versus typical antipsychotic drugs

Inclusion of only those studies of participants with predominantly negative symptoms made no difference to the significance of the results, apart from those for the outcome 'leaving study early – any reason (short term)'; this changed from RR, 0.65; 95% CI, 0.51 to 0.83, a significant result in favour of amisulpride, to a non-significant result (RR, 0.59; 95% CI, 0.30 to 1.17). The result for the outcome 'side-effects – parkinsonian side-effects (long term)' also changed from significance (RR, 0.65; 95% CI, 0.52 to 0.83) to non-significance (RR, 0.71; 95% CI, 0.49 to 1.04) when studies that did not include only participants with negative symptoms were excluded.

Publication bias

It was not possible to undertake analysis of possible publication bias for most of the outcomes in the amisulpride review, as there were too few studies reporting the same outcome for funnel plots to be constructed. When it was possible to construct funnel plots, asymmetry was noted for the outcome 'leaving study early – any reason', although not for the outcomes 'leaving study early – adverse events' and 'leaving study early – lack of efficacy'.

Rare or long-term events

No non-randomised studies of rare or long-term events with amisulpride were found that met the inclusion criteria.

Other systematic reviews

One conference abstract was found in which an investigation of suicidal behaviour was described using a pooled analysis of 11 amisulpride trials.[67] Many methodological details were missing, such as how the studies were selected, although the analysis was restricted to people with schizophrenia. A total of 18/1933 cases of suicide, attempted suicide or suicidal tendency were reported for patients randomised to receive amisulpride. There were no data on suicidal behaviour in control groups.

In the original study, the results of a systematic review of amisulpride[68] agreed with review results in all respects.

Ongoing studies

One ongoing study was listed on the trial registers searched: a 6-month Phase IV comparison of amisulpride and olanzapine in patients with schizophrenia or schizophreniform disorder (Singh V. A 6-month international controlled trial of the therapeutic activity of amisulpride, 200–800 mg/day, versus olanzapine, 5–20 mg/day, in patients with schizophrenic disorders). The trial was expected to end in late 2002.

Chapter 6

Clozapine: effectiveness

Numbers and characteristics of included RCTs

New RCTs

Eight new RCTs were found in this update review: Covington 2000,[69] Fleming 1998,[70] HGCF 2001 (Eli Lilly company submission, commercial-in-confidence), Chowdhury 1999,[71] Salganik 1998,[72] Chow 2000,[73] Bitter 1999,[74] and Cosar 1999.[75] One new report (Tollefson 2001[76]) of an old RCT (Beasley 1999[77]) was found and additional data were included in this update report. Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

In the original review, there were 31 studies of clozapine versus typical antipsychotic drugs (Chiu 1976,[78] Guirguis 1977,[79] Xu 1985,[80] Xu 1989,[81] Xu 1994,[82] Leon 1974,[83] Gerlach 1974,[84] Gerlach 1975,[85] Fischer-Cornelssen 1974,[86] Fischer-Cornelssen 1976a,[87] Fischer-Cornelssen 1976b,[87] Honigfeld 1984,[88] Klieser 1989,[89] Klieser 1994,[90] Singer 1974,[91] Itoh 1977,[92] Erlandsen 1981,[93] Ciurezu 1976,[94] Hong 1997,[95] Shopsin 1979,[96] Gelenberg 1979,[97] Claghorn 1987,[98] Kane 1988,[99] Kane 1994,[100] Lee 1994,[101] Tamminga 1994,[102] Essock 1996,[103] Kumra 1996,[104] Rosenheck 1997,[105] Howanitz 1999,[106] Buchanan 1998[107]) and eight studies of clozapine versus atypical antipsychotic drugs (Meyer-Lindenberg 1996,[108] Beasley 1999,[77] Oliemeulen 2000,[109] Klieser 1994,[90] Bondolfi 1998,[110] Anand 1998,[111] Breier 1999,[112] Wahlbeck 2000[113]). Data extraction sheets for these studies are presented in appendix 3.

Total RCTs

A total of 47 RCTs are included in this part of the review.

Duration

Six trials (Kane 1994,[100] Lee 1994,[114] Tamminga 1994,[102] Essock 1996,[103] Rosenheck 1997,[105] Covington 2000[69]) were longer than 26 weeks (long term); the remainder fell into the short-term category, with a maximum length of 20 weeks.

Participants

In 16 trials, only patients with treatment-resistant schizophrenia were included (Klieser 1989,[89] Hong 1997,[95] Kane 1988,[99] Essock 1996,[103] Kumra 1996,[104] Rosenheck 1997,[105] Rosenheck 1998,[115] HGCF 2001 (Eli Lilly), Chowdhury 1999,[71] Bitter 1999,[74] Beasley 1999,[77] Oliemeulen 2000,[109] Bondolfi 1998,[110] Anand 1998,[111] Wahlbeck 2000[113]). Only one trial was focused on children or adolescents suffering from schizophrenia (Kumra 1996).[104] Two trials (Howanitz 1999,[106] Salganik 1998[72]) included only elderly people.

The vast majority of the trials were in-hospital studies. To our knowledge, only three trials (Kane 1994,[100] Breier 1998,[112] Fleming 1998[70]) were performed in the community. Two long-term trials (Essock 1996,[103] Rosenheck 1997[115]) were hospital-based with follow-up of patients who were discharged.

Interventions

The following control treatments were used by the trialists: haloperidol ($n = 17$), chlorpromazine ($n = 13$), several antipsychotic drugs ($n = 3$), clopenthixol ($n = 1$), thioridazine ($n = 1$), trifluoperazine ($n = 1$), sulpiride ($n = 1$), olanzapine ($n = 5$), risperidone ($n = 6$), remoxipride ($n = 2$), zotepine ($n = 1$). In five trials (Chiu 1976,[78] Leon 1974,[83] Ciurezu 1976,[94] Erlandsen 1981,[93] Honigfeld 1984[88]), low doses of typical neuroleptic treatments were used; this may have been of benefit to the clozapine results in these studies. In two studies (Chiu 1976, Leon 1974) the same doses of clozapine and chlorpromazine were used, while in the others comparatively low doses of haloperidol were used.

Outcomes

Many trialists used symptom scales when assessing treatment effects. These scales are not reported here (see appendix 9).

Quality of included studies

Of the included trials, 16 did not report stringent criteria for the diagnosis of schizophrenia. All the trials were undertaken between 1974 and 1998, and several different sets of diagnostic criteria were used.

Only two studies (Ciurezu 1976,[94] Guirguis 1977[79]) published before 1980 were considered to have adequate concealment of treatment allocation.

Six further studies (Honigfeld 1984,[88] Kane 1994,[100] Kumra 1996,[104] Rosenheck 1997,[105] Howanitz 1999,[106] Wahlbeck 2000[113]) were considered to have adequate concealment of randomisation (although in three instances, Honigfeld 1984, Kane 1994 and Rosenheck 1997, only after personal communication with the authors). At this time, all other studies must be considered to have unclear concealment of randomisation.

Blinding had been applied in most studies: 35 were reported to be double-blind and two single-blind; only three studies (Lee 1994,[101] Essock 1996,[103] Chow 2000[73]) lacked any blinding at all.

A common problem was poor reporting of the causes or numbers of people leaving a study early. In 11 studies (Leon 1974,[83] Gerlach 1974,[84] Gerlach 1975,[85] Honigfeld 1984,[88] Erlandsen 1981,[93] Ciurezu 1976,[94] Shopsin 1979,[96] Kane 1988,[99] Gordon 1996,[104] Rosenheck 1997,[105] Breier 1999[112]), ITT analysis was undertaken in terms of both efficacy and side-effects. The method using 'last observation carried forward' was declared in three studies (Wahlbeck 2000,[113] Beasley 1999,[77] Bondolfi 1998[110]).

The two early crossover trials (Gerlach 1974,[84] 1975[85]) provided very few data for the first arm of the study.

Rosenheck 1997,[105] Shopsin 1979[96] and Gelenberg 1979[97] all had attrition rates greater than 50% and data from all outcomes except 'leaving study early' were not entered into the analysis.

Clozapine versus typical antipsychotic drugs

The results are presented in *Tables 11–16*.

Mortality

No differences between groups were found in 11 trials for which data on mortality were available for either the short or long term. Four deaths occurred in 614 individuals treated with typical antipsychotic drugs compared with three deaths in 629 treated with clozapine (RR, short term, 0.34; 95% CI, 0.01 to 8.14; RR, long term, 0.64; 95% CI, 0.13 to 3.12).

Relapse rate

In both the short and the long term, the relapse rate favoured clozapine (RR, short term, 0.66; 95% CI, 0.47 to 0.91; RR, long term, 0.37; 95% CI, 0.17 to 0.79). Heterogeneity was seen in the long-term result (chi-squared = 8.22, $p = 0.016$); however, this disappeared when the Kane 1994[100] results were removed from the analysis, giving a non-significant result (RR, 1.19; 95% CI, 0.44 to 3.26).

Clinical improvement as defined by study authors

Both short- and long-term studies favoured clozapine (RR, short term, 0.73; 95% CI, 0.67 to 0.80; RR, long term, 0.68; 95% CI, 0.59 to 0.79; risk difference short term, –0.18; 95% CI, –0.23 to –0.13; risk difference long term, –0.28; 95% CI, –0.37 to –0.18). Continuous data for mental state (both overall and negative symptoms) also favoured clozapine.

Readiness for hospital discharge

No differences between treatment groups were found (RR, short term, 0.98; 95% CI, 0.86 to 1.13; RR, long term, 0.96; 95% CI, 0.71 to 1.28).

Not discharged or readmitted within 1 year of discharge

Data were available only from one long-term study (Essock 1996[103]) with 225 participants. No significant benefit of clozapine was detected (RR, 0.88; 95% CI, 0.70 to 1.10).

Working ability

When data from five short-term studies (488 participants) were analysed, no differences between treatment modalities were found (RR, 0.94; 95% CI, 0.82 to 1.08). Heterogeneity was seen in the result (chi-squared = 7.11, $p = 0.069$) but it was unclear which studies were responsible for the heterogeneity. The result should therefore be interpreted with caution.

Acceptability of treatment

Acceptability of treatment was measured by recording the numbers of participants dropping out of treatment groups. Clozapine did not show a significant benefit over typical antipsychotic treatment in the short term (RR, 0.83; 95% CI, 0.68 to 1.02). Clozapine did show a significant benefit over typical antipsychotic drugs in long-term treatment (RR, 0.59; 95% CI, 0.51 to 0.68).

Patient satisfaction

Participants' satisfaction with treatment was no better for clozapine than for conventional antipsychotic drugs (RR, 0.72; 95% CI, 0.40 to 1.30), as expressed by those being treated in two short-term studies.

TABLE 11 *Clozapine versus typical antipsychotic drugs (overall) – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
Death	Guirguis 1977 (50)	0/22	0/28	0.34 (0.01 to 8.14)
	Leon 1974 (50)	0/25	0/25	
	Gerlach 1974 (20)	0/10	0/10	
	Gerlach 1975 (8)	0/4	0/4	
	Honigfeld 1984 (79)	0/39	1/40	
	Erlandsen 1981 (40)	0/19	0/21	
	Gelenberg 1979b (15)	0/7	0/8	
	Kane 1988 (268)	0/126	0/142	
	Kumra 1996b (21)	0/10	0/11	
	Howanitz 1999 (42)	0/24	0/18	
Relapse	Chiu 1976 (64)	5/33	16/31	0.66 (0.47 to 0.91)
	Guirguis 1977 (50)	6/22	8/28	
	Xu 1985 (60)	0/30	2/30	
	Leon 1974 (50)	0/25	0/25	
	Gerlach 1974 (20)	0/10	0/10	
	Gerlach 1975 (8)	0/4	0/4	
	Fischer-Cornelssen 1974 (223)	4/110	6/113	
	Honigfeld 1984 (79)	7/39	15/40	
	Klieser 1989 (32)	2/16	2/16	
	Klieser 1994 (36)	1/18	1/18	
	Singer 1974 (40)	1/20	1/20	
	Erlandsen 1981 (40)	0/19	0/21	
	Hong 1997 (40)	2/7	2/8	
	Claghorn 1987 (151)	13/75	13/76	
	Kane 1988 (268)	3/126	9/142	
	Kumra 1996 (21)	0/10	0/11	
	Buchanan 1998 (75)	6/38	3/37	
Global impression				
Not clinically improved	Chiu 1976 (64)	19/33	20/31	0.73 (0.67 to 0.80)
	Leon 1974 (50)	2/25	10/25	
	Fischer-Cornelssen 1974 (223)	34/110	51/113	
	Fischer-Cornelssen 1976a (74)	23/38	27/36	
	Fischer-Cornelssen 1976b (72)	24/36	18/36	
	Honigfeld 1984 (79)	27/39	36/40	
	Itoh 1977 (88)	4/47	8/41	
	Erlandsen 1981 (40)	9/19	18/21	
	Ciurezu 1976 (40)	4/20	7/20	
	Hong 1997 (40)	15/21	19/19	
	Kane 1988 (268)	88/126	137/142	
	Kumra 1996 (21)	3/10	4/11	
	Buchanan 1998 (41)	12/21	19/20	
Not ready for discharge	Fischer-Cornelssen 1974 (223)	47/110	59/113	0.98 (0.86 to 1.13)
	Fischer-Cornelssen 1976a (74)	30/38	29/36	
	Fischer-Cornelssen 1976b (72)	23/36	14/36	
	Honigfeld 1984 (79)	38/39	38/40	
	Ciurezu 1976 (40)	3/20	4/20	
Unable to work	Fischer-Cornelssen 1974 (223)	48/110	61/113	0.94 (0.82 to 1.08)
	Fischer-Cornelssen 1976a (74)	25/38	30/36	
	Fischer-Cornelssen 1976b (72)	25/36	17/36	
	Honigfeld 1984 (79)	37/39	37/40	
	Ciurezu 1976 (40)	2/20	2/20	
Patient dissatisfaction	Fischer-Cornelssen 1974 (78)	6/39	9/39	0.72 (0.40 to 1.30)
	Klieser 1994 (36)	7/18	9/18	

continued

***TABLE 11* contd** *Clozapine versus typical antipsychotic drugs (overall) – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
Global impression				
Leaving study early	Chiu 1976 (64)	11/33	17/31	0.83 (0.68 to 1.02)
	Guirguis 1977 (50)	6/22	9/28	
	Xu 1985 (60)	0/30	2/30	
	Liu 1994 (40)	3/20	4/20	
	Leon 1974 (50)	0/25	0/25	
	Gerlach 1974 (20)	0/10	0/10	
	Gerlach 1975 (8)	0/4	0/4	
	Fischer-Cornelssen 1974 (223)	6/110	8/113	
	Honigfeld 1984 (79)	8/39	15/40	
	Klieser 1989 (32)	2/16	2/16	
	Klieser 1994 (36)	1/18	1/18	
	Singer 1974 (40)	1/20	1/20	
	Itoh 1977 (88)	4/47	0/41	
	Erlandsen 1981 (40)	0/19	0/21	
	Ciurezu 1976 (40)	1/20	0/20	
	Salganik 1998 (34)	5/17	2/17	
	Hong 1997 (40)	2/21	2/19	
	Shopsin 1979 (31)	6/16	11/15	
	Gelenberg 1979 (15)	4/7	5/8	
	Claghorn 1987 (151)	27/75	36/76	
	Kane 1988 (268)	15/126	18/142	
	Kumra 1996 (21)	3/10	1/11	
	Buchanan 1998 (75)	8/38	3/37	
	Howanitz 1999 (42)	3/24	5/18	
Side-effects				
Blood problems	Chiu 1976 (64)	0/33	0/31	4.70 (1.09 to 20.33)
	Guirguis 1977 (50)	0/22	0/28	
	Leon 1974 (50)	0/25	0/25	
	Fischer-Cornelssen 1974 (141)	0/69	0/72	
	Erlandsen 1981 (40)	0/19	0/21	
	Hong 1997 (40)	1/21	0/19	
	Kane 1988 (268)	0/126	0/142	
	Kumra 1996 (21)	4/10	0/11	
	Buchanan 1998 (75)	1/38	0/37	
	Howanitz 1999 (42)	2/24	0/18	
Drowsiness	Chiu 1976 (64)	9/33	5/31	1.34 (1.15 to 1.57)
	Guirguis 1977 (35)	8/16	8/19	
	Leon 1974 (50)	16/25	15/25	
	Gerlach 1975 (8)	2/4	0/4	
	Fischer-Cornelssen 1974 (141)	55/69	45/72	
	Singer 1974 (38)	14/19	12/19	
	Itoh 1977 (91)	19/47	12/44	
	Erlandsen 1981 (40)	2/19	0/21	
	Ciurezu 1976 (40)	1/20	0/20	
	Hong 1997 (40)	5/21	4/19	
	Claghorn 1987 (151)	16/75	14/76	
	Kane 1988 (268)	26/126	18/142	
	Kumra 1996 (21)	9/10	3/11	
	Buchanan 1998 (75)	20/38	13/37	
	Howanitz 1999 (42)	3/24	6/18	

continued

***TABLE 11* contd** *Clozapine versus typical antipsychotic drugs (overall) – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
***Side-effects* contd**				
Low blood pressure/dizziness	Guirguis 1977 (35)	3/16	5/19	0.89 (0.66 to 1.19)
	Leon 1974 (50)	4/25	0/25	
	Fischer-Cornelssen 1974 (141)	8/69	3/72	
	Singer 1974 (38)	2/19	1/19	
	Itoh 1977 (91)	12/47	5/44	
	Hong 1997 (40)	1/21	0/19	
	Claghorn 1987 (151)	0/75	1/76	
	Kane 1988 (268)	16/126	54/14	
	Buchanan 1998 (75)	19/38	27/37	
	Howanitz 1999 (42)	3/24	4/18	
Salivation – too much	Chiu 1976 (36)	4/22	0/14	3.33 (2.51 to 4.42)
	Guirguis 1977 (35)	2/16	1/19	
	Xu 1985 (60)	24/30	6/30	
	Leon 1974 (50)	16/25	0/25	
	Fischer-Cornelssen 1974 (100)	13/49	10/51	
	Singer 1974 (38)	5/19	2/19	
	Erlandsen 1981 (40)	2/19	0/21	
	Hong 1997 (40)	6/21	1/19	
	Claghorn 1987 (151)	30/75	8/76	
	Kane 1988 (268)	17/126	2/142	
	Kumra 1996 (21)	7/10	2/11	
	Buchanan 1998 (75)	31/38	7/37	
	Howanitz 1999 (42)	6/24	8/18	
Salivation – too little	Chiu 1976 (36)	0/22	7/14	0.36 (0.26 to 0.50)
	Fischer-Cornelssen 1974 (100)	11/49	20/51	
	Singer 1974 (38)	3/19	3/19	
	Itoh 1977 (91)	6/47	11/44	
	Hong 1997 (40)	2/21	7/19	
	Claghorn 1987 (40)	5/75	12/76	
	Kane 1988 (268)	6/126	28/142	
	Buchanan 1998 (75)	7/38	23/37	
Weight gain	Chiu 1976 (64)	4/33	7/31	0.84 (0.51 to 1.41)
	Hong 1997 (40)	4/21	8/19	
	Kumra 1996 (21)	7/10	4/11	
	Howanitz 1999 (42)	5/24	3/18	
Movement disorder	Chiu 1976 (36)	4/22	0/14	0.59 (0.48 to 0.74)
	Guirguis 1977 (35)	1/16	1/19	
	Leon 1974 (50)	9/25	17/25	
	Gerlach 1975 (8)	3/4	4/4	
	Fischer-Cornelssen 1974 (100)	17/49	22/51	
	Klieser 1994 (93)	0/37	25/45	
	Singer 1974 (38)	7/19	6/19	
	Itoh 1977 (88)	28/47	28/41	
	Erlandsen 1981 (40)	0/19	8/21	
	Hong 1997 (40)	1/21	7/19	
	Claghorn 1987 (151)	9/75	19/76	
	Kumra 1996 (21)	0/10	1/11	
	Buchanan 1998 (41)	5/21	3/20	
	Howanitz 1999 (42)	4/24	4/18	

continued

***TABLE 11* contd** *Clozapine versus typical antipsychotic drugs (overall) – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
***Side-effects* contd**				
Fits	Fischer-Cornelssen 1974 (141)	0/69	1/72	1.03 (0.26 to 4.04)
	Hong 1997 (40)	0/21	0/19	
	Claghorn 1987 (151)	0/75	1/76	
	Kumra 1996 (21)	1/10	0/11	
	Buchanan 1998 (75)	1/38	0/37	
	Howanitz 1999 (42)	0/24	0/18	
High temperature	Guirguis 1977 (35)	4/16	0/19	2.33 (1.53 to 3.53)
	Fischer-Cornelssen 1974 (48)	12/23	5/25	
	Itoh 1977 (90)	21/46	11/44	
	Claghorn 1987 (151)	1/75	0/76	
	Kane 1988 (268)	16/126	6/142	
	Buchanan 1998 (75)	1/38	2/37	
	Howanitz 1999 (42)	0/24	0/18	

n, *number of events;* N, *number of participants in group*

TABLE 12 *Clozapine versus typical antipsychotic drugs: children and adolescents – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Death	Kumra 1996 (21)	0/10	0/11	Not estimable
Relapse	Kumra 1996 (21)	0/10	0/11	Not estimable
Global impression: not clinically improved	Kumra 1996 (21)	3/10	4/11	0.83 (0.24 to 2.82)*
Leaving study early	Kumra 1996 (21)	3/10	1/11	3.30 (0.41 to 26.81)
Side-effects				
Blood problems	Kumra 1996 (21)	4/10	0/11	9.82 (0.59 to 162.25)
Drowsiness	Kumra 1996 (21)	9/10	3/11	3.30 (1.23 to 8.85)
Too much salivation	Kumra 1996 (21)	7/10	2/11	3.85 (1.03 to 14.38)
Weight gain	Kumra 1996 (21)	7/10	4/11	1.93 (0.80 to 4.64)
Movement disorder	Kumra 1996 (21)	0/10	1/11	0.36 (0.02 to 8.03)**
Fits	Kumra 1996 (21)	1/10	0/11	3.27 (0.15 to 72.24)

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.06 (95% CI, –0.47 to 0.34)*

** *Risk difference, –0.09 (95% CI, –0.34 to 0.15)*

Blood problems

The review authors defined blood problems as:

(a) any blood problem requiring withdrawal of patient from trial
(b) leukopaenia – defined as a white blood-cell count of < 3000 mm^3
(c) neutropenia – defined as a granulocyte count of < 1500 mm^3.

Such problems occurred more frequently in those treated with clozapine in the short to medium term (RR, 4.70; 95% CI, 1.09 to 20.33). In one small long-term study, no significant difference was seen between groups. Blood problems were reported in 2.2% of clozapine-treated patients and 0.2% of patients in the control group. In the single study in which adolescents and younger people were considered, the

TABLE 13 *Clozapine versus typical antipsychotic drugs (overall) – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Death	Essock 1996 (227)	3/138	3/89	0.64 (0.13 to 3.12)
	Rosenheck 1997 (423)	0/205	0/218	
Relapse	Tamminga 1994 (39)	2/25	0/14	0.37 (0.17 to 0.79)
	Kane 1994 (52)	1/25	17/27	
	Lee 1994 (64)	6/35	5/29	
Global impression: not clinically improved	Marder 1994 (71)	21/37	32/34	0.68 (0.59 to 0.79)
	Essock 1996 (225)	80/136	74/89	
Not ready for discharge	Essock 1996 (225)	60/136	41/89	0.96 (0.71 to 1.28)
Hospitalisation: not discharged or readmitted within 1 year of discharge	Essock 1996 (225)	74/136	55/89	0.88 (0.70 to 1.10)
Leaving study early	Tamminga 1994 (39)	6/25	1/14	0.59 (0.51 to 0.68)
	Kane 1994 (71)	12/37	21/34	
	Lee 1994 (64)	6/35	5/29	
	Essock 1996 (225)	46/136	58/89	
	Rosenheck 1997 (423)	88/205	157/218	
Side-effects				
Blood problems	Tamminga 1994 (39)	1/25	1/14	0.56 (0.04 to 8.28)
Low blood pressure/dizziness	Tamminga 1994 (39)	1/25	0/14	1.73 (0.08 to 39.87)
Fits	Tamminga 1994 (39)	1/25	0/14	2.86 (0.92 to 8.86)
	Essock 1996 (225)	14/136	3/89	

n, *number of events;* N, *number of participants in group*

clozapine-treated group developed blood problems very frequently but the difference between groups was not significant, probably because of the small sample size (RR, 9.82; 95% CI, 0.59 to 162.25).

Other adverse effects

Clozapine commonly caused increased salivation (RR, short term, 3.33; 95% CI, 2.51 to 4.42), as well as troublesome drowsiness (RR, short term, 1.34; 95% CI, 1.15 to 1.57) and temperature increase (RR, short term, 2.33; 95% CI, 1.53 to 3.53) when compared with typical neuroleptic drugs. Heterogeneity was seen in the result for increased salivation (chi-squared = 28.55, $p = 0.0046$), which disappeared when the Howanitz 1999 trial[106] was removed from the analysis. The result remained significant (RR, 3.96; 95% CI, 2.90 to 5.40).

The occurrence of dry mouth (RR, 0.36; 95% CI, 0.26 to 0.50) and extrapyramidal movement adverse effects (RR, 0.59; 95% CI, 0.48 to 0.74; risk difference, –0.15; 95% CI, –0.21 to –0.10) were more frequent in those treated with conventional antipsychotic drugs. Heterogeneity was seen in the result for movement disorders both in the overall analysis (chi-squared = 25.59, $p = 0.019$) and in the analysis restricted to participants with treatment-resistant illness (chi-squared = 4.71, $p = 0.095$). When the Klieser 1994[90] and Erlandsen 1981[93] studies were removed from the overall analysis, the heterogeneity disappeared and the result remained significantly in favour of clozapine over typical antipsychotic drugs (RR, 0.75; 95% CI, 0.60 to 0.92; risk difference, –0.09; 95% CI, –0.15 to –0.03). When the Hong 1997 study[95] was removed from the treatment-resistant analysis, the heterogeneity disappeared and the result remained non-significant (RR, 1.20; 95% CI, 0.38 to 3.79).

For low blood pressure/dizziness, weight gain or fits in the short or long term, no differences were found between clozapine and the typical neuroleptic drugs. Heterogeneity was seen in the result for low blood pressure/dizziness in both the overall analysis (chi-squared = 33.85, $p = 0.0001$) and that restricted to participants with treatment-resistant illness (chi-squared = 21.38, $p < 0.00001$). When the Kane 1988 study[99] was removed from the analysis, the results became

TABLE 14 *Clozapine versus typical antipsychotic drugs: treatment-resistant illness – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Death	Kane 1988 (268)	0/126	0/142	0.64 (0.13 to 3.12)
	Essock 1996 (227)	3/138	3/89	
	Kumra 1996 (21)	0/10	0/11	
	Rosenheck 1997 (423)	0/205	0/216	
Relapse	Klieser 1989 (32)	2/16	2/16	1.04 (0.61 to 1.78)
	Kane 1988 (268)	15/126	19/142	
	Kumra 1996 (21)	0/10	0/11	
	Buchanan 1998 (75)	6/38	3/37	
Global impression: not improved	Hong 1997 (40)	15/21	18/19	0.71 (0.64 to 0.79)
	Kane 1988 (268)	88/126	137/142	
	Kumra 1996 (21)	3/10	4/11	
	Buchanan 1998 (75)	12/21	11/20	
Leaving study early	Klieser 1989 (32)	2/16	2/16	1.19 (0.73 to 1.94)
	Hong 1997 (40)	2/21	2/19	
	Kane 1988 (268)	15/126	19/142	
	Kumra 1996 (21)	3/10	1/11	
	Buchanan 1998 (75)	8/38	3/37	
Side-effects				
Blood problems	Hong 1997 (40)	1/21	0/19	13.93 (0.79 to 245.63)
	Kane 1988 (268)	0/126	0/142	
	Kumra 1996 (21)	4/10	0/11	
	Buchanan 1998 (75)	1/38	0/37	
Drowsiness	Hong 1997 (40)	5/21	4/19	1.65 (1.17 to 2.33)
	Kane 1988 (268)	26/126	18/142	
	Kumra 1996 (21)	9/10	3/11	
	Buchanan 1998 (75)	20/38	13/37	
Low blood pressure/dizziness	Hong 1997 (40)	1/21	0/19	0.64 (0.44 to 0.92)
	Kane 1988 (268)	16/126	54/142	
	Buchanan 1998 (75)	19/38	7/37	
Salivation – too much	Hong 1997 (40)	6/21	1/19	5.17 (2.99 to 8.94)
	Kane 1988 (268)	17/126	2/142	
	Kumra 1996 (21)	7/10	2/11	
	Buchanan 1998 (75)	31/38	7/37	
Salivation – too little	Hong 1997 (40)	2/21	7/19	0.27 (0.16 to 0.45)
	Kane 1988 (268)	6/126	28/142	
	Buchanan 1998 (75)	7/38	23/37	
Weight gain	Hong 1997 (40)	4/21	8/19	0.91 (0.48 to 1.73)
	Kumra 1996 (21)	7/10	4/11	
Movement disorder	Hong 1997 (40)	1/21	7/19	0.54 (0.22 to 1.31)*
	Kumra 1996 (21)	0/10	1/11	
	Buchanan 1998 (41)	5/21	3/20	
High temperature	Kane 1988 (268)	16/126	6/142	2.34 (1.04 to 5.25)
	Buchanan 1998 (75)	1/38	2/37	
Fits	Hong 1997 (40)	0/21	0/19	3.06 (1.05 to 8.91)
	Essock 1996 (225)	14/136	3/89	
	Kumra 1996 (21)	1/10	0/11	
	Buchanan 1998 (75)	1/38	0/37	

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.11 (95% CI –0.25 to 0.03)*

TABLE 15 *Clozapine versus typical antipsychotic drugs: treatment-resistant illness – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global impression: not improved	Essock 1996 (225)	80/136	74/89	0.71 (0.60 to 0.84)
Not ready for discharge	Essock 1996 (225)	60/136	41/89	0.96 (0.71 to 1.28)
Hospitalisation: not discharged or readmitted within 1 year of discharge	Essock 1996 (225)	74/136	55/89	0.88 (0.70 to 1.10)
Leaving study early	Essock 1996 (225)	46/136	58/89	0.52 (0.39 to 0.69)

n, *number of events;* N, *number of participants in group*

TABLE 16 *Clozapine versus typical antipsychotic drugs: elderly people*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Death	Howanitz 1999 (42)	0/24	0/18	Not estimable
Leaving study early – any reason	Salganik 1998 (34) Howanitz 1999 (42)	5/17 3/24	2/17 5/18	0.98 (0.40 to 2.41)
Side-effects				
Blood problems	Howanitz 1999 (42)	2/24	0/18	3.80 (0.19 to 74.61)
Drowsiness	Howanitz 1999 (42)	3/24	6/18	0.38 (0.11 to 1.30)
Low blood pressure/dizziness	Howanitz 1999 (42)	3/24	4/18	0.56 (0.14 to 2.21)
Too much salivation	Howanitz 1999 (42)	6/24	8/18	0.56 (0.24 to 1.33)
Weight gain	Howanitz 1999 (42)	5/24	3/18	1.25 (0.34 to 4.56)
Movement disorder	Howanitz 1999 (42)	4/24	4/18	0.75 (0.22 to 2.60)*
Fits	Howanitz 1999 (42)	0/24	0/18	Not estimable
High temperature	Howanitz 1999 (42)	0/24	0/18	Not estimable

* *Risk difference, –0.06 (95% CI, –0.30 to 0.19)*

significant for both analyses (RR, 1.89; 95% CI, 1.25 to 2.86; and RR, 2.65; 95% CI, 1.29 to 5.45, respectively). Heterogeneity was also seen in the result for weight gain when the analysis was restricted to participants with treatment-resistant illness (chi-squared = 24.55, $p = 0.033$). Only two studies were included in the analysis and both showed no significant differences between groups (Hong 1997:[95] RR, 0.45; 95% CI, 0.16 to 1.26; Kumra 1996:[104] RR, 1.93; 95% CI, 0.80 to 4.64).

Children and adolescents (see Table 12*)*

Clozapine caused more drowsiness (RR, 3.30; 95% CI, 1.23 to 8.85) and hypersalivation (RR, 3.85; 95% CI, 1.03 to 14.38) than typical antipsychotic drugs in one study in children and adolescents.

Elderly people (see Table 16*)*

No significant differences were seen between clozapine and typical antipsychotic treatments for any outcomes in elderly people as measured in two studies.

Clozapine versus typical antipsychotic drugs: treatment-resistant schizophrenia

The results are presented in *Tables 14* and *15*.

Mortality

No differences in mortality were observed in 937 individuals in four studies on people with treatment-resistant schizophrenia.

Relapse rate
Analysis of four homogeneous short-term studies (396 patients) did not reveal any differences in relapse rates between treatment groups (RR, 1.04; 95% CI, 0.61 to 1.78).

Clinical improvement as defined by study authors
In four homogeneous short-term studies with 370 patients, clozapine was favoured (RR, 0.71; 95% CI, 0.64 to 0.79; risk difference, –0.27; 95% CI, –0.34 to –0.19). One long-term study (225 participants) also favoured clozapine but to a lesser extent (RR, 0.71; 95% CI, 0.60 to 0.84; risk difference, –0.24; 95% CI, –0.36 to –0.13).

Readiness for hospital discharge
No significant benefit was observed for clozapine on dischargeability and readmission in one long-term study (225 patients), although there was a trend for better results in the clozapine group (dischargeability: RR, 0.96; 95% CI, 0.71 to 1.28; discharge and no readmission within 1 year: RR, 0.88; 95% CI, 0.70 to 1.10).

Acceptability of treatment
The acceptability of the treatment as measured by the number of people dropping out of the heterogeneous short-term studies (436 patients with treatment-resistant illness) did not favour clozapine (RR, 1.19; 95% CI, 0.73 to 1.94). The long-term study (225 patients) significantly favoured clozapine (RR, 0.52; 95% CI, 0.39 to 0.69).

Publication bias
To look for a possible publication bias (that is, the possibility that studies with negative findings have not reached full publication), funnel graphs for clinical improvement, relapse frequency, number of drop-outs (acceptability) and any other outcome for which more than five studies were included in the analysis were constructed by plotting number of study participants (on the *y* axis) against the logarithmic odds ratios (ORs) (on the *x* axis). Funnel-plot asymmetry was seen in the number of drop-outs reported (in both overall and treatment-resistant analyses), drowsiness (overall analysis) and low blood pressure/dizziness (overall analysis).

Sensitivity analyses
Sensitivity analysis that removed studies with more than 25% attrition (Chiu 1976 (44%),[78] Guirguis 1977 (30%),[79] Honigfeld 1984 (29%),[88] Claghorn 1987 (42%),[98] Marder 1994 (46%),[116] Essock 1996 (46%)[103]) made no substantial differences to the short- to medium-term results but left no long-term data, which suggests that all long-term results should be treated with caution.

When only those studies in which clozapine was compared with haloperidol were included in the analysis, the following changes were seen: for relapse before 6 months, the difference between clozapine and haloperidol was not significant (RR, 0.76; 95% CI, 0.41 to 1.38). There was also no significant difference between clozapine-treated and haloperidol-treated groups for blood problems at less than 6 months (RR, 3.04; 95% CI, 0.73 to 12.69) but the clozapine groups experienced significantly more low blood pressure/dizziness (RR, 2.44; 95% CI, 1.37 to 4.34). There was no significant difference between clozapine and haloperidol for movement disorder (RR, 0.75; 95% CI, 0.56 to 1.02) and no significant difference between clozapine and haloperidol in terms of high temperature (RR, 1.62; 95% CI, 0.91 to 2.88).

Clozapine versus olanzapine

The results for clozapine versus olanzapine in the short to medium term (up to 26 weeks) are presented in *Table 17*.

Mortality
In one study (Beasley 1999[77]), no deaths were reported in either group.

Global state
No difference was seen between groups for the outcome 'clinically not improved' as measured by the CGI-I scale.

Mental state
In two studies (Oliemeulen 2000,[109] Beasley 1999[77]), no differences were seen between groups for the outcome 'not improved' – defined as less than 20% improvement on the BPRS or PANSS scales. These studies also showed no difference between groups for the outcome 'deterioration in mental state or relapse'.

Acceptability of treatment
In one study (Beasley 1999[77]), no difference was found between groups receiving clozapine and olanzapine for the outcomes 'leaving study early' and 'patient dissatisfaction' as measured by direct questioning.

TABLE 17 *Clozapine versus olanzapine – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
All deaths	Beasley 1999 (180)	0/90	0/90	Not estimable
Suicides	Beasley 1999 (180)	0/90	0/90	Not estimable
Global impression: not clinically improved (CGI)	Beasley 1999 (180)	33/90	24/90	1.38 (0.89 to 2.13)*
Mental state				
Not clinically improved (< 20% change in BPRS/PANSS)	Oliemeulen 2000 (36) Beasley 1999 (180)	10/15 43/90	15/21 37/90	1.10 (0.84 to 1.45)**
Deterioration or relapse	Oliemeulen 2000 (36) Beasley 1999 (180)	1/15 22/90	5/21 28/90	0.72 (0.45 to 1.14)
Leaving study early – any reason	Beasley 1999 (180)	37/90	36/90	1.03 (0.72 to 1.46)
Patient dissatisfaction	Beasley 1999 (180)	4/90	9/90	0.44 (0.14 to 1.39)
Side-effects				
EPS	Beasley 1999 (180)	9/90	4/90	2.25 (0.72 to 7.04)***
Nausea/vomiting	Beasley 1999 (180)	15/90	5/90	3.00 (1.14 to 7.91)
Orthostatic dizziness	Beasley 1999 (180)	8/90	1/90	8.00 (1.02 to 62.66)
Hypersalivation	Beasley 1999 (180)	26/90	2/90	13.00 (3.18 to 53.15)
Dry mouth	Beasley 1999 (180)	0/90	4/90	0.11 (0.01 to 2.03)
Insomnia	Beasley 1999 (180)	3/90	7/90	0.43 (0.11 to 1.61)
Hypersomnia (too much sleep)	Beasley 1999 (180)	22/90	12/90	1.83 (0.97 to 3.48)
Somnolence	Beasley 1999 (180)	22/90	12/90	1.83 (0.97 to 3.48)
Weight gain	Beasley 1999 (180)	6/90	6/90	1.00 (0.34 to 2.98)
Constipation	Beasley 1999 (180)	17/90	6/90	2.83 (1.17 to 6.86)
Agitation	Beasley 1999 (180)	4/90	10/90	0.40 (0.13 to 1.23)
Headache	Beasley 1999 (180)	5/90	10/90	0.50 (0.18 to 1.40)
Anxiety	Beasley 1999 (180)	5/90	5/90	1.00 (0.30 to 3.34)
Rhinitis	Beasley 1999 (180)	3/90	5/90	0.60 (0.15 to 2.44)
Influenza syndrome	Beasley 1999 (180)	5/90	3/90	1.67 (0.41 to 6.77)
Fever	Beasley 1999 (180)	5/90	1/90	5.00 (0.60 to 41.95)
Sweating	Beasley 1999 (180)	5/90	2/90	2.50 (0.50 to 12.55)
Dizziness	Beasley 1999 (180)	8/90	1/90	8.00 (1.02 to 62.66)
Teeth disorder	Beasley 1999 (180)	4/90	0/90	9.00 (0.49 to 164.77)
White cell problems	Beasley 1999 (180)	5/90	1/90	5.00 (0.60 to 41.95)

n, *number of events;* N, *number of participants in group*

* *Risk difference, 0.10 (95% CI, –0.04 to 0.24)*

** *Risk difference, 0.05 (95% CI, –0.08 to 0.21)*

*** *Risk difference, 0.06 (95% CI, –0.02 to 0.13)*

Side-effects
Olanzapine was less likely than clozapine to cause nausea and vomiting, orthostatic dizziness, hypersalivation, constipation and dizziness. None of the reported side-effects were more common with olanzapine than with clozapine.

Clozapine versus risperidone

The results for clozapine versus risperidone in the short to medium term (up to 26 weeks) are presented in *Table 18*.

Mortality
In two studies (Breier 1999,[112] Wahlbeck 2000[113]) no deaths were reported in either group.

Hospitalisation
In one study (Wahlbeck 2000[113]), no difference was found between groups for the outcome 'not ready for discharge'.

Mental state
In four studies (Bondolfi 1998,[110] Breier 1999,[112] Wahlbeck 2000,[113] Chowdhury 1999[71]), no differences were found between groups for the outcome 'not improved' (defined as less than 20% improvement on the BPRS or PANSS scales). In three studies (Bondolfi 1998, Anand 1998,[111] Wahlbeck 2000), no differences were found between groups for the outcome 'deterioration in mental state or relapse'. In Bondolfi 1998, no differences were found between groups in terms of concentration difficulties or memory problems.

Acceptability of treatment
In six studies (Klieser 1994,[90] Bondolfi 1998,[110] Anand 1998,[111] Breier 1999,[112] Wahlbeck 2000,[113] Chowdhury 1999[71]), people taking clozapine were found to be no more or less likely to leave the studies early than those taking risperidone. In one study (Wahlbeck 2000), no difference was found between groups for the outcome 'patient dissatisfaction'.

Side-effects
Patients taking risperidone were more likely than those taking clozapine to experience extrapyramidal symptoms, akathisia, dry mouth, insomnia and impotence (borderline significance), whereas those taking clozapine were more likely than those taking risperidone to experience fatigue, hypersalivation and tachycardia.

Clozapine versus zotepine

The results for the short to medium term (up to 26 weeks) are shown in *Table 19*. Clozapine was compared with zotepine in only one study (Meyer-Lindenberg 1996[108]) and as > 50% of participants left the study early, only data for the outcome 'leaving study early' were included. No differences were seen between groups.

Clozapine versus remoxipride/ risperidone/zotepine

The results for the short to medium term (up to 26 weeks) are shown in *Table 20*. Only one study was included (Klieser 1994[90]); the data were presented such that it was impossible to separate results for remoxipride, risperidone and zotepine, so the study is reported separately.

Mental state
No differences were found between groups for the cognitive outcome 'improvement in memory'.

Side-effects
No difference was seen between groups in likelihood to experience extrapyramidal symptoms.

Sensitivity analyses
Removing studies with more than 25% attrition (Anand 1998 (26%),[111] Wahlbeck 2000 (35%),[113] Beasley 1999 (40%)[77]) from pooled estimates made no substantial difference to the results.

Publication bias
Owing to the limited numbers of studies for each outcome, funnel graphs were not constructed for the atypical antipsychotic drugs versus clozapine reviews.

Rare or long-term events
In all, 24 non-randomised studies of rare or long-term adverse events with clozapine were found. Data extraction sheets for these studies can be found in appendix 4. Eight were studies of mortality[117–124] – three specifically looked at suicide.[117,121,124] Ten studies related to the incidence of blood dyscrasias such as agranulocytosis and leucopenia.[125–134]

One was a study of NMS,[135] another of venous thromboembolic complications that occurred during clozapine treatment.[136] Five were studies of epilepsy or seizure rates[122,137–140] and two of tardive dyskinesia.[141,142]

TABLE 18 *Clozapine versus risperidone – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
Death				
All	Breier 1999 (29)	0/14	0/15	Not estimable
	Wahlbeck 2000 (19)	0/10	0/9	
Suicide	Breier 1999 (29)	0/14	0/15	Not estimable
	Wahlbeck 2000 (19)	0/10	0/9	
Global impression: not ready for discharge	Wahlbeck 2000 (20)	5/11	2/9	2.05 (0.51 to 8.16)
Mental state				
Not clinically improved (< 20% change on BPRS/PANSS)	Bondolfi 1998 (86)	15/43	14/43	0.92 (0.65 to 1.29)*
	Breier 1999 (29)	9/14	12/15	
	Wahlbeck 2000 (20)	6/11	3/9	
	Chowdhury 1999 (60)	6/30	10/30	
Deterioration or relapse	Bondolfi 1998 (86)	7/43	8/43	1.13 (0.79 to 1.62)
	Anand 1998 (273)	38/138	34/135	
	Wahlbeck 2000 (20)	4/11	0/9	
Leaving study early – any reason	Klieser 1996 (59)	6/20	22/39	0.98 (0.73 to 1.31)
	Bondolfi 1998 (86)	9/43	9/43	
	Anand 1998 (273)	38/138	34/135	
	Breier 1999 (29)	0/14	0/15	
	Wahlbeck 2000 (20)	6/11	1/9	
	Chowdhury 1999 (60)	6/30	8/30	
Patient dissatisfaction	Wahlbeck 2000 (20)	5/11	4/9	1.02 (0.39 to 2.71)
Side-effects				
Concentration difficulties	Bondolfi 1998 (86)	11/43	7/43	1.57 (0.67 to 3.67)
Memory problems	Bondolfi 1998 (86)	15/43	9/43	1.67 (0.82 to 3.39)
EPS	Bondolfi 1998 (86)	3/43	3/43	0.42 (0.20 to 0.85)**
	Breier 1999 (29)	2/14	10/15	
	Wahlbeck 2000 (19)	3/10	6/9	
Fatigue	Bondolfi 1998 (86)	22/43	12/43	1.83 (1.04 to 3.22)
Nausea/vomiting	Bondolfi 1998 (86)	9/43	7/43	1.29 (0.53 to 3.14)
Orthostatic dizziness	Bondolfi 1998 (86)	9/43	5/43	1.80 (0.66 to 4.93)
Libido decrease	Bondolfi 1998 (86)	2/43	4/43	0.50 (0.10 to 2.59)
Hypersalivation	Chowdhury 1999 (60)	18/30	0/30	37.00 (2.33 to 587)
Dry mouth	Chowdhury 1999 (60)	0/30	14/30	0.03 (0.00 to 0.05)
Seizures	Chowdhury 1999 (60)	1/30	0/30	3.00 (0.13 to 70.83)
	Wahlbeck 2000 (19)	0/10	0/9	
Sedation/drowsiness	Bondolfi 1998 (86)	20/43	13/43	1.58 (0.91 to 2.74)
	Wahlbeck 2000 (19)	1/10	0/9	
Insomnia	Chowdhury 1999 (60)	0/30	10/30	0.21 (0.07 to 0.65)
	Bondolfi 1998 (86)	3/43	6/43	
Hypersomnia (too much sleep)	Bondolfi 1998 (86)	9/43	8/43	1.12 (0.48 to 2.64)
Weight gain	Chowdhury 1999 (60)	13/30	13/30	1.26 (0.81 to 1.95)
	Bondolfi 1998 (86)	16/43	10/43	
Constipation	Chowdhury 1999 (60)	9/30	15/30	0.60 (0.31 to 1.15)
Tachycardia	Chowdhury 1999 (60)	23/30	0/30	47.00 (2.98 to 740)
Impotence	Chowdhury 1999 (60)	0/22	8/23	0.06 (0.00 to 1.00)

continued

***TABLE 18* contd** *Clozapine versus risperidone – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	Pooled RR (95% CI)
***Side-effects* contd**				
White blood cell problems	Bondolfi 1998 (86) Anand 1998 (273) Wahlbeck 2000 (19) Chowdhury 1999 (60)	0/43 1/138 1/10 8/30	1/43 3/135 0/9 0/30	2.05 (0.76 to 5.58)
Akathisia	Chowdhury 1999 (60)	0/30	11/30	0.04 (0.00 to 0.71)
Received antiparkinsonian medication	Wahlbeck 2000 (19)	3/10	6/9	0.45 (0.16 to 1.29)

n, *number of events;* N, *number of participants in the group.*
* *Risk difference, –0.03 (95% CI, –0.16 to 0.10)*
** *Risk difference, –0.17 (95% CI, –0.28 to –0.05)*

TABLE 19 *Clozapine versus zotepine – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early – any reason	Meyer-Lindenberg 1996 (50)	7/25	10/25	0.70 (0.32 to 1.54)

n, *number of events;* N, *number of participants in group*

TABLE 20 *Clozapine versus remoxipride/risperidone/zotepine – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Cognitive functioning: no improvement in memory	Klieser 1994 (135)	13/37	24/98	1.43 (0.82 to 2.51)
Extrapyramidal side-effects	Klieser 1994 (135)	0/37	18/98	0.07 (0.00 to 1.14)*

n, *number of events;* N, *number of participants in group*
* *Risk difference, –0.18 (95% CI, –0.27 to 0.10)*

Mortality

Suicide

In one study of suicide (Margolese 2000[117]), a MEDLINE search of the literature was included, which potentially made the study of good quality; however, details of the individual studies were not included. The study concluded that akathisia and tardive dyskinesia were risk factors for suicide in schizophrenia and that, in the most suicidal patients, clozapine is the preferred antipsychotic treatment; however, no data were presented to support these conclusions.

In another study (Reid 1998[121]), records of deaths in individuals treated with clozapine within the Texas mental healthcare system between 1991 and 1996 were reviewed retrospectively. A suicide rate of 1/1310 was found in clozapine-treated patients (that is, 12.74 per 100,000 persons per year) compared with 33/30,130 (that is, 63.1 per 100,000 persons per year) for all patients; the authors concluded that clozapine therapy was associated with a reduced risk of suicide in those with schizophrenia and schizoaffective disorder.

In an open-label, non-controlled, prospective study with a mean follow-up of 3.5 years (Meltzer 1995[124]), the likelihood of suicide was compared in patients before and after taking clozapine. A significant change over time was found towards a lowering of the likelihood of suicide, and the

authors concluded that the overall morbidity and mortality of patients with neuroleptic-resistant schizophrenia were lower with clozapine treatment than with typical antipsychotic drugs because of the lowered risk of suicide. The authors did not compare clozapine directly with typical antipsychotic treatments.

Other causes

A study of sudden death cause by myocarditis or cardiomyopathy in those taking clozapine found a mortality rate of 6/8000 patients (Killian 1999[118]). The study did not use a control group and looked retrospectively at cases reported under the Australian Adverse Drug Monitoring System between 1993 and 1999.

In one study, which appeared to be a retrospective comparison of individuals who continued with clozapine versus those who discontinued taking the drug over a period of 5 years, a mortality rate of 3/113 was reported in those taking clozapine (Laker 1998[119]). One of the reported deaths was from suicide and the other two were reported as being from natural causes unrelated to clozapine. No data were reported for those who discontinued taking clozapine.

In a larger study (Walker 1997[120]) in which mortality rates in clozapine patients were considered over 3 years using retrospective database analysis (no control group), an all-cause mortality rate of 396/67,072 was reported. The rate of suicide in this study was 75/67,072; the rate for acute myocardial infarction was 11/67,072, for pulmonary embolism 19/67,072, for conduction disorders or sudden death 12/67,072, for respiratory causes 31/67,072, for seizures 4/67,072, and for death caused by blood problems 3/67,072. The study authors gave an all-cause standardised mortality ratio (SMR) for current clozapine users of 0.46 (95% CI, 0.37 to 0.59) and an SMR for suicide in clozapine users of 0.17 (95% CI, 0.10 to 0.30). They concluded that clozapine appeared to reduce mortality in patients with severe schizophrenia by reducing suicide rates. However, they did not compare mortality in clozapine users with mortality in users of other antipsychotic drugs.

In a prospective, uncontrolled Norwegian study (Erlandsen 2000[122]) with a duration of 22 years, a mortality rate was found in clozapine-treated patients with schizophrenia of 12/103 – of this, 4/103 were due to cardiovascular disease, 2/103 to intestinal obstruction, 1/103 to lung carcinoma, 1/103 to being 'mentally weak' and 1/103 to hepatic failure and diabetes. The authors stated that, compared with the Norwegian Central Bureau of Statistic's figures, there was no excess mortality with clozapine.

In a controlled retrospective study of data from an Israeli mental health centre database, combined with interviews with the families of the deceased (Modai 2000[123]), a total death rate for clozapine was reported of 10/561, of which 6/561 were sudden deaths and 2/561 were suicides. In the group not treated with clozapine, the total death rate was 105/4918, of which 14/4918 were sudden deaths and 5/4918 were suicides. The authors stated that there were no significant differences in suicide rates between the two groups and that treatment with clozapine may present a greater risk for sudden death than treatment with other antipsychotic drugs. They also noted that the age at sudden death for clozapine-treated patients was significantly lower (by about 10 years) and the patients were in better physical health than those not treated with clozapine.

Venous thromboembolic complications

In one retrospective uncontrolled study of an adverse reactions database (Hagg 2000[136]), clozapine-treated patients were observed over a period of 11 years; 12 cases of thromboembolism were recorded with five deaths due to pulmonary embolism.

In another cohort-type study that was probably retrospective (Wolstein 2000[143]), no significant difference was found in rates of thromboembolism between groups given clozapine, other neuroleptic drugs or no neuroleptic drugs; the authors suggested that thromboembolism may be caused by risk factors associated with psychiatric illness rather than clozapine.

NMS

In a retrospective analysis of case reports of NMS in users of clozapine and risperidone (Hasan 1998[135]), although 19 cases of NMS were reported in clozapine users and 13 in risperidone users, when the reported cases were assessed using three sets of criteria for NMS, there were probably only nine cases of NMS in clozapine users and eight in risperidone users. No denominator was given for this study.

Agranulocytosis/leucopenia/neutropenia

In a prospective uncontrolled Norwegian study (Erlandsen 2000[122]) with a duration of 22 years, 1/103 individuals developed agranulocytosis and 2/103 developed leucopenia.

In a retrospective uncontrolled study based on data from an Illinois mental health database over a period of 5 years (Buckman 1999[125]), the incidence of agranulocytosis was reported to be 0.9% in 518 individuals.

In a survival analysis of the Clozaril® Patient Management System, that involved 11,555 clozapine-treated patients over an 18-month period (Alvir 1993,[126] Lieberman 1992[132]), a cumulative incidence of agranulocytosis was reported at 1 year of 0.80% (95% CI, 0.61 to 0.99) and at 1.5 years of 0.91% (95% CI, 0.62 to 1.20).

In an uncontrolled retrospective analysis of data from the UK and Ireland Clozaril® Patient Monitoring Service (Atkin 1996[127]), a 1-year risk of agranulocytosis was reported of 46/6316 = 0.7% (95% CI, 0.53 to 1.97). The 1-year risk for fatal agranulocytosis was reported as 2/6316 = 0.03% (95% CI, 0.006 to 0.12) and for neutropenia as 147/6316 = 2.3% (95% CI, 1.97 to 2.73).

A controlled study of data from two psychiatry departments over a 9-year period (Grohmann 1989[128]) gave a rate of agranulocytosis in clozapine-treated patients of 1/1100 compared with 0/6800 in haloperidol-treated patients and 6/6000 in perazine-treated patients. Leucopenia rates were 1/1000 for clozapine-treated patients, 2/6800 for haloperidol-treated patients and 2/6000 for perazine-treated patients.

An uncontrolled retrospective US database study over a 4.5-year period (Honigfield 1996[129]) gave a rate of agranulocytosis of 382/99,502 (0.38%), of which 12/99,502 (0.012%) were fatal, and a leucopenia rate of 2931/99,502 (2.95%).

In a post-marketing database study of clozapine and risperidone compared with typical antipsychotic treatments over a 33-year period (King 1998[130]), the incidence of agranulocytosis was reported as 91/351 for clozapine-treated patients, 0/6064 for risperidone-treated patients and 91/83,953 for those treated with typical antipsychotic drugs.

In an uncontrolled retrospective database analysis from Italy (Lambertenghi 2000[131]), in which 2404 clozapine-treated patients were monitored between 1995 and 1999, an agranulocytosis rate of 16/2404 (0.7%) was reported, with a neutropenia rate of 22/2404 (0.9%) and a leucocytosis rate of 185/2404 (7.7%).

In a retrospective, uncontrolled study of the Sandoz Pharma database in New Zealand between 1988 and 1995 (Miller 1997[133]), 8/693 cases of agranulocytosis were reported (cumulative rate 1.15%), together with 14/693 cases of neutropenia (cumulative rate 2.02%), and no deaths.

In another retrospective, uncontrolled post-marketing database analysis over 3 years (Cho 1999[134]), the rates of neutropenia and agranulocytosis reported were 127/2152 and 11/2152, respectively.

Seizures

In a prospective uncontrolled Norwegian study (Erlandsen 2000[122]) with a duration of 22 years, 2/103 individuals were found to have had epileptiform seizures.

A generalised tonic–clonic seizure rate of 41/1418 was found in a retrospective uncontrolled study of clozapine-treated patients in the USA between 1972 and 1988 (Devinsky 1991[137]). Life-table analysis for up to 3.8 years suggested a cumulative risk of seizure occurrence of 10%.

In a small uncontrolled study of clozapine-treated patients in Gloucester, UK (Macpherson 1998[138]), 1/15 seizures were reported.

A retrospective uncontrolled study of the Clozaril® Patient Management System database over a 6-month period (Pacia 1994[139]) reported 71/5629 generalised tonic–clonic seizures (1.3%).

In a conference abstract containing very few details (Lan 1999[140]), mention was made of a retrospective study of the incidence of epilepsy in those receiving clozapine – and its relationship to dose. An overall epilepsy rate of 11.5% was reported, with the incidences for high-, medium- and low-dose groups being 25.97%, 6.46% and 9.05%, respectively.

Weight gain

In a retrospective chart review of 68 evaluable clozapine-treated patients over a 3–90 month period (Umbricht 1994[144]), a cumulative incidence of a 10% weight gain or more reached 60% within the first 12 months of clozapine therapy. The authors concluded that treatment with clozapine is associated with a high incidence of substantial weight gain, posing a potential long-term health risk.

Myocarditis/cardiomyopathy

A database mining technique was used in one study (Coulter 2001[145]) to find rates of myocarditis

and cardiomyopathy in clozapine- and non-clozapine-treated populations. There were 231/24,730 case reports in the clozapine group and 89/60,775 in the non-clozapine group.

Tardive dyskinesia

In a mainly retrospective controlled study (Peacock 1996[141]) of 100 individuals treated with clozapine versus 100 treated with typical antipsychotic drugs (perphenazine, flupenthixol or zuclopenthixol), a significantly lower prevalence of tardive dyskinesia was found, together with a lower induction rate for new cases and a tendency towards greater disappearance of symptoms in the clozapine-treated group. In another retrospective uncontrolled review of 121 outpatients treated with clozapine (Leppig 1989[142]), 9/121 individuals developed tardive dyskinesia; however, it was not reported how many of the nine had schizophrenia.

Other systematic reviews

No new systematic reviews of clozapine were found.

Ongoing studies

Three ongoing studies were found on the trial registers searched. Two non-randomised studies aimed to address weight gain – one was a parallel group study versus risperidone (Aurora DS, Towle M. Risperidone versus clozapine: comparative effects on weight gain) registered in 1995, and the other was a case-record review versus olanzapine; however, this has not yet begun (Barnes T. Investigation of weight gain with antipsychotic medication in people with schizophrenia). The third was a cross-sectional study of side-effects during clozapine treatment (Yusufi B. Point prevalence and clinical correlates of side-effects during clozapine maintenance treatment – a cross-sectional study) that was expected to be completed in mid-2001.

Another ongoing study was reported in the published literature (Meltzer 1999[146]) – this is the InterSePT study on suicide prevention with clozapine or olanzapine. The results of this study were expected to become available in 2001.

Chapter 7

Olanzapine: effectiveness

Numbers and characteristics of included RCTs

New RCTs

A total of 19 new RCTs were identified for this update report: Naukkarinen 1999,[147] Johnstone 1998,[148] Fleming 1998,[70] Reams 1998,[149] Gomez 2001,[150] Wright 2000,[151] Kolff 2000,[152] Malyarov 1999,[153] Littrell 1999,[154] Szafranski 1999,[155] Zhang 1999,[156,157] Oliemeulen 2000,[109] HGCF 2001 (Eli Lilly, commercial-in-confidence), Study R-0548 (Pfizer, commercial-in-confidence), Ljubin 2000,[158] Bitter 1999,[74] Breier 2000,[159] Breier 2001,[160] Conley 2001.[161]

In addition, nine new reports of RCTs were found that contained additional data on the studies found earlier: Hamilton 2000[162] and Gregor 1999[163] – two reports of a subgroup of Tollefson 1997;[164] Tollefson 1999[165] – another report of Tollefson 1997; Kinon 2000[166] – another report of Tollefson 1997; Tollefson 1998[167] – another report of Beasley 1996a;[168] Edgell 2000[170] – a report of a subgroup of Tran 1997;[171] Tohen 1999[172] – a subgroup of an unspecified large multicentre trial; Sanger 1998[173–175] – a subgroup of Tollefson 1997; Tollefson 2001[76] – another report of Beasley 1999.[176,177]

Two studies (Purdon 2000,[178] David 1999[179]) were found that were further reports of Jones 1998[180] and contained extra cognitive data; however, these data were not included as the study had > 50% attrition and hence all outcomes other than 'leaving study early' were excluded (see below).

Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

The original review considered 20 studies: Altamura 1999,[181] Beasley 1996a,[168] Beasley 1996b,[169] Beasley 1997,[182] Beasley 1999,[176,177] Conley 1998a,[183] HGBJ (Finland, unpublished), HGBL 1997 (unpublished), HGCJ (Hong Kong, unpublished), HGCQ (Turkey, unpublished), HGCU (Taiwan, unpublished), HGDV (Morocco, 1999 unpublished), HGFH (Korea 1998, unpublished), Jakovljevic 1999,[184] Jones 1998,[180] Lecrubier 1999,[42] Loza 1999,[185] Gureje 1998,[186] Tollefsen 1997,[164] Tran 1997.[171] Data extraction sheets for these studies can be found in appendix 3.

Total RCTs

In all, 39 RCTs were included in this update report.

All the included studies were randomised; 29 were double-blind, two were single-blind and three were not blinded. Tollefson 1997[164] was by far the largest study with 1996 participants, while in the Altamura 1999[181] and Littrell 1999[154] studies, only 24 participants were randomised.

Duration

Data on short- to medium-term follow-up (less than 6 months) were presented in 30 studies. Four of these acute phase studies (Beasley 1996a,[168] Beasley 1997,[182] Tollefson 1997,[164] Gregor 1999[163]) lasted for 6 weeks with 'responders' entering a 46-week extension phase. Seven studies fell into the long-term category (6 months or longer), and in two trials no information on duration of treatment was given. The included trials of patients with treatment-resistant illness provided only short- to medium-term data.

Interventions

Olanzapine was given in a wide range of doses, from 1 mg to 25 mg daily. In Beasley 1996b,[169] in which 1 mg daily was used, this was stated to be equivalent to placebo. The same assertion was made in Beasley 1997[182] but this was altered during the study. Hence, in this review, it was decided to stop using 1 mg daily as additional placebo data.

The comparators used were placebo (four studies), chlorpromazine (four studies), haloperidol (15 studies), fluphenazine (two studies), flupentixol (one study), perphenazine (three studies), clozapine (five studies), amisulpride (one study), ziprasidone (one study) and risperidone (seven studies).

In one trial (Wright 2000[151]), a 10 mg intramuscular injection of olanzapine was compared with a 10 mg intramuscular injection of haloperidol given three times daily in acutely agitated patients and, in another (Breier 2001[160]), 2.5, 5, 7.5 or 10 mg intramuscular injections of

olanzapine given three times daily were compared with 7.5 mg injections of haloperidol or placebo, also given three times daily and, again, in acutely agitated patients.

Participants

All but seven studies included participants with operationalised diagnoses using DSM 1994 criteria.[66] The participants in all but one study were diagnosed as suffering from schizophrenia, although nine studies also included individuals with schizoaffective disorder and schizophreniform psychosis. In one trial report (HGCQ (Turkey) 2000), the diagnosis was not mentioned but as the company that supplied these data listed the study as 'schizophrenia and related psychoses', it was included. In Beasley 1996a,[168] women of 'child-bearing potential' were allowed to enter the trial only after approximately two-thirds of the enrolment had been completed; hence, the participants were predominantly male.

In Tollefson 1997,[164] less severely ill people were randomised (mean BPRS scores at baseline in the olanzapine group: Tollefson 1997, 33.1; Beasley 1996a,[168] 42.6; Beasley 1997,[182] 42.3; Jakovljevic 1999,[184] 43.7). This large study[164] also had a large number of participants who were intolerant of their current medication. In a report on a subgroup of this trial (Sanger 1998[173–175]), participants had first-episode psychosis lasting for more than 5 years.

In five studies, participants had treatment-resistant illnesses (Beasley 1999,[176,177] Conley 1998a,[182] Altamura 1999,[181] Bitter 1999,[74] Breier 2000[159]).

In one study (Littrell 1999[154]), only patients with chronic schizophrenia who had been switched from depot medication to atypical antipsychotic drugs were included. In another (Tohen 1999[172]) – a subgroup of a large multicentre trial (possibly Tollefson 1997[164]) – only those with schizoaffective disorder were included.

Olanzapine versus clozapine: commercial-in-confidence data removed.

Trials took place in a mixture of in- and outpatient settings.

Outcomes

The definition of improvement often consisted of a 20–40% reduction in BPRS or PANSS scores. Studies often dichotomised their overall measure of efficacy from continuous scales (BPRS, PANSS).

In seven of the included studies, for which data were supplied by Eli Lilly, only the outcomes of loss to follow-up and side-effects were presented. As far as the reviewers understand, effects on global functioning and mental state are not, as yet, available, even to the funding company.

Quality of included studies

Reporting of randomisation appeared poor in the published papers. As studies have shown that poor reporting of randomisation increases the odds of presenting 'significant' outcomes (Chalmers 1983,[187] Schulz 1995[188]), this was brought to the attention of the company responsible for the trials (Eli Lilly), which has now furnished full reports of randomisation. Patient randomisation was undertaken using computer-generated blocks, for investigative sites or investigator and the company concealed randomisation from the investigators.

Blinding procedures were poorly reported, with adequate precautions clearly described in only one trial (Conley 1998a[183]). Eli Lilly supplied the reviewers with details of blinding. Several studies gave people a medication kit containing their allocation medication in a form that was not clearly different from the comparison drug. Blinding was not tested in any study.

The numbers leaving studies early were high, albeit comparable with trials of other atypical antipsychotic drugs (Fabre 1995,[189] Thornley 1998[190]). In the majority of the trials published in peer-reviewed journals, participant disposition was well described, and the reader was clearly informed of the reason for an individual's withdrawal from a study. Studies that had been presented as posters or presentations did not include data on the follow-up of participants, leaving the reader un-informed as to their whereabouts.

The reports of all the studies stated that their data were analysed on an ITT basis, using the last observation carried forward; this practice may have overestimated any treatment effect.

Olanzapine versus placebo

The results are presented in *Table 21* (up to 26 weeks) and *Table 22* (26 weeks or longer).

In three trials, placebo groups were used for comparison (Beasley 1996a,[168] Beasley 1996b,[169] Lecrubier 1999[42]). The loss to follow-up was high. The degree of assumption within these data was very great (all studies had attrition rates > 50%),

TABLE 21 *Olanzapine versus placebo – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any reason	Beasley 1996a (266) Beasley 1996b (152)	111/198 71/102	46/68 40/50	0.85 (0.74 to 0.98)
Lack of efficacy	Beasley 1996a (266) Beasley 1996b (152)	64/198 42/102	32/68 30/50	0.69 (0.55 to 0.86)
Agitation	Beasley 1996a (266) Beasley 1996b (152)	48/198 16/102	16/68 4/50	1.20 (0.77 to 1.88)
Hostility	Beasley 1996a (266) Beasley 1996b (152)	28/198 14/102	10/68 7/50	0.97 (0.57 to 1.63)
Withdrawal	Beasley 1996a (266)	25/198	10/68	0.86 (0.44 to 1.69)
Side-effects				
Akathisia	Beasley 1996a (266)	12/198	1/68	4.12 (0.55 to 31.11)**
Tremor	Beasley 1996a (266)	7/198	1/68	2.40 (0.30 to 19.19)***
Needing anticholinergic medication	Beasley 1996a (266) Beasley 1996b (152)	36/198 8/102	8/68 8/50	0.90 (0.29 to 2.79)
Dry mouth	Beasley 1996a (266)	14/198	3/68	1.60 (0.47 to 5.41)
Dizziness	Beasley 1996a (266)	23/198	2/68	3.95 (0.96 to 16.31)
Nausea/vomiting	Beasley 1996a (266)	7/198	6/68	0.40 (0.14 to 1.15)
Sleep problems	Beasley 1996a (266) Beasley 1996b (152)	42/198 12/102	15/68 7/50	0.93 (0.59 to 1.45)

n, *number of events;* N, *number of participants in group*

* *Risk difference, 0.00 (95% CI –0.15 to 0.14)*
** *Risk difference, 0.05 (95% CI, 0.00 to 0.09)*
*** *Risk difference, 0.02 (95% CI, –0.02 to 0.06)*

TABLE 22 *Olanzapine versus placebo – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
No response (SANS < 20%, PANSS < 10%)	Lecrubier 1999 (174)	53/140	18/34	0.72 (0.49 to 1.05)
Leaving study early				
Any reason	Beasley 1996a follow-up (266) Lecrubier 1999 (175)	181/198 75/140	66/68 14/35	1.10 (0.60 to 2.01)
Lack of efficacy	Beasley 1996a follow-up (58) Lecrubier 1999 (175)	10/45 13/140	7/13 5/35	0.49 (0.27 to 0.88)

n, *number of events;* N, *number of participants in group*

hence all results must be interpreted with a high degree of caution.

In one trial of olanzapine as an intramuscular injection, a placebo arm was also used (Wright 2000[151]).

Global effect

No important clinical response

In the two studies that reported this outcome, > 50% of trial participants were lost to follow-up; hence, the data were not considered reliable enough for inclusion.

Change in overall state as measured by CGI

Loss to follow-up was > 50% in trials reporting this outcome, so the data are not presented.

Needing additional benzodiazepines

Again, the > 50% loss to follow-up precluded the use of these data.

Mental state

All mental state outcome data were prone to bias, with > 50% loss to follow-up, and were considered too unreliable to be presented here.

Leaving study early

Any reason

In the short term (6 weeks), significantly fewer people allocated to olanzapine than placebo left studies early (RR, 0.85; 95% CI, 0.74 to 0.98).

A maintenance phase was reported in Beasley 1996a.[168] In this study, individuals were counted as 'dropouts' if they were ineligible, or eligible and unwilling, to continue with the study medication beyond the acute phase (6 weeks). At the start of the maintenance phase, 153/198 of those taking olanzapine and 55/68 taking placebo had left the study (RR, 0.96; 95% CI, 0.8 to 1.1). At 52 weeks, only 17 patients on olanzapine and two on placebo were continuing within their allocated groups. When this was combined with data from Lecrubier 1999,[42] there was no significant difference in RR between olanzapine and placebo for those leaving studies early in the long term (RR, 1.10; 95% CI, 0.60 to 2.01).

Lack of efficacy

Participants taking olanzapine were significantly less likely to leave studies early owing to lack of efficacy at 6 weeks (RR, 0.69; 95% CI, 0.55 to 0.86).

Dropout data at 1 year from the original 6-week acute phase study of Beasley 1996a[168] were reported in Dellva 1997.[191] When these were combined with data from Lecrubier 1999[42] at 6 months, significantly fewer of those allocated to olanzapine dropped out because of lack of efficacy (RR, 0.49; 95% CI, 0.27 to 0.88).

Adverse effects

Anticholinergic effects

In Beasley 1996a,[168] dry mouth and dizziness, especially, were reported to be more frequent in the olanzapine-treated group, although neither difference reached conventional levels of statistical significance. No difference in the need for anticholinergic medication was seen between treatment groups.

Extrapyramidal effects

Data on extrapyramidal effects were prone to bias with > 50% loss to follow-up.

Other effects

Olanzapine, in the doses used within these studies, did not clearly increase problems with sedation or agitation, hostility and withdrawal. By 6 weeks, weight had increased in the olanzapine group but not to a statistically significant extent (appendix 9).

Quality of life

In Hamilton 1998,[192] usable quality-of-life data from Beasley 1996a[168] were recorded but not reported. However, some useful information was presented in Lecrubier 1999,[42] which suggested that the olanzapine group did report a higher quality of life than those allocated placebo. This did not reach conventional levels of statistical significance (appendix 9).

Missing outcomes

Data were collected on in- or outpatient status but, again, these were not reported. Mortality, cognitive functioning, satisfaction with treatment, cost-effectiveness, social functioning and self-harm were not reported.

Olanzapine versus typical antipsychotic drugs

The results are summarised in *Tables 23–26.*

In 15 trials (Beasley 1996a,[168] Beasley 1997,[182] Jones 1998,[180,193] Tollefson 1997,[164] Altamura 1999,[181] HGCJ (Hong Kong) 1999, HGCU (Taiwan) 1998, HGFH (Korea) 1998, Reams 1998,[149] Gomez 2001,[150] Gregor 1999,[163] Zhang 1999,[156,157] Breier 2000,[159] Wright 2000,[151] Breier 2001[160]), haloperidol was the comparator, while chlorpromazine was used in Conley 1998a,[183] Loza 1999,[185] HGDV (Morocco) 1999, and HGCQ (Turkey) 2000. In Jakovljevic 1999[184] and Ljubin 2000,[158] olanzapine was compared with fluphenazine; in HGBJ (Finland), Szafranski 1999,[155] and Naukkarinen 1999[147] with perphenazine, and in HGBL 1997, with flupentixol.

In three studies (Beasley 1996a, Beasley 1997 and Jones 1998), the attrition rates were > 50% and data for all outcomes other than 'leaving study early' have been excluded.

Intramuscular olanzapine

The two very short-term studies of intramuscular olanzapine used in acutely agitated patients

TABLE 23 *Olanzapine versus typical antipsychotic drugs: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state				
No response – any dose	Conley 1998a (84)	39/42	42/42	0.84 (0.65 to 1.07)*
	Tollefson 1997 (1996)	718/1336	471/660	
No response (QLS total)	Tollefson 1997 subgroup (778)[a]	455/520	240/258	0.94 (0.90 to 0.99)**
Mental state: no response (BPRS total)	Tollefson 1997 subgroup (778)[a]	255/520	170/258	0.74 (0.66 to 0.84)***
Leaving study early				
Any reason	Altamura 1999 (48)	4/23	9/25	0.73 (0.62 to 0.86)
	Beasley 1996a (266)	111/198	39/69	
	Beasley 1997 (431)	146/350	38/81	
	Conley 1998a (84)	12/42	13/42	
	Gomez 2001 (1658)	16/1112	20/546	
	HGBL 1997 (28)	6/15	3/13	
	HGCJ 1999 (31)	5/17	10/14	
	HGCQ (Turkey) 2000 (30)	5/20	1/10	
	HGCU 1998 (54)	10/26	14/28	
	HGDV 1999 (39)	0/27	2/12	
	HGFH 1998 (104)	13/53	16/51	
	Tollefson 1997 subgroup (778)[a]	201/520	154/258	
	Loza 1999 (41)	3/27	1/14	
	Tollefson 1997 (1996)	448/1336	351/660	
Lack of efficacy	Altamura 1998 (48)	1/23	5/25	0.77 (0.55 to 1.08)
	Beasley 1996a (267)	64/198	19/69	
	Beasley 1997 (231)	40/350	16/81	
	Conley 1998a (84)	5/42	2/42	
	HGBL 1997 (28)	3/15	1/13	
	HGCJ 1999 (31)	1/17	3/14	
	HGCQ 2000 (30)	3/20	0/10	
	HGCU 1998 (54)	2/26	5/28	
	HGFH 1998 (104)	0/53	1/51	
	Loza 1999 (41)	3/27	1/14	
	Tollefson 1997 (1996)	277/1336	212/660	
Side-effects				
Any EPS	Conley 1998a (84)	12/42	21/42	0.43 (0.38 to 0.49)†
	Tollefson 1997 (1996)	256/1336	298/660	
Acute dystonia	Tollefson 1997 (1996)	19/1336	35/660	0.27 (0.15 to 0.47)
Akathisia	Tollefson 1997 (1996)	104/1336	149/660	0.34 (0.27 to 0.44)
Hypertonia	Tollefson 1997 (1996)	140/1336	158/660	0.44 (0.36 to 0.54)
Hypokinesia	Tollefson 1997 (1996)	97/1336	110/660	0.44 (0.34 to 0.56)
New parkinsonism	Tollefson 1997 (1996)	128/1336	177/660	0.36 (0.29 to 0.44)
Dyskinetic movements	Conley 1998a (84)	1/42	15/42	0.28 (0.02 to 3.93)
	Tollefson 1997 (1996)	26/1336	15/660	
Needing additional anticholinergic medication	Tollefson 1997 (1996)	228/1336	315/660	0.36 (0.31 to 0.41)††
Blurred vision	Conley 1998a (84)	4/42	5/42	0.70 (0.57 to 0.86)
	Tollefson 1997 (1996)	169/1336	120/660	
Dizziness	Conley 1998a (84)	6/42	7/42	0.86 (0.31 to 2.84)
Palpitations	Conley 1998a (84)	1/42	7/42	0.43 (0.11 to 1.66)
	Tollefson 1997 (1996)	116/1336	87/660	
Orthostatic changes	Conley 1998a (84)	4/42	30/42	0.13 (0.05 to 0.35)

continued

***TABLE 23* contd** *Olanzapine versus typical antipsychotic drugs: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Dry mouth	Conley 1998a (84) Tollefson 1997 (1996)	16/42 320/1336	31/42 127/660	0.82 (0.34 to 1.95)
Hypersalivation	Tollefson 1997 (1996)	143/1336	148/660	0.48 (0.39 to 0.59)
Urination difficulties	Tollefson 1997 (1996)	77/1336	63/660	0.60 (0.44 to 0.83)
Appetite increase	Tollefson 1997 (1996)	343/1336	103/660	1.65 (1.35 to 2.01)
Nausea	Conley 1998a (84) Tollefson 1997 (1996)	5/42 162/1336	5/42 111/660	0.73 (0.59 to 0.91)
Vomiting	Tollefson 1997 (1996)	97/1336	81/660	0.59 (0.45 to 0.78)
Difficulty in getting to sleep	Conley 1998a (84) Tollefson 1997 (1996)	6/42 329/1336	2/42 207/660	1.22 (0.35 to 4.21)
Drowsiness	Conley 1998a (84) Tollefson 1997 (1996)	15/42 369/1336	22/42 223/660	0.81 (0.71 to 0.92)

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.13 (95% CI, –0.24 to –0.02)*
** *Risk difference, –0.06 (95% CI, –0.10 to –0.01)*
*** *Risk difference, –0.17 (95% CI, –0.24 to –0.10)*
† *Risk difference, –0.26 (95% CI, –0.30 to –0.22)*
†† *Risk difference, –0.31 (95% CI, –0.30 to –0.22)*

[a] *Tollefson 1997 subgroup were responders who continued into extension phase of study; hence results for response are difficult to generalise as group highly selected*

TABLE 24 *Olanzapine versus typical antipsychotic drugs: continuous outcomes – up to 26 weeks*

Comparison or outcome	Included studies	Treatment group		Control group		WMD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	Altamura 1999	22	79.57 (16.54)	25	79.22 (18.59)	1.30 (–9.18 to 10.62)
	HGBL 1997	14	74.57 (13.09)	12	74.50 (17.16)	
	HGCJ 1999	16	64.71 (13.67)	14	59.36 (11.08)	
	HGCQ 2000	20	75.20 (11.38)	10	72.14 (13.19)	
	HGCU 1998	24	70.85 (11.87)	27	63.05 (13.15)	
	HGDV 1999	27	74.48 (10.73)	12	66.58 (7.62)	
	HGFH 1998	51	59.88 (10.83)	39	60.07 (10.90)	
	Loza 1999	27	73.19 (13.47)	14	69.21 (14.86)	
	Tollefson 1997	1303	78.30 (17.02)	633	77.95 (17.92)	

N, *number of participants in group*

(Wright 2000,[151] Breier 2001[160]) did not contain any data that were usable in the meta-analysis. However, in Breier 2001, it was reported that olanzapine at doses of 5, 7.5 or 10 mg per injection significantly reduced agitation (as measured by the PANSS excited component) as early as 30 minutes after the first injection and, similarly to haloperidol, 7.5 mg, at all time points thereafter. The effect was sustained at 24 hours for olanzapine but not for haloperidol. Similar results were reported in Wright 2000 but the effect was sustained at 24 hours for both the olanzapine and haloperidol groups.

Global effect

No important clinical response

Data relevant to this outcome were not available for many of the studies listed above. In Tollefson 1997,[164] patients showing an 'important clinical response' were defined as those who presented with > 40% reduction in psychotic symptoms as measured by any scale. In Conley 1998a,[183] for

TABLE 25 *Olanzapine versus typical antipsychotic drugs: dichotomous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Relapse at 1 year (> 50% loss to follow-up)	Beasley 1996a (267)	181/198	67/69	0.94 (0.89 to 1.00)
Mental state: no response (BPRS total)	Tollefson 1997 subgroup (778)[a]	320/520	201/258	0.79 (0.72 to 0.87)*
Global state: no response (QLS total)	Tollefson 1997 subgroup (778)[a]	447/520	243/258	0.91 (0.87 to 0.96)**
Leaving study early				
Any reason (< 12 months)	HGBJ (46)	11/23	12/23	0.79 (0.51 to 1.22)
	Jakovljevic 1999 (60)	9/30	13/30	
	Malyarov 1999 (33)	0/15	3/18	
Any reason (> 12 months, extension studies)	Beasley 1996a (267)	181/198	67/69	0.90 (0.87 to 0.93)
	Beasley 1997 (431)	334/350	77/81	
	Jones 1998 (44)	9/21	14/23	
	Tollefson 1997 (1996)	1053/1336	590/660	
Lack of efficacy (< 12 months)	HGBJ (46)	5/23	3/23	0.92 (0.33 to 2.62)
	Jakovljevic 1999 (60)	4/30	7/30	
Lack of efficacy (> 12 months, extension studies)	Beasley 1996a (55)	10/45	2/10	0.79 (0.57 to 1.11)
	Beasley 1997 (62)	6/48	3/14	
	Jones 1998 (44)	1/21	1/23	
	Tollefson 1997 (851)	88/648	35/203	

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.16 (95% CI, –0.23 to –0.10)*

** *Risk difference, –0.08 (95% CI, –0.12 to –0.04)*

[a] *Tollefson 1997 subgroup were responders who continued into extension phase of study; hence results for response are difficult to generalise as group was highly selected*

TABLE 26 *Olanzapine versus typical antipsychotic drugs: continuous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies	Treatment group		Control group		WMD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	HGBJ	23	79.31 (12.34)	23	78.59 (20.84)	1.87 (–4.12 to 7.85)
	Jakovljevic 1999	30	78.18 (14.02)	29	75.65 (15.36)	

N, *number of participants in group*

participants with treatment-resistant illness, an important clinical response was defined as a reduction of at least 20% in mental state ratings. The large Tollefson 1997 trial[164] dominated heterogeneous results (chi-squared = 20.93, $p < 0.00001$) for 'any dose of olanzapine' (RR, 0.84; 95% CI, 0.65 to 1.07; risk difference, –0.13; 95% CI, –0.24 to –0.02). When results were presented separately for both studies included in this analysis, the Tollefson 1997 study favoured olanzapine (RR, 0.75; 95% CI, 0.70 to 0.81) and the smaller Conley 1998a study showed a non-significant result (RR, 0.93; 95% CI, 0.85 to 1.01). Data relating to specific doses showed no differences between olanzapine and typical antipsychotic drugs.

In Tollefson 1997,[164] a borderline significant result was found in favour of olanzapine on the Quality of Life Scale (QLS) after 6 weeks and 1 year (6 weeks: RR, 0.94; 95% CI, 0.90 to 0.99; risk difference –0.06; 95% CI, –0.10 to –0.01; 1 year: RR, 0.91; 95% CI, 0.87 to 0.96; risk difference, –0.08; 95% CI, –0.12 to –0.04). However, the results from Tollefson 1997 at 1 year were from a highly selected subgroup who responded to olanzapine initially and, hence, were difficult to generalise.

No response: first-episode psychosis

When response was defined as a 40% improvement in BPRS total score, individuals with first-episode psychosis treated with olanzapine were much more likely to respond than those treated with haloperidol (67.2% versus 29.2%). These data were from a report of a subgroup of Tollefson 1997,[164] so the data could not be pooled in the meta-analysis.

Leaving study early

Any reason

The RR was in favour of olanzapine by 26 weeks (RR, 0.73; 95% CI, 0.62 to 0.86) and after 12 months (RR, 0.90; 95% CI, 0.87 to 0.93) but not between 6 and 12 months (RR, 0.79; 95% CI, 0.51 to 1.22). Heterogeneity was seen in the result for up to 26 weeks (chi-squared = 28.08; $p = 0.0088$) and 12 months (chi-squared = 19.52; $p = 0.0002$). It was unclear which studies were responsible for the heterogeneity, so the results should be interpreted with caution.

Lack of efficacy

When lack of efficacy was cited as a reason for attrition, there were no differences between olanzapine and other drugs at any time point.

Mental state

No response

At both 6 and 52 weeks, olanzapine-treated patients were more likely to respond as measured by BPRS (short term: RR, 0.74; 95% CI, 0.66 to 0.84; risk difference, –0.17; 95% CI, –0.24 to –0.10; long term: RR, 0.79; 95% CI, 0.72 to 0.87; risk difference, –0.16; 95% CI, –0.23 to –0.10) than patients treated with typical antipsychotic drugs.

The PANSS scale data favoured olanzapine for overall and negative symptoms; however, BPRS scale data were not so favourable. In a *post-hoc* analysis (Kinon 2000[166]) of the Tollefson 1997[164] trial, olanzapine-treated participants were reported to have experienced significantly greater improvement in agitation ($p = 0.0002$) than haloperidol-treated patients, and a subgroup who demonstrated predominantly positive symptoms at baseline showed significantly greater improvement in BPRS positive symptoms scores with olanzapine than with haloperidol ($p = 0.013$). Owing to a lack of data, these results could not be entered into the meta-analysis.

Schizoaffective disorder

In one study (Tohen 1999),[172] data were presented on the BPRS mania score for participants with schizoaffective disorder. As this was a subgroup of a previously published trial, the data could not be pooled in the meta-analysis. The study results indicated that people with schizoaffective disorder, bipolar type, currently manic or currently depressed, improved significantly more with olanzapine than with haloperidol. In the same study, currently depressed patients were found to have improved significantly more with olanzapine on the Montgomery–Asberg Depression Rating Scale (MADRS) measure of 'depression' than with haloperidol.

First-episode psychosis

Data on BPRS and PANSS scores were presented in one study (Sanger 1998[173–175]) for individuals with first-episode psychosis. As this related to a subgroup of a previously published trial, the data could not be pooled in the meta-analysis. The results indicated that people with first-episode psychosis treated with olanzapine showed statistically significantly greater reductions in BPRS total, BPRS negative subscale, PANSS total and PANSS positive subscale scores than those treated with haloperidol.

Adverse effects

Anticholinergic effects: specific symptoms

Fewer people taking olanzapine experienced blurred vision, orthostatic changes, hypersalivation and difficulty with urination than those on typical drugs. The results for other effects such as dry mouth and dizziness were equivocal.

Extrapyramidal effects

The olanzapine group required less antiparkinsonian medication than those taking haloperidol (RR, 0.36; 95% CI, 0.31 to 0.41). Data on a whole series of specific extrapyramidal symptoms favoured olanzapine. Participants taking the new drug experienced less acute dystonia, akathisia, hypokinesia, hypertonia and parkinsonism than those allocated to haloperidol.

Extrapyramidal effects: first-episode psychosis

In a report on a subgroup of patients (Sanger 1998)[173–175] from the Tollefson 1997 study,[164] individuals with first-episode psychosis treated with olanzapine showed statistically significant improvements in their Simpson–Angus Scale (SAS) and Barnes Akathisia Scale (BAS) scores, while those treated with haloperidol showed a worsening on both measures.

Gastrointestinal effects

More people taking olanzapine reported an increase in appetite (RR, 1.65; 95% CI, 1.35

to 2.01) and both nausea and vomiting were less frequent in the olanzapine-treated group.

Salivation – dry mouth

The result was non-significant but heterogeneity was noted (chi-squared = 14.12; $p = 0.0002$). When the results of the two studies that were pooled for this outcome were presented separately, the large Tollefson 1997 study[164] showed a significant result in favour of typical antipsychotic treatment (RR, 1.24; 95% CI, 1.04 to 1.49), while the smaller, Conley 1998a,[183] study showed a significant result in favour of olanzapine (RR, 0.52; 95% CI, 0.34 to 0.79).

Arousal

There was no suggestion of a problem of insomnia with olanzapine, and drowsiness seemed to be less of a problem than with haloperidol (RR, 0.81; 95% CI, 0.71 to 0.92). Heterogeneity was noted in the outcome 'difficulty getting to sleep' (chi-squared = 2.89; $p = 0.089$). When the results of the two studies pooled for this outcome were analysed separately, the results of the large Tollefson 1997 study[164] were significantly in favour of olanzapine (RR, 0.79; 95% CI, 0.68 to 0.91), while those from the smaller Conley 1998a study[183] were not significant (RR, 3.00; 95% CI, 0.64 to 14.02).

Weight changes

Data for both short and long term were not conclusive (up to 26 weeks: WMD, 1.30 kg; 95% CI, –9.18 to 10.62; 26 weeks and over: WMD, 1.87 kg; 95% CI, –4.12 to 7.85).

Quality of life

In both Beasley 1996a[168] and Tollefson 1997,[164] data on quality of life were reported in a form that was impossible to use in this review.

Cognitive function

It was not possible to use the data on cognitive functioning reported in Jones 1998.[180] In Ljubin 2000,[158] a significant difference in favour of typical antipsychotic drugs was found on one subscale of the Weschler Adult Intelligence Scale (WAIS).

Sensitivity analysis

When only those studies that compared olanzapine with haloperidol were included in the analysis, the following changes were noted: olanzapine-treated patients were more likely to respond (global response) than haloperidol-treated patients (RR, 0.75; 95% CI, 0.70 to 0.81) and significantly less likely to leave the study early because of lack of efficacy (RR, 0.69; 95% CI, 0.51 to 0.94). Olanzapine-treated patients were significantly less likely to experience palpitations (RR, 0.66; 95% CI, 0.51 to 0.86) or have difficulty getting to sleep (RR, 0.79; 95% CI, 0.68 to 0.91), and significantly more likely to have a dry mouth (RR, 1.24; 95% CI, 1.04 to 1.49) than haloperidol-treated patients.

Olanzapine versus typical antipsychotic drugs for those with treatment-resistant illness

Summaries of the results for patients with treatment-resistant illness are presented in *Tables 27* and *28*.

Global effect: no important clinical response

This was defined in Conley 1998a[183] as the number per group who did not present with > 20% reduction in psychotic symptoms measured by any scale. At 8 weeks, no differences were seen between the two groups (RR, 0.93; 95% CI, 0.85 to 1.01; risk difference, –0.07; 95% CI, –0.16 to 0.02). In Altamura 1999,[181] significance in favour of olanzapine was reported but no data were presented.

Leaving the study early

Any reason

No differences were apparent between those allocated olanzapine and individuals taking either chlorpromazine or haloperidol (RR, 0.76; 95% CI, 0.42 to 1.36).

Lack of efficacy

Again, there were no differences between the groups in one trial (RR, 2.50; 95% CI, 0.51 to 12.18).

Adverse events

The data for adverse effects essentially reflect those already presented for the larger comparison between olanzapine and typical antipsychotic drugs for individuals whose illnesses were not treatment-resistant.

Anticholinergic effects

In Conley 1998a,[183] fewer people on olanzapine were reported as experiencing dry mouth (RR, 0.52; 95% CI, 0.34 to 0.79). Incidences of orthostatic changes were also lower in the olanzapine group (RR, 0.13; 95% CI, 0.05 to 0.35). The power of this study to detect real differences was limited ($n = 84$).

TABLE 27 *Olanzapine versus typical antipsychotic drugs – treatment-resistant illness: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state: no response	Conley 1998a (84)	39/42	42/42	0.93 (0.85 to 1.01)
Leaving study early				
Any reason	Conley 1998a (84) Altamura 1999 (48)	12/42 4/23	13/42 9/25	0.76 (0.42 to 1.36)
Lack of efficacy	Conley 1998a (84)	5/42	2/42	2.50 (0.51 to 12.18)
Side-effects				
Any extrapyramidal	Conley 1998a (84)	12/42	21/42	0.57 (0.32 to 1.01)
Dyskinetic movements	Conley 1998a (84)	1/42	15/42	0.07 (0.01 to 0.48)
Blurred vision	Conley 1998a (84)	4/42	5/42	0.80 (0.23 to 2.77)
Dizziness	Conley 1998a (84)	6/42	7/42	0.86 (0.31 to 2.34)
Orthostatic changes	Conley 1998a (84)	4/42	30/42	0.13 (0.05 to 0.35)
Palpitations	Conley 1998a (84)	1/42	7/42	0.14 (0.02 to 1.11)
Dry mouth	Conley 1998a (84)	16/42	31/42	0.52 (0.34 to 0.79)
Nausea/vomiting	Conley 1998a (84)	5/42	8/42	0.62 (0.22 to 1.75)
Difficulty getting to sleep	Conley 1998a (84)	6/42	2/42	3.00 (0.64 to 14.02)
Drowsiness	Conley 1998a (84)	15/42	22/42	0.68 (0.41 to 1.12)

n, *number of events;* N, *number of participants in group*

TABLE 28 *Olanzapine versus typical antipsychotic drugs – treatment-resistant illness: continuous outcomes – up to 26 weeks*

Comparison or outcome	Included studies	Treatment group		Control group		MD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	Altamura 1999	23	79.57 (16.54)	25	79.22 (18.59)	0.35 (–9.69 to 10.39)

N, *number of participants in group*

Extrapyramidal events

No differences were found in Conley 1998a[183] between individuals taking olanzapine and those taking typical antipsychotic drugs for the outcome 'any extrapyramidal effects' (RR, 0.57; 95% CI, 0.32 to 1.01; risk difference, –0.21; 95% CI, –0.42 to –0.01). Dyskinetic movements were significantly reduced in the olanzapine group in one study (RR, 0.07; 95% CI, 0.01 to 0.48).

Other adverse events

Participants allocated to olanzapine and chlorpromazine reported similar rates of nausea/vomiting and difficulty in getting to sleep or drowsiness. In Altamura 1999 ($n = 48$),[181] body weight at the end of the 14-week study was reported. There was no suggestion of a difference between those randomised to olanzapine and those randomised to haloperidol at this time (mean difference (MD), 0.35 kg; 95% CI, –9.69 to 10.39).

Olanzapine versus atypical antipsychotic drugs

There were 14 trials in which olanzapine was compared with atypical antipsychotic treatments: Beasley 1999,[176,177] Fleming 1998,[70] Oliemeulen 2000,[109] HGCF 2001 (Eli Lilly), Bitter 1999 (clozapine),[74] Jones 1998,[180] Littrell 1999,[154] Tran 1997,[171] Kolff 2000,[152] Malyarov 1999,[153] Conley 2001,[161] Gureje 1998 (risperidone),[186] Lecrubier 1999 (amisulpride),[42] Study R-0548 (ziprasidone: Pfizer, commercial-in-confidence).

The Lecrubier 1999, Gureje 1998 and Jones 1998 studies all had attrition rates of > 50%, so all data from these studies, other than 'leaving study early', were excluded from this review.

Olanzapine versus amisulpride

In one study (Lecrubier 1999[42]), the effect of amisulpride versus olanzapine was evaluated. Improvement and attrition were the only outcomes reported (*Table 29*) and these favoured neither drug (improvement risk difference, –0.05; 95% CI, –0.19 to 0.09). SANS summary scores were also reported and these are presented in appendix 9.

Olanzapine versus clozapine in participants with treatment-resistant illness

Of five studies in which olanzapine was compared with clozapine, in only one (Beasley 1999[176,177]) were the data presented in a form usable in the meta-analysis. All participants had treatment-resistant illness. The results are summarised in *Table 30*.

Death

Unpublished data from Beasley 1999[176,177] revealed no deaths in either group. None of the published trial reports contained mortality data.

Global effect

When olanzapine was compared with clozapine, no important clinical responses were seen as measured by CGI criteria (RR, 0.82; 95% CI, 0.63 to 1.07; risk difference, –0.11; 95% CI, –0.26 to 0.03) or by Kane 1988 criteria[99] (RR, 0.93; 95% CI, 0.75 to 1.16; risk difference, –0.04; 95% CI, –0.18 to 0.10). CGI scale data also did not favour either drug.

Mental state: no important clinical response

No important clinical response was indicated here by a 40% reduction in PANSS total score. The clozapine comparison did not favour either drug (RR, 0.86; 95% CI, 0.62 to 1.19; risk difference, –0.07; 95% CI, –0.21 to 0.08).

Leaving study early

Any reason

Participants taking olanzapine were no more likely to complete the trials than those taking clozapine (RR, 0.81; 95% CI, 0.55 to 1.19).

Adverse events

Patients taking olanzapine were less likely to experience constipation, dizziness, nausea or increased salivation than those taking clozapine. No adverse event appeared to be more common with olanzapine than with clozapine.

Olanzapine versus risperidone

Summaries of the results are presented in *Tables 31–33*.

Death

There were no trials in which mortality data were reported.

Global effect

No differences were seen between groups for 'response' as defined by CGI-I criteria (risk difference, 0.01; 95% CI, –0.08 to 0.11) or for CGI-S ratings of moderate to extremely severe (risk difference, 0.03; 95% CI, –0.09 to 0.15) in the short to medium term.

Mental state

No differences were seen between groups in the short to medium term when response was defined as a 40% decrease in PANSS (risk difference, 0.06; 95% CI, –0.01 to 0.13); the same was true in the long term (risk difference, –0.09; 95% CI, –0.19 to 0.01).

Leaving study early

Any reason

In the short to medium term there were no significant differences between olanzapine- and risperidone-treated groups (RR, 0.81; 95% CI, 0.57 to 1.14). In the long term, individuals were less likely to leave a study early if treated with

TABLE 29 *Olanzapine versus amisulpride – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early	Lecrubier 1999 (210)	75/140	36/70	1.04 (0.79 to 1.37)
Global state: not improved (SANS < 20%; PANSS < 10%)	Lecrubier 1999 (210)	53/140	30/70	0.88 (0.63 to 1.25)

TABLE 30 *Olanzapine versus clozapine – treatment-resistant illness: dichotomous outcomes*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Death	Beasley 1999 (180)	0/90	0/90	Not estimable
Global state				
No response (CGI)	Beasley 1999 (180)	45/90	55/90	0.82 (0.63 to 1.07)*
No response – Kane criteria	Beasley 1999 (180)	56/90	60/90	0.93 (0.75 to 1.16)**
Mental state: no response (40% decrease in PANSS)	Beasley 1999 (180)	37/90	43/90	0.86 (0.62 to 1.19)
Leaving study early – any reason	Beasley 1999 (180)	30/90	37/90	0.81 (0.55 to 1.19)
Side-effects				
Somnolence	Beasley 1999 (180)	12/90	22/90	0.55 (0.29 to 1.03)
Agitation	Beasley 1999 (180)	10/90	4/90	2.50 (0.81 to 7.68)
Headache	Beasley 1999 (180)	10/90	5/90	2.00 (0.71 to 5.62)
Insomnia	Beasley 1999 (180)	7/90	3/90	2.33 (0.62 to 8.74)
Constipation	Beasley 1999 (180)	6/90	17/90	0.35 (0.15 to 0.85)
Weight gain	Beasley 1999 (180)	6/90	6/90	1.00 (0.34 to 2.98)
Anxiety	Beasley 1999 (180)	5/90	5/90	1.00 (0.30 to 3.34)
Rhinitis	Beasley 1999 (180)	5/90	3/90	1.67 (0.41 to 6.77)
Dry mouth	Beasley 1999 (180)	4/90	0/90	9.00 (0.49 to 165)
Vomiting	Beasley 1999 (180)	4/90	5/90	0.80 (0.22 to 2.88)
Influenza syndrome	Beasley 1999 (180)	3/90	5/90	0.60 (0.15 to 2.44)
Asthenia	Beasley 1999 (180)	2/90	6/90	0.33 (0.07 to 1.61)
Increased salivation	Beasley 1999 (180)	2/90	26/90	0.08 (0.02 to 0.31)
Sweating	Beasley 1999 (180)	2/90	5/90	0.40 (0.08 to 2.01)
Dizziness	Beasley 1999 (180)	1/90	8/90	0.12 (0.02 to 0.98)
Fever	Beasley 1999 (180)	1/90	5/90	0.20 (0.02 to 1.68)
Leucopenia	Beasley 1999 (180)	1/90	5/90	0.20 (0.02 to 1.68)
Nausea	Beasley 1999 (180)	1/90	10/90	0.10 (0.01 to 0.77)
Tooth disorder	Beasley 1999 (180)	0/90	4/90	0.11 (0.01 to 2.03)

n, *number of events*; N, *number of participants in group*

* *Risk difference, –0.11 (95% CI, –0.26 to 0.03)*

** *Risk difference, –0.04 (95% CI, –0.18 to 0.10)*

olanzapine than if treated with risperidone (RR, 0.75; 95% CI, 0.62 to 0.91).

Lack of efficacy

No difference was evident between olanzapine and risperidone in the long term.

Adverse effects

Extrapyramidal effects: needing additional anticholinergic medication

Those taking olanzapine received less anticholinergic medication than those taking risperidone in the long term (RR, 0.60; 95% CI, 0.41 to 0.87; risk difference, –0.13; 95% CI, –0.22 to –0.04) but there was no significant difference between groups in the short to medium term.

Extrapyramidal effects: specific symptoms

Significantly fewer people on olanzapine experienced any extrapyramidal event in the long term compared with those taking risperidone (RR, 0.60; 95% CI, 0.41 to 0.88; risk difference, –0.13; 95% CI, –0.22 to –0.03). The incidence of parkinsonism was also less in the olanzapine group (RR, 0.58; 95% CI, 0.36 to 0.94). No differences were seen for akathisia or dyskinetic movements between olanzapine and risperidone in the same study.

TABLE 31 *Olanzapine versus risperidone: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state				
No response on CGI	Conley 2001 (377)	131/189	128/188	1.02 (0.89 to 1.17)
CGI-S rating of moderate to extremely severe	Conley 2001 (377)	76/145	66/133	1.06 (0.84 to 1.33)
Mental state: no response (40% decrease on PANSS)	Conley 2001 (377)	166/189	154/188	1.07 (0.98 to 1.20)
Leaving study early – any reason	Conley 2001 (377)	43/189	53/188	0.81 (0.57 to 1.14)
Needing anticholinergic medication	Conley 2001 (377)	53/189	61/188	0.86 (0.64 to 1.18)
Psychosis	Conley 2001 (377)	8/189	8/188	0.99 (0.38 to 2.60)
Suicide attempt	Conley 2001 (377)	5/189	2/188	2.49 (0.49 to 12.66)
Agitation (serious)	Conley 2001 (377)	3/189	3/188	0.99 (0.20 to 4.87)
Agitation (not serious)	Conley 2001 (377)	40/189	29/188	1.37 (0.89 to 2.12)
Depression (serious)	Conley 2001 (377)	3/189	3/188	0.99 (0.20 to 4.87)
Insomnia (serious)	Conley 2001 (377)	2/189	3/188	0.66 (0.11 to 3.92)`
Insomnia (not serious)	Conley 2001 (377)	35/189	45/188	0.77 (0.52 to 1.15)
Hallucinations	Conley 2001 (377)	3/189	2/188	1.49 (0.25 to 8.83)
Drug abuse	Conley 2001 (377)	3/189	0/188	6.96 (0.36 to 134)
Side-effects				
Cardiovascular symptoms	Conley 2001 (377)	3/189	0/188	6.96 (0.36 to 134)
Gastrointestinal disorders	Conley 2001 (377)	3/189	0/188	6.96 (0.36 to 134)
Somnolence	Conley 2001 (377)	73/189	69/188	1.05 (0.81 to 1.36)
Headache	Conley 2001 (377)	32/189	41/188	0.78 (0.51 to 1.18)
Dry mouth	Conley 2001 (377)	42/189	21/188	1.99 (1.23 to 3.23)
Rhinitis	Conley 2001 (377)	31/189	30/188	1.03 (0.65 to 1.63)
Dizziness	Conley 2001 (377)	27/189	26/188	1.03 (0.63 to 1.70)
Anxiety	Conley 2001 (377)	23/189	20/188	1.14 (0.65 to 2.01)
Vision abnormalities	Conley 2001 (377)	19/189	12/188	1.57 (0.79 to 3.15)
> 7% increase in body weight	Conley 2001 (377)	44/161	18/155	2.35 (1.42 to 3.89)

n, *number of events;* N, *number of participants in group*

Olanzapine was significantly more likely to be associated with dry mouth than risperidone in the short to medium term (RR, 1.99; 95% CI, 1.23 to 3.23). No differences were seen between olanzapine- and risperidone-treated groups for other reported side-effects.

Weight change

Olanzapine was more likely than risperidone to cause weight gain in the short to medium term (RR, 2.35; 95% CI, 1.42 to 3.89) but the results did not reach significance in the long term.

Quality of life

Two separate continuous data scales relating to quality of life were used in the studies. The data from both scales were equivocal.

Olanzapine versus ziprasidone

All data removed from this section: commercial-in-confidence.

Sensitivity analysis

In the olanzapine versus placebo comparison, all studies had > 50% attrition so no sensitivity analysis was undertaken. In the olanzapine versus atypical antipsychotic treatment comparison, all studies had > 25% attrition so no sensitivity analysis was undertaken. When studies with > 25% attrition were removed from the olanzapine versus typical antipsychotic treatment comparison (Beasley 1996a (56%),[168] Beasley 1997 (95%),[182]

TABLE 32 *Olanzapine versus risperidone: dichotomous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state: no response (40% decrease on PANSS)	Tran 1997 (339)	111/172	123/167	0.88 (0.76 to 1.01)
Leaving study early				
Any reason	Tran 1997 (339)	70/172	88/167	0.75 (0.62 to 0.91)
	Jones 1998 (42)	9/21	14/21	
	Littrell 1999 (24)	2/12	1/12	
	Malyarov 1999 (25)	0/15	2/10	
	Gureje 1998 (65)	15/32	21/33	
Lack of efficacy	Jones 1998 (42)	1/21	4/21	0.25 (0.03 to 2.05)
Side-effects				
Any extrapyramidal	Tran 1997 (339)	32/172	52/167	0.60 (0.41 to 0.88)
Akathisia	Tran 1997 (339)	17/172	18/167	0.92 (0.49 to 1.72)
New parkinsonism	Tran 1997 (339)	22/172	37/167	0.58 (0.36 to 0.94)
Dyskinetic movements	Tran 1997 (339)	4/172	5/167	0.78 (0.21 to 2.84)
Needing anticholinergic medication	Tran 1997 (339)	34/172	55/167	0.60 (0.41 to 0.87)

n, *number of events;* N, *number of participants in group*

TABLE 33 *Olanzapine versus risperidone: continuous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies	Treatment group		Control group		MD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	Tran 1997	166	80.85 (19.39)	165	78.69 (15.51)	2.18 (–0.63 to 4.98)
Quality of life: QoL scale endpoint scores	Tran 1997	118	62.03 (27.25)	122	59.61 (22.68)	2.42 (–3.93 to 8.77)

N, *number of participants in group*

Jones 1998 (52%)[180]), no substantial changes in results were seen except for the PANSS negative score; this had previously been non-significant and now became significant in favour of olanzapine in the sensitivity analysis (WMD, –1.11; 95% CI, –1.75 to –0.47).

Publication bias

Because of time constraints it was not possible to construct funnel plots to look for publication bias in this review.

Rare or long-term events

Ten non-randomised studies of rare or long-term adverse events with olanzapine were identified. Data extraction sheets for these studies can be found in appendix 4. Two related to weight change,[194,195] six to mortality (of which two were in the manufacturer's submission and two in the sertindole submission),[196–198] one to cardiac conductivity,[199] and one to tardive dyskinesia.[200]

Mortality

Suicide

In a retrospective analysis of a post-marketing database over 12 months (Fung 1998[197]), 134 attempted suicides were reported (crude incidence, 0.02%; suicide attempt rate, 85/100,000 patient-years).

In an analysis of four double-blind studies and retrospective data from the manufacturer's database (Eli Lilly 2001[201]), suicide attempts per year were reported to be 0.046 for olanzapine-treated patients and 0.062 for haloperidol-treated patients.

In another analysis of an RCT (HGBG study 1997) from the manufacturer's database (Eli Lilly 2001[201]), identical rates of suicide attempts (0.6% for each group) were reported for risperidone- and olanzapine-treated patients.

Other causes

In a retrospective uncontrolled analysis of data from the Canadian Adverse Drug Reaction Monitoring Programme between 1996 and 2000 (Cadario 2000[196]), olanzapine was reported as a suspected drug in 22 deaths: eight suicide/overdose; two NMS; three arrhythmia; one myocardial infarction; two heart failure/pneumonia; one sepsis; one sudden death; one mesenteric thrombosis; one choking; one unknown. However no denominator was given for this study.

Commercial-in-confidence data removed.

NMS

One suspected case of NMS was reported in a cohort of 8858 patients prescribed olanzapine over an 18-month period in a retrospective post-marketing surveillance study (Biswas 2000[202]).

Weight change

In an observational prospective study of 2967 patients, in which olanzapine was compared with other antipsychotic drugs, including risperidone, over a 6-month period (Gomez 2000[194]), weight gain (146/2128) was reported to be statistically significantly more common in the olanzapine group than in the risperidone (8/417) or haloperidol groups (1/112).

In an analysis of data from an RCT with open-label follow-up to 3 years for the olanzapine arm (Kinon 2001[195]), the mean weight change for the olanzapine-treated group was 6.26 kg after a median follow-up of 2.54 years, and for the haloperidol-treated group the mean weight change was 0.69 kg after a median follow-up of 1.15 years.

Cardiac conductivity

In a study that presented ECG recordings from four RCTs (Czekella 2001[199]), Q-Tc readings from olanzapine-treated patients were compared with placebo-, haloperidol- and risperidone-treated patients; olanzapine did not contribute to prolonged Q-Tc.

Tardive dyskinesia

The results of three RCTs were pooled in a study that compared olanzapine with haloperidol over a period of up to 2.6 years (Tamura 1998[200]); the estimated 1-year risk of tardive dyskinesia was reported to be 0.52% for olanzapine and 7.45% for haloperidol (both results based on 6-month data).

Other systematic reviews

Peuskens and colleagues[203] conducted a meta-analysis of the clinical efficacy and safety of risperidone and olanzapine. Their results suggested that risperidone and olanzapine are more advantageous than typical antipsychotic treatments in reducing the PANSS score, and that risperidone-treated patients may have a lower risk of withdrawal. In terms of safety, risperidone-treated patients required less anti-EPS medication than patients treated with typical antipsychotic drugs. They also reported that risperidone may show clearer benefits in terms of efficacy than olanzapine. Significant heterogeneity between studies was also reported but these results were fairly similar to those reported here.

The following systematic reviews were found for the earlier review.

In a systematic review of olanzapine,[204] individuals treated with olanzapine were found to be more likely to improve than those treated with typical antipsychotic drugs (RR, 1.43; 95% CI, 1.28 to 1.61) and were less likely to experience extra-pyramidal side-effects. Olanzapine caused more weight gain than typical antipsychotic drugs. In another review,[205] more improvement and less attrition was also found in those treated with olanzapine than in those treated with typical comparators. In a third review,[206] olanzapine was found to be equivalent in effectiveness to typical antipsychotic drugs and produced fewer movement disorders. None of these findings differed substantially from the findings of the Cochrane review.[206a] Unpublished data provided by the manufacturer of olanzapine were included in this last review, so that the authors' conclusion that olanzapine is equivalent to typical drugs in improving symptoms is probably more robust than the conclusion that it is better at improving symptoms, as found in the other reviews.

In the Leucht review,[205] negative symptoms were also found to improve with olanzapine compared with typical antipsychotic drugs; however, the Cochrane review did not find this.[206a] This could be because of the way in which data were handled in the ITT analysis; in the Cochrane review, missing participants were given a 'bad'

outcome while the Leucht review used the last observation carried forward.

Ongoing studies

Three ongoing studies of olanzapine were found in the trials registers searched. One was an RCT comparing olanzapine with aripiprazole; this was expected to end in mid-2002 (Ramamurthy V. A multicentre, double-blind, randomised comparative study of aripiprazole and olanzapine in the treatment of patients with acute schizophrenia). Another was an RCT of the cost-effectiveness of olanzapine versus haloperidol that was expected to end in late 2001 (Collins JF. The clinical and economic impact of olanzapine treatment on refractory schizophrenia), and the third was a prospective non-randomised study of the incidence of tardive dyskinesia in people receiving olanzapine or risperidone (Kane JM. Prospective study of tardive dyskinesia development. No end date given).

Chapter 8

Quetiapine: effectiveness

Numbers and characteristics of included RCTs

New RCTs

Two new RCTs of quetiapine were identified for this update review: Astrazeneca 2000 (QUEST, commercial-in-confidence)[207] (also published in abstract form as Mullen 1999[208] and Reinstein 1999[209]); Velligan 1999.[210]

In addition, two new reports of old RCTs were identified which contained additional data to be included in this update review: Purdon 2001[211] – a further report of Purdon 2000;[212] Murasaki 2000[213] – another report of Murasaki 1999.[214]

Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

Eleven RCTs were included in the original review: Link 1994,[215] Fleischhacker 1995,[216] Fleischhacker 1996,[217] Purdon 2000,[212] Kudo 1999,[218] Murasaki 1999,[214] Emsley 1999,[219] Arvanitis 1996,[220] Fabre 1995,[189] Borison 1996,[221] Small 1997.[222] Data extraction sheets for these trials can be found in appendix 3.

Total RCTs

A total of 13 RCTs were included in this update review.

Duration

All but one of the included studies were randomised, double-blind, controlled trials of short to medium duration. Apart from one 3-week study (Fabre 1995 (USA 004)[189]), the others were 6, 8, 16 (QUEST) or 24 weeks long (Velligan 1999[210]). One study (Purdon 2000[212]) was of 6 months duration with a 2-day washout period.

Interventions

The risks/benefits of quetiapine at different doses were compared in four studies: Fleischhacker 1995 (Multi-country 012);[216] Arvanitis 1996 (North America 013);[220] Velligan 1999;[210] Small 1997 (USA–Europe 008).[222] Quetiapine was compared with placebo in four studies: Arvanitis 1996 (North America 013);[220] Fabre 1995 (USA 004);[189] Borison 1996 (USA 006);[221] Small 1997 (USA–Europe 008).[210] In eight studies, the risks–benefits of quetiapine were compared with those of classical antipsychotic treatments – haloperidol, mosapramine (used only in Japan) and chlorpromazine: Link 1997 (Europe–Africa 007);[215] Fleischhacker 1996 (Multi-country 014);[217] Kudo 1999;[218] Murasaki 1999;[214] Purdon 2000;[225] Emsley 1999;[219] Velligan 1999;[210] Arvanitis 1996 (North America 013).[220]

In one study (QUEST), the risks/benefits of quetiapine were compared with those of risperidone: Astrazeneca 2001 (commercial-in-confidence);[207] Mullen 1999;[208] Reinstein 1999.[209]

Participants

The participants, mostly men in their thirties and forties, all met the DSM-III-R or -IV[66] or ICD-10 diagnostic criteria of schizophrenia, and were at least moderately ill (CGI ≥ 4). With the exception of two very small studies (n = 12, Fabre 1995 (USA 004);[189] n = 25, Purdon 2000[212]), the number of participants ranged from 58 to 751. In one study (Emsley 1999),[219] participants had not responded to previous antipsychotic drug treatment.

Outcomes

Some outcomes were presented in graphic form, as p-values of differences, or as statements of significant or non-significant differences. These presentations made it impossible to acquire the raw data for synthesis. All included studies used the last observation carried forward strategy for the ITT analysis of continuous data.

When dichotomous data were presented, the various dose regimes of quetiapine were combined.

Dichotomous (improved/not improved) data on positive or negative symptoms were not available in the published papers and, in addition, none of the studies reported service utilisation, economic data or quality of life/satisfaction. Lastly, although score data for various movement disorder scales were used (Abnormal Involuntary Movement Scale (AIMS), BAS and SAS), none of the studies reported these.

Quality of included studies

With the exception of Small 1997 (USA–Europe 008),[222] none of the studies had any details about

the methods of randomisation. The first randomised, placebo-controlled trial (Fabre 1995 (USA 004)[189]) allocated people into quetiapine and placebo groups in a ratio of 2:1.

Although all studies except one (QUEST) were conducted on a double-blind basis, none of them contained an explicit description of how this and the testing of the blindness of raters, clinicians and trial participants were undertaken.

The investigators excluded data relating to three and five individuals in Borison 1996 (USA 006)[221] and Link 1997 (Europe–Africa 007),[215] respectively, because of lack of post-baseline data. With the exception of one study (Fabre 1995 (USA 004)[189]), and one trial in which loss to follow-up was not reported (Velligan 1999[210]), every trial had > 30% loss to follow-up.

Quetiapine versus risperidone: commercial-in-confidence data removed.

There was a fair amount of heterogeneity between the results of trials. Within the different dose comparisons, the heterogeneity could be explained by pooling data from the fairly wide range of doses that were described as 'high' (250–750 mg/day). The heterogeneity within the quetiapine versus classical antipsychotic drugs comparison, especially as regards side-effects, could be at least partially explained by the different antipsychotic treatments used as controls. While in Link 1997 (Europe–Africa 007)[215] quetiapine was compared with chlorpromazine, in Fleischhacker 1996 (Multi-country 014)[217] and Arvanitis 1996 (North America 013)[220] it was compared with haloperidol. Although the direction of effect was as expected, there were also substantial differences between the two haloperidol-controlled studies that are difficult to explain.

Quetiapine versus placebo

The results for the short to medium term (up to 26 weeks) are presented in *Table 34*. All the included studies in which quetiapine was compared with placebo had > 50% attrition, so their results should be treated with caution.

Leaving study early

The proportions of people leaving studies early were high in both groups: 53% of those allocated to quetiapine and 61% of those in the placebo group. However, the risk of leaving a study early was lower in the quetiapine group (RR, 0.84; 95% CI, 0.73 to 0.97). Nevertheless all other results within this comparison should be viewed with this in mind and, the reviewers suggest, with great caution. Heterogeneity was observed in the result for 'leaving study early due to adverse events' (chi-squared 5.45; $p = 0.065$).

Death

Two of the four studies (Borison 1996 (USA 006);[221] Small 1997 (USA–Europe 008)[222]) specifically reported that no deaths had occurred during the study periods.

Global state and psychotic symptoms

No important improvement

Although CGI was used to assess patients' global state in all studies, this was reported as a dichotomous result (improved/not improved) in only one (RR, 0.95; 95% CI, 0.76 to 1.18; risk difference, –0.04; 95% CI, –0.21 to 0.12). The dichotomous data relating to no improvement in psychotic symptoms (measured by BPRS or PANSS) showed a significant improvement in the quetiapine group (RR, 0.79; 95% CI, 0.67 to 0.92; risk difference, –0.14; 95% CI, –0.23 to –0.04).

Side-effects

Movement disorders

No significant differences were found with regard to needing medication for extra-pyramidal side-effects, as well as in the incidences of parkinsonism or dystonia. Because of heterogeneity (chi-squared = 3.55; degrees of freedom (df) = 1; $p = 0.059$), pooled data relating to the incidence of akathisia should be regarded with caution. When data from the two studies included in the comparison were analysed separately, one was significantly in favour of quetiapine (Arvanitis 1996: RR, 0.15; 95% CI, 0.03 to 0.64)[220] and one was non-significant (Small 1997: RR, 0.76; 95% CI, 0.32 to 1.79).[222]

General

While the incidences of dizziness and dry mouth were significantly higher in the quetiapine group (RR, 2.23; 95% CI, 1.12 to 4.42; and RR, 3.67; 95% CI, 1.25 to 10.83, respectively), the incidences of constipation and low blood pressure (postural) were not different between quetiapine and placebo. Owing to the heterogeneity of the data relating to sleepiness (chi-squared = 6.48; df = 3; $p = 0.09$), the pooled incidence was difficult to interpret.

Quetiapine versus risperidone: commercial-in-confidence data removed.

TABLE 34 *Quetiapine versus placebo – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any cause	Arvanitis 1996 (309)	143/258	35/51	0.84 (0.73 to 0.97)
	Fabre 1995 (12)	0/8	1/4	
	Borison 1996 (109)	26/54	33/55	
	Small 1997 (286)	102/190	57/96	
Adverse events	Arvanitis 1996 (309)	1/258	2/51	1.37 (0.60 to 3.12)
	Fabre 1995 (12)	0/8	0/4	
	Borison 1996 (109)	3/54	2/55	
	Small 1997 (286)	14/190	3/96	
Death (any cause)	Borison 1996 (109)	0/54	0/55	Not estimable
	Small 1997 (286)	0/190	0/96	
Global state – no important improvement	Borison 1996 (109)	39/54	42/55	0.95 (0.76 to 1.18)
Mental state (BPRS or PANSS) – no important improvement	Arvanitis 1996 (309)	140/258	33/51	0.79 (0.67 to 0.92)
	Fabre 1995 (12)	0/8	2/4	
	Small 1997 (286)	94/190	61/96	
Side-effects				
Needing medication for EPS	Borison 1996 (109)	7/54	9/55	0.62 (0.34 to 1.15)*
	Small 1997 (286)	10/190	10/96	
Parkinsonism	Arvanitis 1996 (309)	13/258	5/51	0.87 (0.63 to 1.19)
	Borison 1996 (109)	27/54	31/55	
	Small 1997 (286)	19/190	9/96	
Akathisia	Arvanitis 1996 (309)	3/258	4/51	0.52 (0.26 to 1.06)
	Small 1997 (286)	12/190	8/96	
Dystonia	Arvanitis 1996 (309)	2/258	1/51	0.40 (0.04 to 4.28)
Constipation	Arvanitis 1996 (309)	21/258	3/51	1.88 (0.95 to 3.74)
	Borison 1996 (109)	6/54	4/55	
	Small 1997 (286)	17/190	3/96	
Dizziness	Arvanitis 1996 (309)	21/258	4/51	2.23 (1.12 to 4.42)
	Fabre 1995 (12)	2/8	1/4	
	Borison 1996 (109)	5/54	3/55	
	Small 1997 (286)	21/190	1/96	
Dry mouth	Borison 1996 (109)	9/54	3/55	3.67 (1.25 to 10.83)
	Small 1997 (286)	10/190	1/96	
Low blood pressure (postural)	Arvanitis 1996 (309)	25/258	4/51	1.92 (0.79 to 4.70)
	Borison 1996 (109)	5/54	0/55	
Sleepiness	Arvanitis 1996 (309)	22/258	4/51	2.00 (1.32 to 3.04)
	Fabre 1995 (12)	4/8	0/4	
	Borison 1996 (109)	21/54	4/55	
	Small 1997 (286)	42/190	14/96	

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.05 (95% CI, –0.11 to 0.02)*

Quetiapine versus typical antipsychotic drugs

The results are summarised in *Table 35*. Two studies, Arvanitis 1996[220] and Purdon 2000,[212,225] had attrition rates of > 50%, so all data from these studies other than for the outcome 'leaving study early' have been excluded.

Leaving study early

The proportions of people leaving the studies early were just significantly in favour of quetiapine (RR, 0.87; 95% CI, 0.76 to 0.99). However, dropout rates in both groups were high, at about 36% in each group. Heterogeneity was seen in the result for 'leaving study early due to adverse events' (chi-squared = 7.94; $p = 0.095$), the source of which was unclear. Again, all results should be viewed with great caution. When reasons for leaving the study early were given, these are shown in *Table 35*.

Death

None of the studies reported whether death had or had not occurred.

Global and mental states

No important improvement

None of the studies reported the CGI dichotomous outcome of 'improved' or 'not improved'. The dichotomous data relating to BPRS and PANSS showed no significant differences between the two groups (RR, 0.89; 95% CI, 0.79 to 1.01; risk difference, –0.06; 95% CI, –0.12 to 0.01). However, heterogeneity was seen in the result (chi-squared = 7.49; $p = 0.024$); the source of this was unclear so the result should be viewed with caution. CGI scale data favoured comparator drugs over quetiapine, whereas BPRS and PANSS scale data favoured neither quetiapine nor the comparator drugs.

Side-effects

Movement disorders

The results favoured quetiapine for producing lower incidences of parkinsonism (RR, 0.24; 95% CI, 0.15 to 0.39) and akathisia (RR, 0.27; 95% CI, 0.16 to 0.46) but not dystonia (RR, 0.21; 95% CI, 0.01 to 3.48) than typical antipsychotic treatments. Individuals taking quetiapine were less likely to take medication for EPS (RR, 0.32; 95% CI, 0.21 to 0.48; risk difference, –0.25; 95% CI, –0.42 to –0.09). Heterogeneity was seen in this result (chi-squared = 8.29; $p = 0.081$), the source of which was unclear, so the result should be viewed with caution. Heterogeneity was also seen in the result for dystonia (chi-squared = 2.75; $p = 0.097$). When the results of the two studies that were pooled for this analysis were presented separately, one was non-significant (Link 1997: RR, 0.99; 95% CI, 0.06 to 15.61)[215] and one was significantly in favour of quetiapine (Fleischhacker 1996: RR, 0.06; 95% CI, 0.01 to 0.45).[217]

General

There were no differences in the incidences of dizziness and Q-Tc prolongation between groups. Owing to the heterogeneity of the data, the pooled incidences of constipation, sleepiness, dry mouth and low blood pressure should be interpreted with caution.

Sensitivity analysis

When only those studies in which quetiapine was compared with haloperidol were included in the analysis, the following changes were seen: leaving study early (any cause) was no longer significantly different between groups (RR, 0.88; 95% CI, 0.76 to 1.03), the incidence of dystonia was significantly less in the quetiapine group than in the haloperidol group (RR, 0.06; 95% CI, 0.01 to 0.45), constipation occurred significantly more frequently in the quetiapine group than in the haloperidol group (RR, 2.91; 95% CI, 1.17 to 7.25), and sleepiness was significantly less likely in the quetiapine group than in the haloperidol group (RR, 0.81; 95% CI, 0.69 to 0.96).

Quetiapine: high versus low dose

All the studies included in this comparison had > 50% attrition and hence the results must be interpreted with caution.

Leaving study early

There were significantly fewer people leaving the four studies in the high dose group (RR, 0.84; 95% CI, 0.74 to 0.94). However, the dropout rates in both groups were high: 48% in the high dose group and 60% in those allocated to low dose. As a result, all subsequent results must be viewed with great caution.

Death

Two studies reported death as an outcome. It was rare but was seen less in the high dose group (RR, 0.10; 95% CI, 0.00 to 2.12).

Global state and psychotic symptoms

No important improvement

The CGI was reported in a dichotomous form (improved/not improved) in only one study. This suggested a marginal but statistically significant improvement for the high dose group (RR, 0.85; 95% CI, 0.73 to 0.99; risk

TABLE 35 *Quetiapine versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any cause	Link 1997 (201)	31/101	36/100	0.87 (0.76 to 0.99)
	Kudo 1999 (180)	26/90	33/90	
	Murasaki 1999 (197)	34/100	43/97	
	Fleischhacker 1996 (448)	69/221	80/227	
	Emsley 1999 (288)	31/143	28/145	
	Arvanitis 1996 (310)	143/258	34/52	
Adverse events	Link 1997 (201)	4/101	9/100	0.43 (0.30 to 0.62)
	Kudo 1999 (180)	15/90	21/90	
	Murasaki 1999 (197)	11/100	25/97	
	Fleischhacker 1996 (448)	4/221	18/227	
	Arvanitis 1996 (310)	1/258	4/52	
Treatment failure	Fleischhacker 1996 (448)	34/221	28/227	1.26 (0.92 to 1.72)
	Arvanitis 1996 (310)	107/258	17/52	
Mental state (BPRS or PANSS) – no important improvement	Link 1997 (201)	35/101	48/100	0.89 (0.79 to 1.01)
	Fleischhacker 1996 (448)	124/221	120/227	
	Emsley 1999 (288)	68/143	90/145	
Side-effects				
Needing medication for EPS	Link 1997 (201)	10/101	15/100	0.32 (0.21 to 0.48)
	Kudo 1999 (180)	21/90	55/90	
	Fleischhacker 1996 (448)	29/221	111/227	
	Emsley 1999 (288)	3/143	17/145	
	Velligan 1999 (58)	3/43	8/15	
Parkinsonism	Fleischhacker 1996 (448)	18/221	77/227	0.24 (0.15 to 0.39)
Akathisia	Link 1997 (201)	5/101	14/100	0.27 (0.16 to 0.46)
	Fleischhacker 1996 (448)	11/221	46/227	
Dystonia	Link 1997 (201)	1/101	1/100	0.21 (0.01 to 3.48)
	Fleischhacker 1996 (448)	1/221	17/227	
EPS	Murasaki 1999 (197)	29/100	62/97	0.45 (0.32 to 0.64)*
Constipation	Link 1997 (201)	2/101	8/100	0.92 (0.08 to 10.32)
	Fleischhacker 1996 (448)	17/221	6/227	
Dizziness	Link 1997 (201)	2/101	5/100	0.94 (0.27 to 3.26)
	Fleischhacker 1996 (448)	16/221	11/227	
Dry mouth	Link 1997 (201)	8/101	6/100	2.85 (1.46 to 5.57)
	Fleischhacker 1996 (448)	23/221	5/227	
Low blood pressure (postural)	Link 1997 (201)	5/101	18/100	0.69 (0.12 to 3.98)
	Fleischhacker 1996 (448)	16/221	10/227	
Any adverse event	Murasaki 1999 (197)	67/100	80/97	0.81 (0.69 to 0.96)
Sleepiness	Link 1997 (201)	14/101	16/100	1.35 (0.61 to 3.01)
	Fleischhacker 1996 (448)	44/221	23/227	

n, *number of events;* N, *number of participants in group*

* *Risk difference, –0.35 (95% CI, –0.48 to -0.22)*

difference, –0.09; 95% CI, –0.17 to 0.00). The BPRS and PANSS dichotomous outcomes for improved/not improved mental state showed no differences between the doses (risk difference, –0.04; 95% CI, –0.10 to 0.02).

Side-effects

Movement disorders

The incidences of akathisia, dystonia, parkinsonism and requiring medication because of extra-pyramidal side-effects (risk difference, 0.01; 95% CI, –0.02 to 0.05) were the same for both doses of quetiapine.

General

There were no differences between high and low doses of quetiapine for the outcomes of constipation, dry mouth, low blood pressure, and sleepiness, although all the data suggested that there could indeed be fewer of each of these side-effects at the lower dose; however, the meta-analysis was too underpowered to highlight any such effect. Dizziness was less common in the low dose group (RR, 1.81; 95% CI, 1.07 to 3.08).

Quetiapine versus risperidone

Quetiapine was compared with risperidone in one study; however, the only outcome reported in a usable form for meta-analysis was leaving the study early.

Leaving study early

Quetiapine versus risperidone: table and text removed as all data commercial-in-confidence.

Global state and mental state

In one study (Reinstein 1999),[209] a significantly greater improvement in depression was reported, as measured by the Hamilton rating scale for depression, in participants given quetiapine than in those given risperidone ($p = 0.028$). Other measures of efficacy (CGI, PANSS and Drug Awareness Inventory (DAI)-10) did not appear to show any significant differences between groups.

Side-effects

In one study (Reinstein 1999),[209] participants in the risperidone group were reported to be more likely than participants in the quetiapine group to have an extrapyramidal event and more likely ($p < 0.001$) to have one that required adjustment of study or adjunctive medication.

Sensitivity analysis

All the included studies had > 25% attrition, hence a sensitivity analysis could not be undertaken.

Publication bias

Owing to the limited number of studies within each comparison, the assessment of publication bias by construction of funnel plots could not be undertaken for this review.

Rare or long-term events

Five non-randomised studies of rare or long-term events with quetiapine were identified for this review. Data extraction sheets for these studies can be found in appendix 4. Two related to weight change,[226,227] one to suicidality,[228] another was on cardiac conductivity,[229] and one reported some information on mortality and leucopenia.[229a]

Mortality

Suicide

A retrospective uncontrolled analysis of the manufacturer's database covering 77,000–116,000 patient-years of quetiapine use (Meltzer 2000)[228] produced the following results: suicidal ideation 37 patients; attempted suicide 41; completed suicide 9.

Other causes

Using pooled data from open-label extensions of RCTs, in one study (Arvanitis 1997)[229a] 2/1085 deaths were reported in quetiapine-treated patients; neither death was attributed to quetiapine.

Cardiac conductivity

Commercial-in-confidence: data removed.

Leucopenia

Using pooled data from open-label extensions of RCTs, 8/1085 quetiapine-treated patients were reported to have withdrawn because of leucopenia (Arvanitis 1997).[229a]

Weight change

In one study that combined data from controlled, uncontrolled and open-label extension trials (Jones 2000),[226] weight gain in 9–12 months of quetiapine-treated patients only was reported to range from 1.38 to 3.83 kg. The dose of quetiapine did not appear to affect weight change.

In another study that included quetiapine-treated patients (but no controls) from controlled, uncontrolled and open-label extension studies (Rak 1998),[227] weight gain in 9–12 months was reported to be 2.77 kg.

Other systematic reviews

Schulz[230] conducted a meta-analysis on the efficacy of quetiapine compared with haloperidol and placebo for short-term treatment of acute schizophrenia. There was no indication of heterogeneity between the included studies and quetiapine was superior to placebo and haloperidol in terms of response rates on the Brief Psychiatric Rating scale. This was reported only in a short abstract, which made it difficult to comment on the validity of the results.

Haddad and colleagues[231] conducted a systematic review of 11 studies on the efficacy of quetiapine for the treatment of patients with predominantly negative symptoms compared with olanzapine and risperidone. The improvements in negative symptom scores (according to the PANSS scale) observed with quetiapine were reported to be comparable to those observed with risperidone and olanzapine. The comparisons were indirect and, hence, the results must be interpreted with caution. This was a conference poster report and important details were missing, which made it difficult to comment on the validity of the results.

Chapter 9

Risperidone: effectiveness

Numbers and characteristics of included RCTs

New RCTs

A total of 22 new RCTs were identified for this update review: Tys 1999,[232] Kolff 2000,[152] Malyarov 1999,[153] Heck 2000,[233] Littrell 1999,[154] Lecrubier 2000,[43] Rabinowitz 2001,[234] QUEST (AstraZeneca 2000 – commercial-in-confidence,[207] Mullen 1999,[208] Reinstein 1999[209]), Liu 2000,[235] Wirshing 1999,[236] Kern 1999,[237] Kern 1998,[238] Kee 1998,[239] Muller-Siecheneder 1998,[240] Cetin 1999,[241] Study 128-117[242] and Study 128-302[243] (both Pfizer – commercial-in-confidence), Conley 2001,[161] Chowdhury 1999,[71] Barak 2000,[244] Janicak 1999,[245] Csernansky 2000.[246–248]

In addition, three new reports of 'old' RCTs were identified that contained additional data for inclusion in this review: Purdon 2001[211] was another report of Jones 1998[193]; Bouchard 2000[249] was another report of Bouchard 1998;[250] Edgell 2000[170] was a report on a subgroup of Tran 1997.[171]

Two studies (Purdon 2000,[178] David 1999[179]) were further reports of Jones 1998[180] and contained extra cognitive data; however, these data were not included as the study had > 50% attrition and thus all outcomes other than 'leaving study early' were excluded (see below).

Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

In the original review, 23 studies were identified for inclusion: Blin 1996,[251] Borison 1991,[252] Bouchard 1998,[253] Ceskova 1993,[254] Chouinard 1993,[255] Claus 1991,[256] Emsley 1995,[257] Hoyberg 1993,[258] Huttunen 1995,[259] Mahmoud 1998,[260] Marder 1994,[116] Mesotten 1991,[261] Min 1993,[262] Peuskens 1995,[263] Fleurot 1997,[62] Bondolfi 1998,[110] Anand 1998,[111] Breier 1999,[112] Wahlbeck 2000,[113] Tran 1997,[171] Klieser 1996,[264] Jones 1998,[193] Gureje 1998.[186] Data extraction sheets for these studies are presented in appendix 3.

Total RCTs

A total of 45 trials were included in this review.

Patient allocation was randomised in all 45 trials. Double-blinding was described in 32, two were single-blind and four were open, and in seven trials the degree of blinding was unclear. Mahmoud (1998)[260] was a rare pragmatic study with minimal interference by the protocol in everyday care.

The 15-nation, multicentre study (Peuskens 1995[263]) had 1362 participants. Next in size was QUEST[207–209] with 751 randomised, and then Mahmoud 1998[260] with 675 participants randomised. Chouinard 1993[255] and Marder 1994[116] were, in effect, one study – sometimes referred to as the North American study – in which 523 individuals were collectively randomised. In Rabinowitz 2001,[234] 453 people were randomised. All other studies had comparatively few participants, ranging from 365 (Csernansky 2000[246–248]) down to only 19 (Wahlbeck 2000[113]).

Duration

The short–medium term category comprised 34 studies, with durations ranging from 4 weeks (Blin 1996[251]) to 4 months (QUEST[207–209]). There were 11 studies in the long-term category: Barak 2000,[244] 18 months; Bouchard 1998,[253] 2 years; Tran 1997,[171] 28 weeks; Jones 1998,[193] 54 weeks; Gureje 1998,[186] 30 weeks; Malyarov 1999,[153] 6 months; Lecrubier 2000,[43] 6 months; Csernansky 2000,[246–248] Littrell 1999[154] and Mahmoud 1998[260] – all 1 year in length.

Study 128-117 (Pfizer): commercial-in-confidence data removed.

Interventions

Doses of risperidone varied and were fixed or flexible, ranging from a fixed minimum of 1 mg, given to one group in the multicentre European trial (Peuskens 1995[263]), to a fixed maximum of 16 mg (Peuskens 1995, Chouinard 1993[255]). The remaining studies allowed the dose to be individually titrated according to response. The mean daily dose at endpoint in these trials varied from a minimum of 6.1 mg (Emsley 1995[257]) to a maximum of 12 mg (Claus 1991[256]).

In 23 trials, haloperidol was the control intervention. Only two small studies (total $n = 205$) compared risperidone to a typical antipsychotic drug other than haloperidol (perphenazine – Hoyberg

1993;[258] zuclopenthixol – Huttenen 1995[259]). In Mahmoud (1998),[260] risperidone was compared with 'conventional treatment strategy' and in Bouchard (1998)[253] with 'classical neuroleptics'.

In the multicentre European study (Peuskens 1995[263]), a fixed dose of haloperidol, 10 mg, was used as the control intervention; in Chouinard 1993[255] and Marder 1994,[116] 20 mg was used. In all other trials flexible dose regimes were used, with the dose being individually titrated according to response. In these trials, the mean daily dose of haloperidol at endpoint varied from a minimum of 5.6 mg (Emsley 1995[257]) to a maximum of 15 mg (Borison 1991[252]).

There were three comparison groups in one trial (Blin 1996[251]): risperidone, methotrimeprazine and haloperidol. Data relating to methotrimeprazine were not used in this review as, despite being a phenothiazine, it is not in common usage. Its inclusion would have introduced a potential source of heterogeneity while gaining little extra external validity.

Risperidone was compared with amisulpride in two studies, with clozapine in six, with olanzapine in seven, with quetiapine in one, and with ziprasidone in two.

Participants

Most studies included only those individuals with a diagnosis of schizophrenia or schizophreniform disorder according to DSM-III-R,[66] DSM-IV or ICD-10. Six trials (Ceskova 1993,[254] Mesotten 1991,[261] Tran 1997,[171] Gureje 1998,[186] Muller-Siecheneder 1998,[240] Csernansky 2000[246–248]) also included participants diagnosed with schizoaffective disorder. One trial (Mullen 1999[208]) included individuals with mood disorders but some results were presented for those with schizophrenia and schizoaffective disorder separately. In one trial (Janicak 1999[245]) inclusion was restricted to those with schizoaffective disorder.

Most participants had previously been admitted to hospital (on average six times); the mean duration of current hospitalisation was about 6 months. In one study (Emsley 1995[257]), only those experiencing their first episode of schizophrenia were included.

Three trials versus clozapine and four versus haloperidol focused exclusively on individuals with treatment-resistant schizophrenia. Only people who had already experienced disturbing extrapyramidal symptoms on typical antipsychotic treatment were included in one trial (Heck 2000[233]). Another included only those with chronic schizophrenia who had been switched from depot medication to atypical antipsychotic medication (Littrell 1999[154]). A third (Barak 2000[244]) included only elderly people with schizophrenia (aged 65 years or more).

Outcomes

Clinical improvement was defined as a 20% reduction in total PANSS score from baseline in 15 studies, while in one trial (Mahmoud 1998[260]) 20%, 40% and 60% reductions were used. A 40% reduction in PANSS was used in two trials (Tran 1997,[171] Conley 2001[161]). Clinical improvement was defined solely in terms of a 20% reduction in total BPRS score from baseline in one trial (Borison 1991[252]) and as a 50% reduction in total PANSS score from baseline in two others (Emsley 1995,[257] Lecrubier 2000[43]). In two, improvement was defined according to the CGI-I scale (Lecrubier 2000, Conley 2001). The use of antiparkinsonian medication and the percentages of individual adverse events experienced by each group were also reported in most studies.

Study 128-302 (Pfizer): commercial-in-confidence data removed.

Quality of included studies

Overall, the quality of reporting of randomisation and allocation concealment was poor.

Numbers of drop-outs were reported for all trials; in most, an attempt was made to ascribe the reasons for dropping out. An ITT analysis was undertaken in some trials; the large, Peuskens 1995 study[263] was an exception to this and, owing to limited information, it was not possible to determine if ITT analysis had been used in the Bouchard 1998 study.[253] In five trials, ITT analysis was undertaken for side-effects only.

The numbers leaving the study early were high, albeit comparable to trials of other atypical antipsychotic drugs (Fabre 1995,[189] Thornley 1998[190]). They ranged from 0% (Breier 1999[112]) to 55% (Jones 1998,[193] Gureje 1998[186]).

Risperidone versus typical antipsychotic drugs: short- to medium-term studies

The results from studies lasting up to 26 weeks are presented in *Table 36*.

TABLE 36 *Risperidone versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Not clinically improved				
CGI	Claus 1991 (183)	29/99	25/84	0.89 (0.76 to 1.04)
	Hoyberg 1993 (107)	15/55	18/52	
	Marder 1994 (512)	105/256	129/256	
	Mesotten 1991 (60)	14/28	13/32	
	Min 1993 (35)	7/16	4/19	
PANSS 20% threshold	Blin 1996 (41)	4/21	8/20	0.86 (0.77 to 0.97)
	Chouinard 1993 (113)	44/92	11/21	
	Claus 1991 (44)	15/22	17/22	
	Hoyberg 1993 (107)	18/55	22/52	
	Huttunen 1995 (98)	20/48	29/50	
	Marder 1994 (322)	139/256	46/66	
	Min 1993 (35)	6/16	5/19	
	Peuskens 1995 (1362)	457/1136	97/226	
PANSS 40% threshold	Emsley 1995 (183)	37/99	37/84	0.85 (0.60 to 1.21)
Mental state				
Anxiety/tension	Chouinard 1993 (113)	42/92	13/21	1.05 (0.79 to 1.38)
	Emsley 1995 (183)	8/99	7/84	
	Hoyberg 1993 (107)	24/55	22/52	
	Marder 1994 (322)	15/256	1/66	
	Peuskens 1995 (1362)	62/1136	10/226	
Depression	Ceskova 1993 (62)	0/31	1/31	0.72 (0.41 to 1.25)
	Hoyberg 1993 (107)	15/55	19/52	
Behaviour				
Agitation	Chouinard 1993 (113)	45/92	12/21	0.77 (0.54 to 1.09)
	Emsley 1995 (183)	8/99	9/84	
	Marder 1994 (272)	29/256	11/66	
Use of sedatives	Blin 1996 (41)	10/21	8/20	1.04 (0.79 to 1.37)
	Chouinard 1993 (113)	66/92	15/21	
	Claus 1991 (44)	8/22	8/22	
Cognitive				
Concentration difficulties	Claus 1991 (44)	14/22	9/22	0.90 (0.75 to 1.07)
	Hoyberg 1993 (107)	25/55	25/52	
	Min 1993 (35)	4/16	10/19	
	Peuskens 1995 (1362)	314/1136	72/226	
Memory difficulties	Hoyberg 1993 (107)	10/55	12/52	0.84 (0.69 to 1.03)
	Peuskens 1995 (1362)	307/1136	72/226	
Discharge	Ceskova 1993 (62)	15/31	16/31	0.94 (0.57 to 1.54)
Leaving study early: any reason (totals)	Blin 1996 (41)	4/21	6/20	0.83 (0.73 to 0.94)
	Borison 1991 (106)	26/53	31/53	
	Ceskova 1993 (62)	0/31	3/31	
	Chouinard 1993 (113)	36/92	13/21	
	Claus 1991 (44)	1/22	5/22	
	Emsley 1995 (183)	20/99	26/84	
	Heck 2000 (77)	15/40	15/37	
	Hoyberg 1993 (107)	14/55	15/52	
	Huttunen 1995 (98)	17/48	23/50	
	Kee 1998 (20)	1/10	1/10	
	Marder 1994 (322)	122/256	38/66	
	Mesotten 1991 (60)	6/28	3/32	
	Min 1993 (35)	3/16	0/19	
	Peuskens 1995 (1362)	280/1136	63/226	
Acceptability of treatment as measured by direct questioning	Mesotten 1991 (60)	11/28	18/32	0.70 (0.40 to 1.21)

continued

***TABLE 36* contd** *Risperidone versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Side-effects				
Overall	Blin 1996 (41)	11/21	12/20	0.93 (0.85 to 1.01)
	Ceskova 1993 (62)	27/31	29/31	
	Emsley 1995 (183)	77/99	76/84	
	Hoyberg 1993 (98)	44/48	45/50	
	Mesotten 1991 (60)	19/28	21/32	
Movement disorders, EPS	Chouinard 1993 (113)	30/92	14/21	0.64 (0.56 to 0.73)
	Emsley 1995 (183)	58/99	70/84	
	Huttunen 1995 (98)	16/48	25/50	
	Marder 1994 (322)	36/256	17/66	
	Mesotten 1991 (60)	13/28	13/32	
	Min 1993 (35)	6/16	13/19	
	Peuskens 1995 (1362)	177/1136	60/226	
Use of antiparkinsonian drugs	Blin 1996 (41)	5/21	7/20	0.66 (0.58 to 0.75)
	Chouinard 1993 (113)	35/92	15/21	
	Claus 1991 (44)	4/22	6/22	
	Emsley 1995 (183)	49/99	63/84	
	Heck 2000 (77)	11/40	10/37	
	Hoyberg 1993 (107)	15/55	17/52	
	Huttunen 1995 (98)	13/48	26/50	
	Marder 1994 (322)	72/256	31/66	
	Mesotten 1991 (60)	9/28	12/32	
	Peuskens 1995 (1362)	224/1136	68/226	
Tardive dyskinesia	Ceskova 1993 (62)	1/31	1/31	1.00 (0.07 to 15.28)
Akathisia	Ceskova 1993 (62)	10/31	15/31	0.67 (0.36 to 1.25)
Dystonia	Ceskova 1993 (62)	3/31	1/31	0.72 (0.26 to 1.99)
	Hoyberg 1993 (107)	3/55	7/52	
Parkinsonism	Ceskova 1993 (62)	24/31	27/31	0.89 (0.70 to 1.12)
Tremor	Blin 1996 (41)	6/21	8/20	0.97 (0.51 to 1.83)
	Mesotten 1991 (60)	7/28	6/32	
Dry mouth	Blin 1996 (41)	7/21	10/20	0.80 (0.59 to 1.09)
	Ceskova 1993 (62)	1/31	1/31	
	Claus 1991 (44)	3/22	6/22	
	Hoyberg 1993 (107)	0/55	3/52	
	Peuskens 1995 (1362)	145/1136	32/226	
Blurred vision	Ceskova 1993 (62)	0/31	1/31	0.83 (0.62 to 1.10)
	Claus 1991 (44)	9/22	3/22	
	Hoyberg 1993 (107)	5/55	8/52	
	Mesotten 1991 (60)	3/28	0/32	
	Peuskens 1995 (1362)	145/1136	40/226	
Constipation	Blin 1996 (41)	2/21	9/20	1.02 (0.77 to 1.35)
	Claus 1991 (44)	4/22	3/22	
	Emsley 1995 (183)	8/99	7/84	
	Hoyberg 1993 (107)	7/55	0/52	
	Marder 1994 (322)	23/256	3/66	
	Peuskens 1995 (1362)	172/1136	36/226	
Difficulties passing urine	Blin 1996 (41)	0/21	0/20	0.24 (0.03 to 2.12)
	Ceskova 1993 (62)	0/31	1/31	
	Hoyberg 1993 (107)	0/55	2/52	

continued

***TABLE 36* contd** *Risperidone versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Insomnia	Chouinard 1993 (113)	52/92	14/21	0.94 (0.72 to 1.23)
	Emsley 1995 (183)	10/99	13/84	
	Marder 1994 (322)	33/256	8/66	
	Peuskens 1995 (1362)	114/1136	21/226	
Decreased duration or quality of sleep	Blin 1996 (41)	4/21	6/20	0.89 (0.69 to 1.14)
	Hoyberg 1993 (107)	4/55	7/52	
	Peuskens 1995 (1362)	235/1136	50/226	
Increased duration of sleep	Hoyberg 1993 (107)	10/55	10/52	0.95 (0.76 to 1.18)
	Peuskens 1995 (1362)	309/1136	65/226	
Somnolence	Blin 1996 (41)	9/21	11/20	0.89 (0.78 to 1.01)
	Ceskova 1993 (62)	6/31	4/31	
	Claus 1991 (44)	12/22	14/22	
	Emsley 1995 (183)	9/99	3/84	
	Hoyberg 1993 (107)	10/55	14/52	
	Huttunen 1995 (98)	34/48	44/50	
	Mesotten 1991 (60)	5/28	5/32	
	Min 1993 (35)	7/16	5/19	
	Peuskens 1995 (1362)	388/1136	90/226	
Weight loss	Hoyberg 1993 (107)	3/55	6/52	1.23 (0.98 to 1.56)
	Peuskens 1995 (1362)	368/1136	57/226	
Weight gain	Emsley 1995 (183)	8/99	4/84	1.37 (1.10 to 1.71)
	Hoyberg 1993 (107)	21/55	10/52	
	Peuskens 1995 (1362)	369/1136	57/226	
Dyspepsia	Marder 1994 (322)	18/256	3/66	1.55 (0.47 to 5.09)
Nausea	Claus 1991 (44)	8/22	9/22	1.18 (0.57 to 2.44)
	Marder 1994 (322)	11/256	1/66	
Vomiting	Marder 1994 (322)	10/256	4/66	0.64 (0.21 to 1.99)
Dizziness	Blin 1996 (41)	5/21	5/20	1.13 (0.89 to 1.43)
	Claus 1991 (44)	6/22	1/22	
	Emsley 1995 (183)	6/99	2/84	
	Hoyberg 1993 (107)	8/55	7/52	
	Marder 1994 (322)	15/256	0/66	
	Peuskens 1995 (1362)	263/1136	53/226	
Headache	Blin 1996 (41)	3/21	3/20	1.02 (0.79 to 1.32)
	Chouinard 1993 (113)	16/92	5/21	
	Claus 1991 (44)	17/22	13/22	
	Emsley 1995 (183)	10/99	9/84	
	Hoyberg 1993 (107)	7/55	3/52	
	Marder 1994 (322)	29/256	5/66	
	Peuskens 1995 (1362)	110/1136	26/226	
Tachycardia	Ceskova 1993 (62)	2/31	3/31	0.85 (0.39 to 1.82)
	Marder 1994 (322)	11/256	1/66	
	Min 1993 (35)	4/16	9/19	
Palpitations	Blin 1996 (41)	1/21	2/20	0.85 (0.32 to 2.26)
	Claus 1991 (44)	5/22	5/22	
Low blood pressure	Blin 1996 (41)	6/21	5/20	0.96 (0.38 to 2.43)
	Ceskova 1993 (62)	1/31	2/31	
Erectile dysfunction	Claus 1991 (29)	3/16	0/13	1.55 (0.58 to 4.20)
	Hoyberg 1993 (77)	6/40	5/37	

continued

***TABLE 36* contd** *Risperidone versus typical antipsychotic drugs – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Ejaculatory dysfunction	Claus 1991 (29)	2/16	0/13	4.12 (0.21 to 78.90)
Orgastic dysfunction	Hoyberg 1993 (107)	4/55	2/52	1.89 (0.36 to 9.89)
Diminished sexual desire	Hoyberg 1993 (107) Peuskens 1995 (1362)	3/55 131/1136	3/52 27/226	0.96 (0.66 to 1.41)
Amenorrhea	Claus 1991 (15) Hoyberg 1993 (30)	2/6 1/15	2/9 0/15	1.86 (0.42 to 8.17)
Menorrhagia	Hoyberg 1993 (30)	1/15	0/15	3.00 (0.13 to 68.26)
Rhinitis	Emsley 1995 (183)	6/99	0/84	11.05 (0.63 to 193.32)
Sweating	Blin 1996 (41) Ceskova 1993 (52) Claus 1991 (44) Hoyberg 1993 (107) Peuskens 1995 (1362)	4/21 0/21 2/22 8/55 125/1136	3/20 2/31 6/22 5/52 35/226	0.75 (0.55 to 1.02)
Too much saliva	Emsley 1995 (183)	2/99	4/84	0.42 (0.08 to 2.26)

n, *number of events*; N, *number of participants in group*

In one study (Borison 1991[252]), > 50% of participants left the study early; hence, all data from this study were excluded apart from the outcome 'leaving study early'.

Clinical improvement (as defined in individual studies)

In eight studies in which this was defined as a 20% reduction in total PANSS, an analysis of homogeneous data for this outcome favoured risperidone (RR, 0.86; 95% CI, 0.77, 0.97; risk difference, –0.07; 95% CI, –0.12 to –0.02). Funnel plot analysis for this outcome was asymmetrical and showed a greater effect size in favour of risperidone among the smaller studies. Thus these estimates of the superiority of risperidone in producing clinical improvement are likely to be exaggerated.

One study (Emsley 1995[257]), in which clinical improvement was defined as a 40% reduction in total PANSS, was analysed for this outcome. Patients on risperidone were no more likely to have improved than those on typical antipsychotic treatments (RR, 0.85; 95% CI, 0.60 to 1.21).

In five studies, 'clinical global impression' was assessed by a categorical scale (CGI). Some studies presented such data in a dichotomous form or the reviewers converted data. In five studies, no difference was found between risperidone and the control medication (RR, 0.89; 95% CI, 0.76 to 1.04; risk difference, –0.05; 95% CI, –0.11 to 0.01) for the outcome 'global clinical impression – not improved'. Funnel plot analysis for this outcome suggested a relative absence of smaller studies favouring risperidone, which suggests that this estimate was unduly biased towards control treatments.

PANSS and CGI scale data did not favour risperidone but BPRS data did.

In the study of people with schizoaffective disorder (Janicak 1999[245]), data were not presented in a usable form for the meta-analysis; however, no differences were found between risperidone- and haloperidol-treated groups for PANSS subscales.

Anxiety

This was specified *a priori* as an outcome of interest as it was reported to be a 'common' side-effect of risperidone by the manufacturer, Janssen-Cilag.[264a] Data from side-effect rating scales were subject to wide CIs, making it impossible to tell whether risperidone or typical antipsychotic drugs were superior or if there was, in fact, no difference (RR, 1.05; 95% CI, 0.79 to 1.38). Data were derived from five studies (2087 participants). Funnel plot analysis did reveal asymmetry.

Agitation

This was also specified *a priori* as an outcome of interest as it too was reported to be a 'common'

side-effect of risperidone. Data from three studies (447 participants) favoured neither drug (RR, 0.77; 95% CI, 0.54 to 1.09).

Cognitive function
Data from side-effect lists or scales revealed no differences between risperidone and control groups in terms of memory (RR, 0.84; 95% CI, 0.69 to 1.03) and concentration (RR, 0.90; 95% CI, 0.75 to 1.07) in the short term.

Discharge
This was reported as an outcome in only one study (Ceskova 1993[254]). Data from this one underpowered study were subject to wide CIs, making it impossible to tell whether risperidone or typical antipsychotic treatments were superior or if there was, in fact, no difference (RR, 0.94; 95% CI, 0.57 to 1.54).

Leaving study early
Fewer people discontinued their medication in the risperidone group than in the control group (RR, 0.83; 95% CI, 0.73 to 0.94). Funnel plot asymmetry was not demonstrated.

When reasons for participants dropping out were subdivided into those caused by adverse effects and those caused by treatment inefficacy, there were no differences between the two groups. Further, there was no firm evidence of funnel plot asymmetry among studies that reported these outcomes separately.

In some studies there was an attempt to assess the acceptability of treatment directly by direct questioning of trial participants. In one study (Mesotten 1991),[261] this outcome was subject to wide CIs, making it impossible to tell whether risperidone or typical antipsychotic drugs were superior or if there was no difference (RR, 0.70; 95% CI, 0.40 to 1.21).

Movement disorders (extrapyramidal side-effects)
Movement disorders occurred far less frequently in those who were treated with risperidone. Data from seven studies favoured risperidone (RR, 0.64; 95% CI, 0.56 to 0.73; risk difference, –0.14; 95% CI, –0.19 to –0.10). Funnel plot asymmetry was not demonstrated.

As antiparkinsonian medication is used to alleviate extrapyramidal symptoms, the numbers requiring this medication is a useful index of the severity of such symptoms. Data from ten studies strongly favoured risperidone (RR, 0.66; 95% CI, 0.58 to 0.75). The funnel plot was again suggestive of a bias in favour of risperidone. Scale data also favoured risperidone (see appendix 9).

In the study of patients with schizoaffective disorder (Janicak 1999[245]), data were not presented in a usable form for the meta-analysis but haloperidol was reported to produce significantly less EPS than risperidone (SAS, $p < 0.04$).

Insomnia
This too was reported to be a 'common' side-effect of risperidone. Analysis of the data from side-effect scales from four studies (1764 participants) suggested no differences between risperidone and control groups for this outcome (RR, 0.94; 95% CI, 0.72 to 1.23). Similarly, there were no differences between risperidone and control groups for either 'increased duration of sleep', 'somnolence' or 'reduced duration of sleep'.

Headache
None of the trials suggested that this was more common in those treated with risperidone (RR, 1.02; 95% CI, 0.79 to 1.32).

Anticholinergic side-effects
There were no differences between the risperidone and control groups in terms of dry mouth, blurred vision, constipation and difficulties in passing urine. The results relating to blurred vision (chi-squared = 8.43; $p = 0.077$) and constipation (chi-squared = 9.69; $p = 0.084$) were heterogeneous and should therefore be viewed with caution.

Weight gain
Individuals treated with risperidone were more likely to gain weight than those in the control group (RR, 1.37; 95% CI, 1.10 to 1.71).

Other side-effects
There were no differences between the risperidone and control groups in terms of other side-effects, such as gastrointestinal upset, cardiovascular difficulties, CNS problems, rhinitis and difficulties with sexual or menstrual functioning.

Risperidone versus typical antipsychotic drugs: long-term studies

The results from studies lasting for at least 26 weeks are presented in *Table 37*.

TABLE 37 *Risperidone versus typical antipsychotic drugs – 26 weeks and over*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Not clinically improved				
PANSS 20% threshold	Bouchard 1998 (184) Mahmoud 1998 (675)	65/93 126/349	77/91 170/326	0.73 (0.65 to 0.83)
PANSS 40% threshold	Mahmoud 1998 (675)	185/349	231/326	0.75 (0.66 to 0.84)
PANSS 60% threshold	Mahmoud 1998 (675)	278/349	290/326	0.90 (0.84 to 0.96)
Behaviour: agitation	Csernansky 2000 (365)	18/177	34/188	0.56 (0.33 to 0.96)
Cognitive: no improvement in verbal learning (CVLT)	Csernansky 2000 (265)	152/177	122/188	1.32 (1.17 to 1.49)
Leaving study early: any reason (totals)	Bouchard 1998 (184) Csernansky 2000 (365) Mahmoud 1998 (675) Malyarov 1999 (28)	6/93 78/177 52/349 2/10	13/91 99/188 72/326 3/18	0.75 (0.63 to 0.90)
Relapse at 1 year	Csernansky 2000 (365)	41/177	65/188	0.67 (0.48 to 0.93)
Side-effects				
Movement disorders, EPS	Csernansky 2000 (365)	14/177	28/188	0.53 (0.29 to 0.98)
Tardive dyskinesia	Bouchard 1998 (184)	41/93	51/91	0.79 (0.59 to 1.05)
Hyperkinesia	Csernansky 2000 (365)	9/177	38/188	0.25 (0.13 to 0.51)
Somnolence	Csernansky 2000 (365)	25/177	47/188	0.56 (0.36 to 0.88)

n, *number of events*; N, *number of participants in group*

Clinical improvement (as defined in individual studies)

In two studies, analysis of homogeneous data for a 20% reduction in total PANSS favoured risperidone (RR, 0.73; 95% CI, 0.65 to 0.83; risk difference, –0.16; 95% CI, –0.22 to –0.09).

One study (Mahmoud 1998[260]) was analysed for a 40% reduction in total PANSS. Patients on risperidone were more likely to have improved in the long term (RR, 0.75; 95% CI, 0.66 to 0.84; risk difference, –0.18; 95% CI, –0.25 to –0.11).

In the same study (Mahmoud 1998) a 60% reduction in total PANSS was also considered and, again, the result favoured risperidone (RR, 0.90; 95% CI, 0.84 to 0.96).

Agitation

This outcome was specified *a priori* as of interest, as it was reported to be a 'common' side-effect of risperidone. Data from one study with 365 participants favoured risperidone (RR, 0.56; 95% CI, 0.33 to 0.96).

Cognitive function

Risperidone was less likely than typical antipsychotic drugs to lead to an improvement in verbal learning skills (RR, 1.32; 95% CI, 1.17 to 1.49).

Relapse at 1 year

One study (Csernansky 2000[246–248]) reported relapse at 1 year; the results favoured risperidone over haloperidol (RR, 0.67; 95% CI, 0.48 to 0.93).

Leaving study early

Fewer people discontinued their medication in the risperidone group than the control group (RR, 0.75; 95% CI, 0.63 to 0.90).

Movement disorders (extrapyramidal side-effects)

Movement disorders occurred far less frequently in those who were treated with risperidone. Data from one study favoured risperidone (RR, 0.53; 95% CI, 0.29 to 0.98; risk difference, –0.07; 95% CI, –0.13 to –0.01). Scale data also favoured risperidone (see appendix 9).

Somnolence

Risperidone appeared to be less likely than control medication to cause daytime sleepiness (somnolence) (RR, 0.56; 95% CI, 0.36 to 0.88).

Sensitivity analysis

When only those studies in which risperidone was compared with haloperidol were included in the analysis, the following changes were seen: response (PANSS) was of only borderline significance (RR, 0.89; 95% CI, 0.79 to 1.00); individuals treated with risperidone were more likely to experience weight loss than those treated with haloperidol (RR, 1.28; 95% CI, 1.01 to 1.63) and less likely to experience sweating (RR, 0.69; 95% CI, 0.50 to 0.95). In the long term, patients treated with risperidone were no more or less likely to leave the study early than those treated with haloperidol (RR, 0.84; 95% CI, 0.68 to 1.05).

If studies with at least 25% attrition were excluded (Blin 1996, 32%;[251] Chouinard 1993, 43%;[255] Emsley 1995, 25%;[257] Hoyberg 1993, 27%;[258] Huttunen 1995, 41%;[259] Marder 1994, 50%[116]), the following changes in results occurred: BPRS change scores (scale data) no longer significantly favoured risperidone; Extrapyramidal Syndrome Rating Scale (ESRS) total scores no longer favoured risperidone; weight loss significantly favoured the comparator drugs (RR, 1.28; 95% CI, 1.01 to 1.63); those in the risperidone groups sweated significantly less than those in the comparator groups (RR, 0.66; 95% CI, 0.47 to 0.93).

Subgroups

In one trial (Emsley 1995[257]), only patients experiencing their first episode of schizophrenia were included. The results appeared to be consistent with those from other studies and excluding this trial did not materially change the results of this review for the main outcomes of interest. This suggests that those experiencing their first episode of schizophrenia do not differ substantially in their treatment response.

Difficulties in differentiating negative symptoms from movement disorders, such as slowness and poverty of movement (Van Putten 1987[265]), may have favoured risperidone over haloperidol, especially when haloperidol was used at relatively high doses. It was noteworthy that less difference in terms of negative symptoms was observed between risperidone and haloperidol in the European study, in which haloperidol, 10 mg daily, was used (Peuskens 1995[263]), than in the North American studies in which haloperidol, 20 mg daily, was used (Chouinard 1993,[255] Marder 1994[116]).

The study of risperidone versus haloperidol in elderly patients with schizophrenia (Barak 2000[244]) did not contain data suitable for meta-analysis; however, the reported results suggested that risperidone improved CGI-I and PANSS total and positive scores more than haloperidol ($p < 0.05$) and caused fewer side-effects in this population.

Risperidone versus clozapine

All the studies were short term – 16 weeks and under in duration – and are combined together. The results are presented in *Table 38*.

Leaving study early

For the six studies in which risperidone was compared with clozapine, there were no significant differences in terms of the numbers of patients leaving the study early (RR, 1.02; 95% CI, 0.76 to 1.37).

Clinical response

There were no significant differences demonstrated between either compound for most of the reported endpoints of clinical response – unnecessarily wide CIs (owing to small sample sizes) and insufficient data prevented any assumptions about the clinical equivalence of these two compounds being made.

Trialists generally reported mental state as change and endpoint scores on both PANSS and BPRS. Clinical response was generally defined as a 20% reduction from baseline.

When clinical response was operationally defined as a 20% reduction in PANSS endpoint score at 6 weeks, there were no differences between groups (pooled RR, 1.09; 95% CI, 0.77 to 1.54; risk difference, 0.03; 95% CI, –0.10 to 0.16).

No significant differences were seen in measures of cognitive abilities between those receiving risperidone and those receiving clozapine (Bondolfi 1998[110]).

Extrapyramidal side-effects

There were no significant differences between the two compounds in terms of the numbers of patients who received antiparkinsonian medication (RR, 2.22; 95% CI, 0.77 to 6.37) in the short term (however, as this result was based on only one study with 19 participants, it may not be reliable).

TABLE 38 *Risperidone versus clozapine – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state				
Not improved (< 20% decrease in PANSS)	Bondolfi 1998 (86) Breier 1999 (29) Chowdhury 1999 (60) Wahlbeck 2000 (19)	14/43 12/15 10/30 3/9	15/43 9/14 6/30 6/11	1.09 (0.77 to 1.54)
Negative symptoms not improved (< 20% decrease in PANSS negative subscale score)	Chowdhury 1999 (60)	19/30	22/30	0.86 (0.61 to 1.22)
Positive symptoms not improved (< 20% decrease in PANSS positive subscale score)	Chowdhury 1999 (60)	20/30	24/30	0.83 (0.61 to 1.14)
Not feeling even a little better (PGI)	Wahlbeck 2000 (19)	4/9	4/10	1.11 (0.39 to 3.19)
Cognitive functioning				
Concentration difficulties	Bondolfi 1998 (86)	7/43	11/43	0.64 (0.27 to 1.49)
Memory problems	Bondolfi 1998 (86)	9/43	15/43	0.60 (0.29 to 1.22)
Leaving study early	Klieser 1996 (59) Bondolfi 1998 (86) Anand 1998 (273) Breier 1999 (29) Chowdhury 1999 (60) Wahlbeck 2000 (20)	22/39 9/43 34/135 0/15 8/30 1/9	6/20 9/43 38/138 0/14 6/30 6/11	1.02 (0.76 to 1.37)
Side-effects				
Dizziness (orthostatic)	Bondolfi 1998 (86)	5/43	9/43	0.56 (0.20 to 1.52)
Decrease in libido	Bondolfi 1998 (86)	4/43	2/43	2.00 (0.39 to 10.35)
Extrapyramidal	Bondolfi 1998 (86) Breier 1999 (29) Wahlbeck 2000 (19)	3/43 10/15 6/9	3/43 2/14 3/10	2.40 (1.17 to 4.90)
Nausea/vomiting	Bondolfi 1998 (86)	7/43	9/43	0.78 (0.32 to 1.90)
Drowsiness	Bondolfi 1998 (86) Wahlbeck 2000 (19)	13/43 0/9	20/43 1/10	0.63 (0.36 to 1.07)
Insomnia	Bondolfi 1998 (86) Chowdhury 1999 (60)	6/43 10/30	3/43 0/30	4.71 (1.54 to 14.43)
Hypersomnia	Bondolfi 1998 (86)	8/43	9/43	0.89 (0.38 to 2.09)
Weight gain	Bondolfi 1998 (86) Chowdhury 1999 (60)	10/43 13/30	16/43 13/30	0.79 (0.51 to 1.23)
White blood cell problems	Bondolfi 1998 (86) Chowdhury 1999 (60) Anand 1998 (273) Wahlbeck 2000 (19)	1/43 0/30 3/135 0/9	0/43 8/30 1/138 1/10	0.49 (0.18 to 1.32)
Antiparkinsonian medication required	Wahlbeck 2000 (19)	6/9	3/10	2.22 (0.77 to 6.37)
Akathisia	Chowdhury 1999 (60)	11/30	0/30	23.00 (1.42 to 373)
Constipation	Chowdhury 1999 (60)	15/30	9/30	1.67 (0.87 to 3.20)
Hypersalivation	Chowdhury 1999 (60)	0/30	18/30	0.03 (0.00 to 0.43)
Dry mouth	Chowdhury 1999 (60)	14/30	0/30	29.00 (1.81 to 465)
Seizure	Chowdhury 1999 (40) Wahlbeck 2000 (19)	0/30 0/9	1/30 0/10	0.33 (0.01 to 7.87)

continued

***TABLE 38* contd** *Risperidone versus clozapine – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Impotence	Chowdhury 1999 (45)	8/23	0/22	16.29 (1.00 to 266)
Tachycardia	Chowdhury 1999 (60)	0/30	23/30	0.02 (0.00 to 0.34)
Fatigue	Bondolfi 1998 (86)	12/43	22/43	0.55 (0.31 to 0.96)
Not discharged from hospital	Wahlbeck 2000 (19)	2/9	4/10	0.56 (0.13 to 2.34)

n, *number of events*; N, *number of participants in group*

More risperidone-treated than clozapine-treated patients reported extrapyramidal side-effects (RR, 2.40; 95% CI, 1.17 to 4.90), including akathisia (RR, 23.00; 95% CI, 1.42 to 373). Wide CIs did not allow the equivalence of the two compounds nor the superiority of either compound to be assumed for these outcomes.

Other side-effects

Risperidone was significantly less likely than clozapine to cause tachycardia (RR, 0.02; 95% CI, 0.00 to 0.34) and hypersalivation (RR, 0.03; 95% CI, 0.00 to 0.43), and significantly more likely to cause dry mouth (RR, 29.0; 95% CI, 1.81 to 465), impotence (RR, 16.29; 95% CI, 1.00 to 266 – borderline significance) and insomnia (RR, 4.71; 95% CI, 1.54 to 14.43). Other side-effects were either not reported in sufficient detail or had such wide CIs as to preclude interpretation.

Service use

Only in Wahlbeck 2000[113] was any aspect of service use reported, by describing which patients were able to leave hospital – although the study was insufficiently powered to give precise estimates of this outcome (RR of not leaving hospital, 0.56; 95% CI, 0.13 to 2.34).

Quality of life

Quality of life was not generally examined in the included studies, although in Wahlbeck 2000[113] patients were asked a simple question – enquiring if they 'felt a little better'. There were no significant differences in this respect, although the study was not sufficiently powered to answer the question (n = 19; RR, 1.11; 95% CI, 0.39 to 3.19).

Death

Two studies contained statements that no deaths occurred.

Subgroup and sensitivity analyses

Removing studies with > 25% attrition from the analysis (Klieser 1996, 47%;[264] Anand 1998, 42%;[111] Wahlbeck 2000, 30%[113]) made no substantial difference to the results.

Patients with treatment-resistant illness

Most of the data presented above related to patients with treatment-resistant illness (Bondolfi 1998,[110] Anand 1998,[111] Wahlbeck 2000[113]); the exclusion of patients without treatment-resistant illness did not materially alter the results.

Patients with negative or first-episode schizophrenia

None of the studies presented such data or focussed exclusively on these populations.

Risperidone versus olanzapine

Outcomes for the seven studies in which these two drugs were compared are presented below. All except Littrell 1999[154] showed high levels of attrition and the results should therefore be interpreted with caution. Two studies (Jones 1998,[193] Gureje 1998[186]) had attrition rates of > 50% and all data from these studies (apart from for the outcome 'leaving study early') have been excluded from this review.

The results are summarised in *Tables 39–42*.

Leaving study early

No significant differences between olanzapine- and risperidone-treated groups were seen in the short term (RR, 1.24; 95% CI, 0.87 to 1.75).

In the longer-term studies, olanzapine seemed more acceptable than risperidone when numbers of patients leaving the study early for any reason were compared (RR, 1.31; 95% CI, 1.08 to 1.59).

TABLE 39 *Risperidone versus olanzapine: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state				
No important clinical response (CGI-I)	Conley 2001 (377)	128/188	131/189	0.98 (0.86 to 1.13)
No important clinical response (CGI-S)	Conley 2001 (377)	66/133	76/145	0.95 (0.75 to 1.19)
Mental state				
No important clinical response (< 40% reduction in PANSS)	Conley 2001 (377)	154/188	166/189	0.93 (0.86 to 1.02)
No important clinical response (< 20% reduction in PANSS)	Conley 2001 (377)	119/188	121/189	0.99 (0.85 to 1.15)
Leaving study early				
Any reason	Conley 2001 (377)	53/188	43/189	1.24 (0.87 to 1.75)
Adverse events	Conley 2001 (377)	22/188	17/189	1.30 (0.71 to 2.37)
Psychosis/relapse	Conley 2001 (377)	8/188	8/189	1.01 (0.39 to 2.62)
Hallucinations/relapse	Conley 2001 (377)	2/188	3/189	0.67 (0.11 to 3.97)
Suicide attempt	Conley 2001 (377)	2/188	5/189	0.40 (0.08 to 2.05)
Serious agitation	Conley 2001 (377)	3/188	3/189	1.01 (0.21 to 4.92)
Serious depression	Conley 2001 (377)	3/188	3/189	1.01 (0.21 to 4.92)
Serious insomnia	Conley 2001 (377)	3/188	2/189	1.51 (0.25 to 8.92)
Drug abuse	Conley 2001 (377)	0/188	3/189	0.14 (0.01 to 2.76)
Side-effects				
Cardiovascular symptoms	Conley 2001 (377)	0/188	3/189	0.14 (0.01 to 2.76)
Gastrointestinal disorders	Conley 2001 (377)	0/188	3/189	0.14 (0.01 to 2.76)
Increase of ≥ 7% body weight	Conley 2001 (316)	18/155	44/161	0.42 (0.26 to 0.70)
Somnolence	Conley 2001 (377)	69/188	73/189	0.95 (0.73 to 1.23)
Insomnia	Conley 2001 (377)	45/188	35/189	1.29 (0.87 to 1.91)
Headache	Conley 2001 (377)	41/188	32/189	1.29 (0.85 to 1.95)
Agitation	Conley 2001 (377)	29/188	40/189	0.73 (0.47 to 1.12)
Dry mouth	Conley 2001 (377)	21/188	42/189	0.50 (0.31 to 0.82)
Dizziness	Conley 2001 (377)	26/188	27/189	0.97 (0.59 to 1.59)
Anxiety	Conley 2001 (377)	20/188	23/189	0.87 (0.50 to 1.54)
Vision abnormalities	Conley 2001 (377)	12/188	19/189	0.63 (0.32 to 1.27)
Rhinitis	Conley 2001 (377)	30/188	31/189	0.97 (0.61 to 1.54)
Any extrapyramidal	Conley 2001 (377)	45/188	38/189	1.19 (0.81 to 1.74)
Antiparkinsonian medication required	Conley 2001 (377)	61/188	53/189	1.16 (0.85 to 1.57)

n, *number of events*; N, *number of participants in group*

TABLE 40 *Risperidone versus olanzapine: continuous outcomes – up to 26 weeks*

Comparison or outcome	Included studies	Treatment group		Control group		MD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	Conley 2001 (change)	155	1.54 (3.54)	161	3.27 (5.08)	–1.73 (–2.69 to –0.77)

N, *number of participants in group*

TABLE 41 *Risperidone versus olanzapine: dichotomous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state: no important clinical response (< 40% reduction in PANSS)	Tran 1997 (339)	123/167	111/172	1.14 (0.99 to 1.32)
Leaving study early				
Any reason	Jones 1998 (42)	14/21	9/21	1.34 (1.10 to 1.62)
	Littrell 1999 (24)	1/12	2/12	
	Gureje 1998 (65)	21/33	15/32	
	Tran 1997 (339)	88/167	70/172	
	Malyarov 1999 (25)	2/10	0/15	
Lack of efficacy	Jones 1998 (42)	4/21	1/21	4.00 (0.49 to 32.87)
Side-effects				
Any EPS	Tran 1997 (339)	52/167	32/172	1.67 (1.15 to 2.41)
Akathisia	Tran 1997 (339)	18/167	17/172	1.09 (0.58 to 2.04)
New parkinsonism	Tran 1997 (339)	37/167	22/172	1.73 (1.07 to 2.81)
Dyskinetic movements	Tran 1997 (339)	5/167	4/172	1.29 (0.35 to 4.71)
Antiparkinsonian medication required	Tran 1997 (339)	55/167	34/172	1.67 (1.15 to 2.41)

n, *number of events*; N, *number of participants in group*

TABLE 42 *Risperidone versus olanzapine: continuous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies	Treatment group		Control group		MD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)	Tran 1997 (endpoint)	165	78.69 (15.51)	166	80.85 (19.39)	–2.16 (–5.94 to 1.62)
Quality of life – endpoint scores	Tran 1997	122	59.61 (22.68)	118	62.03 (27.25)	–0.10 (–0.35 to 0.16)

N, *number of participants in group*

Clinical response

When clinical response was dichotomised into a 40% reduction in PANSS score, there was no significant benefit for olanzapine in the short term (RR, 0.93; 95% CI, 0.86 to 1.02; risk difference, –0.06; 95% CI, –0.13 to 0.01) or in the long term (RR, 1.14; 95% CI, 0.99 to 1.32; risk difference, 0.09; 95% CI, –0.01 to 0.19). CGI and PANSS scale data did not favour either drug.

Extrapyramidal side-effects

Those taking olanzapine reported fewer extrapyramidal side-effects in the long term (RR, 1.67; 95% CI, 1.14 to 2.46; risk difference, 0.13; 95% CI, 0.03 to 0.22), fewer new episodes of parkinsonism (long-term RR, 1.73; 95% CI, 1.07 to 2.81) and received less antiparkinsonian medication in the long term (RR, 1.67; 95% CI, 1.15 to 2.41). In the short term, no significant differences were seen between groups in terms of extrapyramidal side-effects or use of antiparkinsonian medication.

Other side-effects

Risperidone caused less weight gain than olanzapine in the short term (RR, 0.42; 95% CI, 0.26 to 0.70; MD, –1.73 kg; 95% CI, –2.69 to –0.77). No significant difference was seen between groups in terms of weight gain in the long term (MD, –2.16 kg; 95% CI, –5.94 to 1.62). Risperidone was less likely to be associated with a dry mouth than olanzapine (RR, 0.50; 95% CI, 0.31 to 0.82).

Quality of life

Quality of life was examined in one trial (Tran 1997[171]) but no difference was found between the two compounds ($n = 240$; MD, –0.10; 95% CI, –0.35 to 0.16).

Death
None of the trials reported mortality data.

Subgroup and sensitivity analyses

Excluding high attrition studies
All studies had > 25% attrition, so it was not possible to carry out a sensitivity analysis.

Patients with treatment-resistant illness
None of the studies exclusively included patients with treatment-resistant illness.

Patients with negative or first-episode schizophrenia
None of the studies presented these data or focussed exclusively on these populations.

Risperidone versus amisulpride

Two studies were found in which these two drugs were compared (Fleurot 1997,[62] Lecrubier 2000[43]). Both were short to medium term in duration (up to 26 weeks). The results are summarised in *Table 43*.

TABLE 43 *Risperidone versus amisulpride – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any reason	Fleurot 1997 (228)	32/113	37/115	0.88 (0.59 to 1.31)
Lack of efficacy	Fleurot 1997 (228)	10/113	8/115	1.27 (0.52 to 3.11)
Adverse events	Fleurot 1997 (228)	14/113	15/115	0.95 (0.48 to 1.88)
Global state				
Not improved (CGI-I)	Lecrubier 2000 (310)	55/158	35/152	1.51 (1.05 to 2.17)
No response (subjective, Van Putten scale)	Lecrubier 2000 (310)	131/158	141/152	0.89 (0.82 to 0.97)
Social functioning < 50% improved (SOFA)	Lecrubier 2000 (310)	122/158	102/152	1.15 (1.00 to 1.32)
Mental state				
No clinical improvement (PANSS < 50% decrease)	Lecrubier 2000 (310)	76/158	53/152	1.38 (1.05 to 1.81)
No clinical improvement (< 50% decrease BPRS)	Lecrubier 2000 (310)	66/158	43/152	1.48 (1.08 to 2.02)
Side-effects				
At least one endocrine symptom	Fleurot 1997 (228)	7/113	7/115	1.02 (0.37 to 2.81)
Constipation	Fleurot 1997 (228)	1/113	8/115	0.13 (0.02 to 1.00)
Saliva – increased	Fleurot 1997 (228)	5/113	9/115	0.57 (0.20 to 1.64)
Vomiting	Fleurot 1997 (228)	4/113	7/115	0.58 (0.18 to 1.93)
Any extrapyramidal	Fleurot 1997 (228)	13/113	17/115	0.78 (0.40 to 1.53)*
Hyperkinesia	Fleurot 1997 (228)	11/113	15/115	0.75 (0.36 to 1.55)
Hypertonia	Fleurot 1997 (228)	6/113	9/115	0.68 (0.25 to 1.84)
Tremor	Fleurot 1997 (228)	8/113	5/115	1.63 (0.55 to 4.83)
Antiparkinsonian medication required	Fleurot 1997 (228)	26/113	35/115	0.76 (0.46 to 1.17)
Agitation	Fleurot 1997 (228)	4/113	14/115	0.29 (0.10 to 0.86)
Anxiety	Fleurot 1997 (228)	7/113	10/115	0.71 (0.28 to 1.81)
Insomnia	Fleurot 1997 (228)	8/113	10/115	0.81 (0.33 to 1.99)
Weight gain	Fleurot 1997 (228)	6/113	4/115	1.53 (0.44 to 5.27)

n, *number of events*; N, *number of participants in group; SOFA, Social Functioning Assessment*

* *Risk difference, –0.03 (95% CI, –0.12 to 0.05)*

Leaving study early
Total discontinuations were similar for both drugs (n = 228; RR, 0.88; 95% CI, 0.59 to 1.31). When the reason for discontinuation was specified as either lack of efficacy or adverse events, there were no significant differences, although wide CIs meant that the equivalence of these two drugs could not be assumed for these outcomes.

Clinical response
Response as defined by the CGI-I scale or by a 50% reduction in PANSS or BPRS score was higher for amisulpride than risperidone (CGI-I: RR, 1.51; 95% CI, 1.05 to 2.17; risk difference, 0.12; 95% CI, 0.02 to 0.22; PANSS: RR, 1.38; 95% CI, 1.05 to 1.81; risk difference, 0.13; 95% CI, 0.02 to 0.24; BPRS: RR, 1.48; 95% CI, 1.08 to 2.02; risk difference, 0.13; 95% CI, 0.03 to 0.24) and almost higher for amisulpride on the social functioning scale (RR, 1.15; 95% CI, 1.00 to 1.32).

Side-effects
No significant differences were seen between risperidone and amisulpride for any reported side-effects except for agitation, which was less frequent with risperidone than with amisulpride (RR, 0.29; 95% CI, 0.10 to 0.86). Constipation was of borderline significance in favour of risperidone (RR, 0.13; 95% CI, 0.02 to 1.00).

Sensitivity analysis

Data from the two included studies were not pooled so there was no need to carry out a sensitivity analysis.

Risperidone versus quetiapine

In one study, the QUEST trial (AstraZeneca 2001,[207] Mullen 1999,[208] Reinstein 1999[209]), risperidone was compared with quetiapine; 751 people were randomised for 16 weeks.

AstraZeneca: commercial-in-confidence data removed.

Global state and mental state
A significantly greater improvement in depression, as measured by the Hamilton rating scale for depression, was reported (Reinstein 1999[209]) in participants given quetiapine than in those given risperidone (p = 0.028). Other measures of efficacy (CGI, PANSS and DAI-10) did not appear to show any significant differences between groups.

Side-effects
Participants in the risperidone group were reported (Reinstein 1999[209]) to be more likely to have an extrapyramidal event and more likely ($p < 0.001$) to have one that required adjustment of study or adjunctive medication than participants in the quetiapine group.

Table containing commercial-in-confidence data removed.

Sensitivity analysis

As only one study was included, no sensitivity analysis could be performed.

Risperidone versus ziprasidone

Section containing commercial-in-confidence data removed.

Sensitivity analysis

The included studies had attrition rates of at least 25% and were not pooled, so it was not possible to carry out a sensitivity analysis.

Publication bias

Because of time constraints, it was not possible to construct funnel plots to assess publication bias for the comparisons of risperidone with other atypical antipsychotic drugs.

Rare or long-term events

Six studies of rare or long-term events with risperidone were identified for this review. Data extraction sheets for these studies can be found in appendix 4. One was on tardive dyskinesia,[266] one on NMS,[135] one included information on both tardive dyskinesia and NMS,[267] and three contained information on mortality.

Mortality
In one uncontrolled retrospective survey of general practitioners (GPs) prescribing risperidone to 14,282 patients between 1993 and 1996 (MacKay 1998[268]), a suicide attempt/drug overdose rate of 2.1 per 1000 patient months was reported.

Risperidone versus sertindole and olanzapine: commercial-in-confidence data removed.

Tardive dyskinesia

One study pooled data from 15 RCTs and 12 open-label studies comparing risperidone with haloperidol, placebo and other typical antipsychotic drugs (Amery 1998[266]). The probability of developing tardive dyskinesia in 3298 risperidone-treated patients was reported to be 0.0034 per treatment-year compared with 0.019 per treatment-year in 588 haloperidol-treated patients.

A retrospective post-marketing database analysis calculated yearly reporting rates for risperidone and other agents over a 4-year period (Tooley 1997[267]). A yearly rate of tardive dyskinesia was reported in risperidone-treated patients of 0.0006% compared with 3–5% for other agents (not specified).

Weight change

In a study in which data from 15 RCTs and 12 open-label studies comparing risperidone with haloperidol, placebo and other typical antipsychotic drugs were pooled (Amery 1998[266]), a mean weight gain of 3.3 kg was reported in 424 patients treated with risperidone for at least 1 year; however, weight change data for any comparators were not reported.

NMS

In a retrospective analysis of case reports of NMS in users of clozapine and risperidone (Hasan 1998[135]), while 19 cases of NMS were reported in clozapine users and 13 in risperidone users, when these were assessed using three sets of criteria for NMS, there were probably nine cases of NMS in clozapine users and eight in risperidone users. No denominator was given for this study.

A retrospective post-marketing database analysis, in which yearly reporting rates were calculated for risperidone and other agents over a 4-year period (Tooley 1997[267]), reported a yearly rate of NMS in risperidone-treated patients of 0.017% compared with 0.2% for other antipsychotic treatments.

Other systematic reviews

Peuskens and colleagues[203] conducted a meta-analysis of the clinical efficacy and safety of risperidone and olanzapine. Their results suggested that risperidone and olanzapine were more advantageous than typical antipsychotic drugs in reducing the PANSS score and that risperidone-treated patients might have a lower risk of withdrawal. In terms of safety, they found that risperidone-treated patients required less anti-EPS medication compared with patients treated with typical antipsychotic drugs. They also reported that risperidone might show clearer benefits in terms of efficacy than olanzapine. Significant heterogeneity was reported between studies but the results were fairly similar to those reported here.

The results of another systematic review[269] agreed with those presented here in all respects. One RCT was excluded from this review because it used perphenazine as the comparator drug (all the included RCTs used haloperidol); other than this, the authors could find no obvious differences in the conduct of the two reviews.

In a meta-analysis by Lemmens and colleagues[270,271] presented as a conference abstract, data were combined from 12 double-blind, short-term trials of risperidone compared with typical antipsychotic drugs for individuals with chronic schizophrenia and seven trials on risperidone compared with typical antipsychotic drugs in those with acute exacerbation of schizophrenia. Many methodological details were missing from the conference abstract, such as how the studies were selected. Both those with chronic schizophrenia and with acute exacerbation benefited more from risperidone than from typical antipsychotic treatments in terms of PANSS total and positive subscale scores. Patients with chronic schizophrenia also benefited more from risperidone than typical antipsychotic drugs in terms of PANSS negative and general subscales and cognition, affective symptoms, anxiety and hostility.

In another systematic review,[272] Bech and colleagues compared risperidone with typical antipsychotic drugs in patients with chronic schizophrenia. Six trials were found that met the inclusion criteria (although details of the literature search were not given). Inclusion was restricted by the outcome measures reported. The validity of included studies was not assessed and details of the review process (how many reviewers, for example) were not given. The included studies were not reported in detail. Risperidone was reported to be more effective than typical antipsychotic drugs in terms of PANSS scores, and produced fewer extrapyramidal side-effects (as measured by the ESRS scale), similar to the results presented here.

Systematic reviews identified in the original review

One review[273] agreed with the Cochrane review[14] that improvement of symptoms was more frequent in the risperidone-treated group. In two reviews[205,274] it was found that risperidone was more effective in relieving the negative symptoms of schizophrenia than typical antipsychotic drugs. The Cochrane review did not find this. The Carman review[274] used ORs as the measure of effect: in the case of relief of negative symptoms, this was inappropriate because about 50% of trial participants' symptoms were not relieved and ORs should only be used when an event rate is low. RR, as used in the Cochrane review, would have given a more accurate estimate. It is likely that the RR measurement would cross the line of 'no effect', as the OR estimate is only just significant (OR, 1.43; 95% CI, 1.1 to 1.8). The more positive results in the Leucht review[205] may be explained by the way data were handled in the ITT analysis: in the Cochrane review, missing participants were given a 'bad' outcome whereas in the Leucht review the last observation was carried forward.

Ongoing studies

Only one ongoing study of risperidone was found in the trial registers searched. This was a prospective, non-randomised study of the incidence of tardive dyskinesia in patients receiving olanzapine or risperidone (Kane JM. Prospective study of tardive dyskinesia development. No end date given).

Chapter 10

Sertindole: effectiveness

Numbers and characteristics of included RCTs

New RCTs

One new RCT of sertindole was identified for this update review, Hale 2000.[275] Sertindole was withdrawn from the UK market in 1999 for reasons related to abnormal cardiac potentials, and is now only prescribed for patients with schizophrenia who had already been stabilised on the drug at the time of its withdrawal. The data extraction sheet for this trial can be found in appendix 2.

Old RCTs

Two studies were identified for inclusion in the original review: Daniel 1998,[276] Van Kammen 1996.[277] Data extraction tables for these studies can be found in appendix 3.

Total RCTs

All three trials were randomised and double-blind. They were reported as having been sponsored by Abbott Laboratories and had a company employee as a named author.

The largest study (Hale 2000[275]) had 617 participants, Daniel 1998[276] had 282 participants and Van Kammen 1996[277] had 205. Only one trial (Daniel 1998) reported a power calculation, the results of which showed that their sample size was too small (recommended sample size was 150 participants in each treatment group).

Duration

Two trials (Van Kammen 1996,[277] Hale 2000[275]) were of short duration (6–8 weeks) and Daniel 1998[276] was a comparatively long-term study, lasting 1 year.

Interventions

In Van Kammen 1996,[277] three different doses of sertindole (ranging from 8 mg to 20 mg daily) were investigated, four different doses were investigated in Hale 2000[275] (from 8 to 24 mg daily), and in Daniel 1998,[276] 24 mg daily was used. Placebo was used as the comparison drug in one study (Van Kammen 1996) and haloperidol, 10 mg daily, in the other two RCTs.

Participants

All three trials included participants who met the operationalised diagnosis of schizophrenia by DSM criteria.[66]

Van Kammen 1996[277] only included individuals with active psychosis of at least moderate severity (combination score of at least eight on any two of the positive symptoms of the BPRS) and also those who had a history of previous response to antipsychotic drugs. Daniel 1998[276] only included participants with a positive response to a neuroleptic agent (excluding clozapine) in the 5 years before the trial. Stable outpatients with moderate illness, as defined by a CGI (part 1) score of ≤ 4, were enrolled. Both trials were reported to have excluded individuals with tardive dyskinesia as measured by AIMS.

None of the trials were noted to have included participants with treatment-resistant schizophrenia or with predominantly negative or positive symptoms. In addition, none of the included trials considered participants who were experiencing their first episode of schizophrenia.

Two trials (Van Kammen 1996,[277] Hale 2000[275]) included participants who were in hospital and the other (Daniel 1998[276]) recruited participants attending outpatient departments.

Outcomes

None of the included trials reported data on improvement. In Van Kammen 1996,[277] however, a responder for PANSS and BPRS was defined as a 10%, 20%, 30%, and 50% improvement from baseline to final evaluation, and for CGI a responder was defined as very much improved, at least much improved, and at least minimally improved from baseline. Only data on the outcome 'very much improved' for the sertindole, 20 mg, and placebo treatment groups were presented in the published report.

All the included trials coded adverse events according to the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) III dictionary. All the studies collected data on the use of medication for EPS and measured the incidence of EPS-related adverse events, as well

as using specific movement rating scales.
Data on the outcome 'leaving study early' were reported in all trials.

Quality of included studies

The method of randomisation was not stated in any of the three included trials. Although all were reported to be double-blind, none described the blinding process in detail. More than 75% of the participants completed one trial (Daniel 1998[276]). However, in Van Kammen 1996[277] the loss to follow-up was 49% and in Hale 2000[275] 39%. All trials stated that data were analysed on an ITT basis using last observation carried forward.

Sertindole versus placebo

The results for the short to medium term (up to 26 weeks) are presented in *Table 44*.

Global effect

A single trial (Van Kammen 1996[277]) reported CGI endpoint scores, at 6 weeks, for three different doses of sertindole (20, 12 and 8 mg). The findings showed skewed data for the sertindole, 20 mg, group. The positive skewness was minimal and, hence, a decision was made to deviate from the protocol. When these data were included in the analyses, the average difference for the sertindole, 20 mg, group showed a significant decline in favour of sertindole compared with placebo (n = 78; MD, –0.90; 95% CI, –1.57 to –0.23). For all doses of sertindole combined, there was no significant difference between sertindole and placebo (MD, –0.3; 95% CI, –0.72 to 0.04). Some results on improvement according to CGI (part III) were also reported in this trial. A significantly greater number of participants (n = 8/40) treated with sertindole, 20 mg, were reported as being 'very much improved' compared with those taking placebo (n = 1/38; RR, 0.82; 95% CI, 0.70 to 0.97; risk difference, –0.17; 95% CI, –0.31 to –0.04). Data relating to doses of sertindole of either 8 or 12 mg were not reported.

Leaving study early

There was no significant difference between the sertindole and placebo groups in terms of the number of participants leaving the study early. In the sertindole group 26% (41/157) left early because of ineffective treatment, and in the placebo group 33% (16/48) (RR, 0.78; 95% CI, 0.49 to 1.26). In the sertindole group 7% (11/157) left the study early because of adverse events, and in the placebo group 6% (3/48) (RR, 1.12; 95% CI, 0.33 to 3.85) (Van Kammen 1996[277]).

Adverse effects

Cardiovascular problems

In the Van Kammen 1996 trial,[277] no significant difference was found between participants taking sertindole and those in the placebo group for the incidence of either postural hypotension or peripheral oedema (RR, 3.36; 95% CI, 0.45 to 25.39; RR, 4.03; 95% CI, 0.23 to 70.30, respectively).

Gastrointestinal problems

The findings of Van Kammen 1996[277] study suggested that there was no difference between sertindole and placebo for the outcome of dyspepsia (RR, 0.71; 95% CI, 0.29 to 1.75). The same study also reported no significant difference between sertindole and placebo for the outcome of constipation (RR, 1.73; 95% CI, 0.53, 5.66).

Movement disorders

No significant differences were found between sertindole and placebo for the outcomes of akathisia (RR, 0.93; 95% CI, 0.04 to 22.48), tremor (RR, 0.92; 95% CI, 0.10 to 8.62), hypertonia (RR, 2.79; 95% CI, 0.15 to 50.94) and cogwheel rigidity (RR, 0.06; 95% CI, 0.00 to 1.27), as reported in a single study (Van Kammen 1996[277]). The incidence of extrapyramidal symptoms was also reported in the same study (RR, 0.52; 95% CI, 0.22 to 1.26; risk difference, –0.07; 95% CI, –0.18 to 0.04), as were extrapyramidal-related events (RR, 0.87; 95% CI, 0.36 to 2.07) and use of medication to avoid extrapyramidal symptoms (RR, 0.46; 95% CI, 0.13 to 1.56). These results suggested that although the incidences were lower in the placebo group, there were no significant differences between the sertindole and placebo groups.

Sleep problems

According to Van Kammen 1996,[277] there were no significant differences between sertindole and placebo for the outcomes of somnolence (RR, 2.14; 95% CI, 0.50 to 9.09) and insomnia (RR, 0.71; 95% CI, 0.39 to 1.29).

Other problems

The findings of Van Kammen 1996 study[277] suggested that there were no clear differences between sertindole and placebo for the outcomes of headache (RR, 1.03; 95% CI, 0.61 to 1.75), infection (RR, 0.82; 95% CI, 0.34 to 1.97), dizziness (RR, 0.92; 95% CI, 0.31 to 2.71), dry mouth (RR, 2.14; 95% CI, 0.27 to 16.96), increased salivation (RR, 0.31; 95% CI, 0.02 to 4.80) and myalgia (RR, 0.82; 95% CI, 0.34 to 1.97). Also, no significant differences between

TABLE 44 *Sertindole versus placebo – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state: not improved or worse (CGI)	Van Kammen 1996 (78)	32/40	37/38	0.82 (0.70 to 0.97)
Leaving study early				
Ineffective treatment	Van Kammen 1996 (205)	41/157	16/48	0.78 (0.49 to 1.26)
Adverse events	Van Kammen 1996 (205)	11/157	3/48	1.12 (0.33 to 3.85)
Side-effects				
Postural hypotension	Van Kammen 1996 (205)	11/157	1/48	3.36 (0.45 to 25.39)
Peripheral oedema	Van Kammen 1996 (205)	6/157	0/48	4.03 (0.23 to 70.30)
Dyspepsia	Van Kammen 1996 (205)	14/157	6/48	0.71 (0.29 to 1.75)
Constipation	Van Kammen 1996 (205)	17/157	3/48	1.73 (0.53 to 5.66)
Akathisia	Van Kammen 1996 (205)	1/157	0/48	0.93 (0.04 to 22.48)
Hypertonia	Van Kammen 1996 (205)	4/157	0/48	2.79 (0.15 to 50.94)
Tremor	Van Kammen 1996 (205)	3/157	1/48	0.92 (0.10 to 8.62)
Cogwheel rigidity	Van Kammen 1996 (205)	0/157	2/48	0.06 (0.00 to 1.27)
Extrapyramidal symptoms	Van Kammen 1996 (205)	12/157	7/48	0.52 (0.22 to 1.26)
Incidence of EPS-related events	Van Kammen 1996 (205)	17/157	6/48	0.87 (0.36 to 2.07)
Use of EPS medication	Van Kammen 1996 (205)	6/157	4/48	0.46 (0.13 to 1.56)
Insomnia	Van Kammen 1996 (205)	28/157	12/48	0.71 (0.39 to 1.29)
Somnolence	Van Kammen 1996 (205)	14/157	2/48	2.14 (0.50 to 9.09)
Dizziness	Van Kammen 1996 (205)	12/157	4/48	0.92 (0.31 to 2.71)
Dry mouth	Van Kammen 1996 (205)	7/157	1/48	2.14 (0.27 to 16.96)
Fever	Van Kammen 1996 (205)	8/157	0/48	5.27 (0.31 to 89.71)
Headache	Van Kammen 1996 (205)	44/157	13/48	1.03 (0.61 to 1.75)
Infection	Van Kammen 1996 (205)	16/157	6/48	0.82 (0.34 to 1.97)
Myalgia	Van Kammen 1996 (205)	16/157	6/48	0.82 (0.34 to 1.97)
Rhinitis	Van Kammen 1996 (205)	30/157	5/48	1.83 (0.75 to 4.47)
Increased salivation	Van Kammen 1996 (205)	1/157	1/48	0.31 (0.02 to 4.80)

n, *number of events*; N, *number of participants in group*

sertindole and placebo were reported for the outcomes of rhinitis and fever, although the incidence was perhaps marginally higher in the sertindole group (RR, 1.83; 95% CI, 0.75 to 4.47; RR, 5.27; 95% CI, 0.31 to 89.71, respectively).

Sertindole versus haloperidol

The results for sertinidole versus haloperidol are summarised in *Table 45*.

Global effect and mental state

In Hale 2000,[275] individuals treated with sertindole, 24 mg daily, were found to be as likely to improve (defined as a 30, 40 or 50% reduction in PANSS score) as those treated with haloperidol (RR, 0.91; 95% CI, 0.73 to 1.13; risk difference, –0.05; 95% CI, –0.18 to 0.07; RR, 0.94; 95% CI, 0.71 to 1.24; risk difference, –0.03; 95% CI, –0.15 to 0.10; RR, 0.87; 95% CI, 0.60 to 1.26; risk difference, –0.05; 95% CI, –0.16 to 0.07, respectively).

Leaving study early

In only one trial (Daniel 1998[276]) was the outcome reported of leaving the study early owing to non-compliance; this was found to be significantly higher in the haloperidol group (13/141) than in the sertindole group (2/141) (RR, 0.15; 95% CI, 0.04 to 0.67).

For the outcome of leaving the same study early due to adverse events, 25 participants (18%) treated with sertindole discontinued their treatment early compared with 30 (21%) in the haloperidol group. The difference between the

TABLE 45 *Sertindole versus haloperido: dichotomous outcomes*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state: requiring psychiatric hospitalisation	Daniel 1998 (282)	2/141	12/141	0.17 (0.04 to 0.73)
Leaving study early				
Any reason	Daniel 1998 (282) Hale 2000 (242)	27/141 45/117	43/141 49/125	0.81 (0.63 to 1.05)
Non-compliance	Daniel 1998 (282)	2/141	13/141	0.15 (0.04 to 0.67)
Adverse events	Daniel 1998 (282)	25/141	30/141	0.83 (0.52 to 1.34)
Prolonged Q-T interval	Daniel 1998 (282)	2/141	1/141	2.00 (0.18 to 21.81)
Leucopenia	Daniel 1998 (282)	2/141	0/141	5.00 (0.24 to 103.23)
Elevated SGPT/ALT	Daniel 1998 (282)	1/141	0/141	3.00 (0.12 to 73.03)
Elevated glucose (non-diabetic)	Daniel 1998 (282)	1/141	0/141	3.00 (0.12 to 73.03)
Mental state				
Response (PANSS 30% reduction) 24 mg	Hale 2000 (238)	63/115	74/123	0.91 (0.73 to 1.13)
Response (PANSS 40% reduction) 24 mg	Hale 2000 (238)	51/115	58/123	0.94 (0.71 to 1.24)
Response (PANSS 50% reduction) 24 mg	Hale 2000 (238)	35/115	43/123	0.87 (0.60 to 1.26)
Q-T interval in excess of 500 ms	Daniel 1998 (282)	1/141	0/141	3.00 (0.12 to 73.03)
Q-Tc interval of at least 500 ms	Daniel 1998 (282)	11/141	0/141	23.00 (1.37 to 386.60)
Side-effects				
Dyspepsia	Daniel 1998 (282)	12/141	17/141	0.71 (0.35 to 1.42)
Nausea	Daniel 1998 (282)	18/141	18/141	1.00 (0.54 to 1.84)
Vomiting	Daniel 1998 (282)	11/141	16/141	0.69 (0.33 to 1.43)
Weight gain	Daniel 1998 (282)	19/141	3/141	6.33 (1.92 to 20.92)
Extrapyramidal, 20 mg	Hale 2000 (252)	3/128	12/125	0.24 (0.07 to 0.84)*
Extrapyramidal, 24 mg	Hale 2000 (242)	4/117	12/125	0.36 (0.12 to 1.07)
Akathisia, 24 mg	Daniel 1998 (282) Hale 2000 (242)	19/141 8/117	34/141 25/125	0.47 (0.31 to 0.71)
Asthenia, 24 mg	Daniel 1998 (282) Hale 2000 (242)	22/141 4/117	17/141 12/125	0.91 (0.55 to 1.51)
Hypertonia, 24 mg	Daniel 1998 (282) Hale 2000 (242)	12/141 5/117	26/141 13/125	0.45 (0.26 to 0.76)
Tremor, 24 mg	Daniel 1998 (282) Hale 2000 (242)	13/141 5/117	30/141 21/125	0.36 (0.22 to 0.60)
Insomnia	Daniel 1998 (282)	44/141	48/141	0.92 (0.66 to 1.28)
Somnolence, 24 mg	Daniel 1998 (282) Hale 2000 (242)	28/141 5/117	40/141 12/125	0.64 (0.43 to 0.95)
Increased coughing	Daniel 1998 (282)	15/141	15/141	1.00 (0.51 to 1.97)
Postural hypotension, 24 mg	Hale 2000 (242)	15/117	6/125	2.67 (1.07 to 6.65)
Dizziness, 24 mg	Daniel 1998 (282) Hale 2000 (242)	23/141 9/117	25/141 9/125	0.96 (0.61 to 1.50)
Dry mouth	Daniel 1998 (282)	22/141	12/141	1.83 (0.94 to 3.56)

continued

***TABLE 45* contd** *Sertindole versus haloperido: dichotomous outcomes*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Headache	Daniel 1998 (282) Hale 2000 (242)	47/141 17/117	38/141 15/125	1.23 (0.90 to 1.68)
Infection	Daniel 1998 (282)	31/141	33/141	0.94 (0.61 to 1.45)
Accidental injury	Daniel 1998 (282)	9/141	15/141	0.60 (0.27 to 1.33)
Myalgia	Daniel 1998 (282)	21/141	23/141	0.91 (0.53 to 1.57)
Overdose	Daniel 1998 (282)	8/141	17/141	0.47 (0.21 to 1.05)
Psychosis	Daniel 1998 (282)	11/141	17/141	0.65 (0.31 to 1.33)
Abnormal ejaculation, 24 mg	Hale 2000 (242)	9/117	2/125	4.81 (1.06 to 21.79)
Rhinitis, 24 mg	Daniel 1998 (282) Hale 2000 (242)	49/141 7/117	26/141 1/125	2.09 (1.09 to 3.13)

n, *number of events*; N, *number of participants in group*

* *Risk difference, –0.06 (95% CI, –0.12 to 0.00)*

two groups was not significant (RR, 0.83; 95% CI, 0.52 to 1.34).

The number of participants having to leave the study early because of other related complications was also reported in this study: three patients discontinued treatment because of prolonged Q-T intervals, two of whom were treated with sertindole and one with haloperidol (RR, 2.00; 95% CI, 0.18 to 21.81). Two members of the sertindole group were reported to have discontinued treatment owing to leukopenia, compared with none in the haloperidol group (RR, 5.00; 95% CI, 0.24 to 103.23). Two further patients discontinued sertindole because of abnormal blood chemistry values: one had elevated serum glutamate pyrovate transaminase/alanine aminotransferase (SGPT/ALT) and one had elevated glucose without a known history of diabetes mellitus (RR, 3.00; 95% CI, 0.12 to 73.03).

No differences between sertindole- (at any dose) and haloperidol-treated patients were reported in terms of leaving the study early for any reason in Hale 2000.[275] At doses of 8, 16 or 24 mg, sertindole-treated patients were more likely to leave the study early because of an adverse event than haloperidol-treated patients (8 mg: RR, 17.70; 95% CI, 1.03 to 303.4; 16 mg: RR, 22.64; 95% CI, 1.35 to 380.1; 24 mg: RR, 28.83; 95% CI, 1.73 to 479.6).

Adverse effects

Cardiovascular problems

The incidence of adverse events relating to Q-T and Q-Tc intervals was reported in Daniel 1998.[276] Only one participant from the sertindole group had a Q-T interval that exceeded 500 ms (RR, 3.0; 95% CI, 0.12 to 73.03). However, 11 sertindole-treated participants had Q-Tc intervals of at least 500 ms, compared with none in the haloperidol-treated group (RR, 23.00; 95% CI, 1.37 to 386.60).

Weight gain

Only one study (Daniel 1998[276]) reported usable data on the incidence of weight gain. A significantly greater number of sertindole-treated participants ($n = 19/141$) were reported to have gained weight compared with haloperidol-treated participants ($n = 3/141$) (RR, 6.33; 95% CI, 1.92 to 20.92).

Gastrointestinal problems

The outcomes of nausea (RR, 1.0; 95% CI, 0.54 to 1.84), vomiting (RR, 0.69; 95% CI, 0.33 to 1.43) and dyspepsia (RR, 0.71; 95% CI, 0.35 to 1.42) were also reported for this study. The results showed no significant differences between the sertindole- and haloperidol-treated groups for these outcomes.

Movement disorders

The outcomes of akathisia, hypertonia and tremor were reported in two trials. The results for all three outcomes showed a significantly higher incidence rate among haloperidol-treated participants compared with those in the sertindole group (akathisia: RR, 0.47; 95% CI, 0.31 to 0.71; risk difference, –0.12; 95% CI, –0.18 to –0.06; hypertonia: RR, 0.45; 95% CI, 0.26 to 0.76; risk difference, –0.08; 95% CI, –0.13 to –0.03; tremor:

RR, 0.36; 95% CI, 0.22 to 0.60; risk difference, –0.12; 95% CI, –0.18 to –0.07).

The outcome of asthenia was considered in the same trials – no significant difference was found (RR, 0.91; 95% CI, 0.55 to 1.51; risk difference, –0.01; 95% CI, –0.06 to 0.04).

Sleep problems

There was no significant difference between sertindole and haloperidol for the outcome of insomnia as reported by a single study (Daniel 1998: RR, 0.92; 95% CI, 0.66 to 1.28).[276] Pooled results from two trials showed sertindole was associated with less somnolence than haloperidol (RR, 0.64; 95% CI, 0.43 to 0.95).

Other problems

There was a significantly higher incidence rate of rhinitis among participants taking sertindole compared with those in the haloperidol group (RR, 2.09; 95% CI, 1.09 to 3.13) and also of abnormal ejaculation (RR, 4.81; 95% CI, 1.06 to 21.79) (Daniel 1998[276]).

In another study (Hale 2000[275]), individuals taking sertindole, 24 mg daily, were more likely to experience postural hypotension than those taking haloperidol (RR, 2.67; 95% CI, 1.07 to 6.65).

The differences between haloperidol-treated participants and those taking sertindole for the reported outcomes of psychosis (RR, 0.65; 95% CI, 0.31 to 1.33), accidental injury (RR, 0.60; 95% CI, 0.27 to 1.33), overdose (RR, 0.47; 95% CI, 0.21 to 1.05), headache (RR, 1.23; 95% CI, 0.90 to 1.60) and dry mouth (RR, 1.83; 95% CI, 0.94 to 3.56) were not significant.

There were no clear differences between sertindole and haloperidol for the outcomes of infection (RR, 0.94; 95% CI, 0.61 to 1.45), dizziness (RR, 0.96; 95% CI, 0.61 to 1.50), myalgia (RR, 0.91; 95% CI, 0.53 to 1.57) and increased coughing (RR, 1.00; 95% CI, 0.51 to 1.97) (Daniel 1998[276]).

Service utilisation

In Daniel 1998,[276] service utilisation was measured in terms of the number of participants who required psychiatric hospitalisation, the number of psychiatric inpatient days and number of psychiatric hospitalisations. This was a long-term study (1 year) that included participants attending outpatient clinics. A significantly greater number of participants treated with haloperidol were reported to have required psychiatric hospitalisation than those taking sertindole (RR, 0.17; 95% CI, 0.04 to 0.73). There were 11 psychiatric hospitalisations in the sertindole group compared with 29 in the haloperidol group. In addition, those treated with sertindole (n = 94) were reported to have spent a total of 630 days in hospital compared with 1613 days for those treated with haloperidol (n = 109).

Sensitivity analysis

When the study with > 25% attrition was excluded from the analysis (Hale 2000 (39%)[275]), no substantial differences were seen in the results except that there was no longer a significant difference between the sertindole and haloperidol groups for the outcome of somnolence (RR, 0.70; 95% CI, 0.46 to 1.07).

Publication bias

Owing to the small number of included studies, it was not possible to construct funnel plots to assess the presence of publication bias in this review.

Number of ongoing studies

Commercial-in-confidence data removed.

Rare or long-term events

Commercial-in-confidence data on seven non-randomised studies removed.

One study (Moore 1999[278]) was also published as a conference abstract. The data extraction sheet for this study can be found in appendix 4.

Mortality

One study (Moore 1999[278]) reported that the overall risk of death in sertindole-treated patients was 1.9 per 100 patient-years, and of cardiac death 0.8 per 100 patient-years. Rates for olanzapine and risperidone were not significantly different once differing lengths of follow-up were taken into account.

Commercial-in-confidence data removed.

Other systematic reviews

No new systematic reviews of sertindole were found.

Chapter 11

Ziprasidone: effectiveness

Ziprasidone is not currently licensed in the UK but is expected to be granted a licence soon, hence its inclusion in this review. It has been suggested that the delay in granting a licence is because ziprasidone may cause abnormal cardiac effects but the reviewers have seen no evidence relating to such an effect.

Numbers and characteristics of included RCTs

New RCTs

One new RCT of ziprasidone was identified from the literature searches for this update review – Gunnar 1999.[279] Nine new, unpublished (commercial-in-confidence) studies were submitted by the manufacturer (Pfizer): Study 128-108,[280] Study 128-115,[281] Study 128-117,[242] Study 128-301,[282] Study 128-302,[243] Study 128-305,[46] Study NY-97-001,[283] Study R-0548[283] and Study 128-104.[284] The manufacturer also submitted unpublished long-term extensions of studies 128-302,[285] 128-301[282] and Hirsch 1999;[286] these were also commercial-in-confidence.

One new report of an old RCT was identified that contained additional information for inclusion in this review – Brook 2000,[287] a further report of Brook 1998.[288]

Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

Seven RCTs were included in the original review: Arato 1997,[289] Brook 1998,[288] Daniel 1999,[290] Goff 1998,[291] Hirsch 1999,[292] Keck 1998,[293] Swift 1998.[294] Data extraction sheets for these studies can be found in appendix 3.

Total RCTs

All 17 included trials were randomised, 13 were double-blind, one open label and three (all intramuscular studies) were single-blind. Details of three double-blind studies were published as full journal articles and eight as full clinical reports; details of the remainder were obtained from abstracts and conference proceedings posters, which gave very little information on outcomes. Company employees from Pfizer were named authors in 16 studies.

In Swift 1998,[294] there were 306 participants, in Daniel 1999[290] 302, in Hirsch 1999[292] 301 and in Arato 1997[289] 294. Only in Goff 1998,[291] with 90 participants, was a power calculation reported to demonstrate a 25% difference between groups on BPRS with 80% power. There were only eight participants on Gunnar 1999.[279]

Pfizer Study 128-108, Study 128-301, Study NY-97-001, Study 128-115, Study 128-117, Study 128-302, Study R-0548, Study 128-104 and Study 128-305: commercial-in-confidence data removed.

Duration

Three studies (in which intramuscular preparations of ziprasidone were used) were of very short duration, lasting only 1 week, and ten studies were of short- to medium-term duration, as defined in the protocol of this review, lasting between 4 and 26 weeks. Four studies were long term, one lasting 6 months, two for 1 year, and one for 40 weeks.

Pfizer Study NY-97-001: commercial-in-confidence data removed.

Interventions

Five trials were placebo-controlled and in two, haloperidol, 15 mg, was used as a comparator; in another haloperidol, 10 mg and 20 mg, was used as the comparator. In six studies (including all intramuscular studies), a flexible dose of haloperidol was used as the control medication. Doses of ziprasidone ranged from 4 mg daily to 200 mg daily.

Commercial-in-confidence data removed.

Participants

All participants met the DSM criteria[66] for operationalised diagnoses of schizophrenia and schizoaffective disorder. Patients with schizoaffective disorder were included in all but one study (Arato 1997[289]). Three studies of intramuscular ziprasidone included all 'acutely psychotic' patients, including those with bipolar and delusional disorders. In Daniel 1999,[290] Goff 1998[291] and Keck 1998,[293] only those with

acute exacerbation of chronic or sub-chronic illness were included; in Arato 1997[289] and Hirsch 1999[292] (both long-term studies) only those with chronic stable schizophrenia were included. In three studies (Daniel 1999, Goff 1998, Keck 1998), patients were not previously resistant to neuroleptic treatment but, according to their ratings on BPRS or PANSS, were quite ill. Those with organic problems or who were prone to substance abuse were largely excluded.

Most participants in the short-term studies were in hospital when the study began. All of those in the Arato 1997 study were in hospital. In the long-term studies, most participants were attending outpatient clinics.

Commercial-in-confidence data removed.

Outcomes

The reported outcomes included: improvement – definition of improvement consisted of a score of 1 or 2 on the CGI-I scale (Daniel 1999,[290] Keck 1998[293]), a 30% or more decrease in PANSS (Daniel 1999), a 20% decrease in PANSS negative subscale score (Hirsch 1999[292]), or a 30% decrease in BPRS total score (Keck 1998).

Quality of included studies

In none of the studies were adequate precautions for blinding of treatment clearly described. In the three trials of intramuscular ziprasidone, treatment was not given blind for practical reasons. None of the included trials tested the adequacy of the blinding of those rating outcomes.

In 14 studies, more than one quarter of participants left before the study ended. Such rates of attrition (some occurring in studies as short as 12 weeks) are extremely high and mean that all results need to be viewed with caution.

The intramuscular studies had lower rates of attrition (12% or less), probably because of their short durations, and in one long-term study (Arato 1997[289]), attrition was incompletely reported. Exactly why people decided to leave or were excluded was not explicit. In 14 studies, data were analysed on an ITT basis, using the last observation carried forward.

Commercial-in-confidence data removed.

Ziprasidone versus placebo

The results for ziprasidone versus placebo are summarised in *Tables 46–48.*

Global effect

In three studies, lack of response was defined as a CGI-I score of > 2. Ziprasidone was not superior to placebo in these short studies (RR, 0.91; 95% CI, 0.83 to 1.01; risk difference, –0.07; 95% CI, –0.13 to –0.01); however, heterogeneity was seen in the result (chi-squared = 8.36; $p = 0.039$), so it should be viewed with caution.

Mental state

In Daniel 1999,[290] response was defined as a 30% decrease in PANSS and, in Keck 1998,[293] as a 30% decrease in BPRS total score. When summated and analysed as 'no response', this outcome was clearly avoided more frequently with ziprasidone than placebo (RR, 0.86; 95% CI, 0.77 to 0.95; risk difference, –0.11; 95% CI, –0.17 to –0.04). The outcome, 'impending relapse', defined as a CGI-I score of > 5 and/or as a score of > 5 on PANSS items P7 (hostility) or G8 (uncooperativeness) on two successive days, was reported at 6 months (Arato 1997[289]). Again, ziprasidone was superior to placebo (RR, 0.71; 95% CI, 0.58 to 0.87).

Ziprasidone, 120 mg/day, was favoured over placebo for all global and mental state scale data (see appendix 9).

Leaving study early

Overall, the difference was just in favour of ziprasidone (RR, 0.85; 95% CI, 0.73 to 0.99) but, when lack of efficacy was cited as the reason for attrition, the ziprasidone group continued to retain more participants than the placebo group (RR, 0.67; 95% CI, 0.52 to 0.87). When adverse events were blamed for loss to follow-up, no difference was seen in favour of ziprasidone (RR, 2.65; 95% CI, 0.71 to 9.86).

Side-effects

No differences between placebo and ziprasidone were seen for 'any adverse event' at any dose. In three short-term trials, there were no differences in the frequency of nausea, vomiting, dyspepsia, diarrhoea and constipation. More people in the group receiving placebo required additional sedation medication than in the ziprasidone group (RR, 0.92; 95% CI, 0.85 to 0.98). Ziprasidone increased daytime sleepiness (RR, 2.07; 95% CI, 1.13 to 3.79) and individuals treated with ziprasidone were more likely to take antiparkinsonian medication (RR, 1.57; 95% CI, 1.03 to 2.37). A number of other adverse effects were reported but none showed differences between ziprasidone and placebo. In Arato 1997,[289] a small decrease in weight from baseline was reported in both groups but there were no significant differences between groups.

TABLE 46 *Ziprasidone versus placebo: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state: no response (CGI)	Daniel 1999 (302)	131/210	68/92	0.91 (0.83 to 1.01)
	Keck 1998 (139)	69/91	42/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Mental state				
No response (BPRS/PANSS)	Daniel 1999 (302)	147/210	76/92	0.86 (0.77 to 0.95)
	Keck 1998 (139)	55/91	36/48	
	Study 128-104 (105)	Commercial-in confidence: data removed		
Impending relapse (CGI-I score > 5)	Arato 1997 (294)	108/219	52/75	0.71 (0.58 to 0.87)
Leaving study early				
Any reason	Daniel 1999 (302)	91/210	47/92	0.85 (0.73 to 0.99)
	Keck 1998 (139)	39/91	24/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
	Study 128-115 (161)	Commercial-in-confidence: data removed		
Lack of efficacy	Daniel 1999 (302)	43/210	32/92	0.67 (0.52 to 0.87)
	Study 128-104 (105)	Commercial-in-confidence: data removed		
	Study 128-115 (161)	Commercial-in-confidence: data removed		
Adverse events	Daniel 1999 (302)	10/210	1/92	2.65 (0.71 to 9.86)
	Study 128-104 (105)	Commercial-in-confidence: data removed		
	Study 128-115 (161)	Commercial-in-confidence: data removed		
Side-effects				
Any adverse event	Daniel 1999 (302)	185/210	79/92	1.01 (0.93 to 1.10)
	Keck 1998 (139)	71/91	36/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Dizziness	Daniel 1999 (302)	28/210	8/92	1.65 (0.82 to 3.33)
	Keck 1998 (139)	5/91	1/48	
Constipation	Daniel 1999 (302)	21/210	13/92	1.02 (0.58 to 1.77)
	Keck 1998 (139)	8/91	2/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Diarrhoea	Keck 1998 (139)	2/91	0/48	2.66 (0.13 to 54.38)
Dyspepsia	Daniel 1999 (302)	24/210	8/92	1.32 (0.73 to 2.39)
	Keck 1998 (139)	8/91	3/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Nausea	Daniel 1999 (302)	22/210	8/92	1.53 (0.82 to 2.84)
	Keck 1998 (139)	6/91	2/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Vomiting	Daniel 1999 (302)	18/210	14/92	0.59 (0.33 to 1.06)
	Keck 1998 (139)	3/91	2/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Agitation	Daniel 1999 (302)	19/210	10/92	0.83 (0.51 to 1.35)
	Keck 1998 (139)	3/91	6/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Akathisia	Daniel 1999 (302)	28/210	6/92	1.77 (0.90 to 3.49)
	Keck 1998 (139)	4/91	3/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Use of beta-blockers for akathisia	Daniel 1999 (302)	16/210	6/92	1.17 (0.47 to 2.89)
Extrapyramidal	Daniel 1999 (302)	9/210	1/92	3.05 (0.69 to 13.47)*
	Keck 1998 (139)	4/91	1/48	
Hypertonia	Keck 1998 (139)	3/91	1/48	1.58 (0.17 to 14.81)

continued

***TABLE 46* contd** *Ziprasidone versus placebo: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Cogwheel rigidity	Keck 1998 (139)	2/91	0/48	2.66 (0.13 to 54.38)
Tremor	Keck 1998 (139)	3/91	0/48	3.73 (0.20 to 70.73)
Antiparkinsonian medication required	Daniel 1999 (302)	47/210	12/92	1.57 (1.03 to 2.37)
	Keck 1998 (139)	18/91	6/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Use of additional sedation	Daniel 1999 (302)	176/210	85/92	0.92 (0.85 to 0.98)
	Keck 1998 (139)	76/91	43/48	
Insomnia	Daniel 1999 (302)	25/210	13/92	0.68 (0.40 to 1.15)
	Keck 1998 (139)	1/91	2/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Somnolence	Daniel 1999 (302)	40/210	5/92	2.07 (1.13 to 3.79)
	Keck 1998 (139)	7/91	4/48	
	Study 128-104 (105)	Commercial-in-confidence: data removed		
Asthenia	Keck 1998 (139)	3/91	0/48	3.73 (0.20 to 70.73)
Dry mouth	Daniel 1999 (302)	17/210	4/92	1.86 (0.64 to 5.38)
Abdominal pain	Daniel 1999 (302)	13/210	5/92	1.14 (0.42 to 3.10)
Headache	Daniel 1999 (302)	50/210	30/92	0.73 (0.50 to 1.07)
Pain – unspecified site	Daniel 1999 (302)	16/210	8/92	0.96 (0.64 to 1.43)
	Keck 1998 (139)	34/91	18/48	
Respiratory problems	Keck 1998 (139)	12/91	3/48	2.11 (0.63 to 7.12)
Skin problems	Keck 1998 (139)	7/91	0/48	7.99 (0.47 to 136.97)

n, *number of events*; N, *number of participants in group*

[*] *Risk difference, 0.03 (95% CI, 0.00 to 0.06)*

TABLE 47 *Ziprasidone versus placebo: dichotomous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state: impending relapse (CGI-I > 5)	Arato 1997 (294)	108/219	52/75	0.71 (0.58, 0.87)
Any adverse event	Arato 1997 (294)	160/219	58/75	0.94 (0.82, 1.09)
Agitation	Arato 1997 (294)	29/219	13/75	0.76 (0.42, 1.39)
Insomnia	Arato 1997 (294)	78/219	24/75	1.11 (0.77, 1.62)
Anxiety	Arato 1997 (294)	25/219	12/75	0.71 (0.38, 1.35)

n, *number of events*; N, *number of participants in group*

TABLE 48 *Ziprasidone versus placebo: continuous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies	Treatment group		Control group		WMD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Body weight (kg)						
40 mg dose	Arato 1997	72	69.99 (12.47)	70	68.90 (12.28)	1.09 (–2.98 to 5.16)
80 mg dose	Arato 1997	69	67.12 (13.43)	70	68.90 (12.28)	–1.78 (–6.06 to 2.50)
160 mg dose	Arato 1997	70	68.75 (16.77)	70	68.90 (12.28)	–0.15 (–5.02 to 4.72)

N, *number of participants in group*

Ziprasidone versus haloperidol

All the included studies had attrition rates > 50%, so all results should be treated with caution.

The results are summarised in *Tables 49–51.*

Commercial-in-confidence data removed from both text and tables.

Global effect

Commercial-in confidence data removed.

Mental state

When a 20% decrease in the PANSS negative subscale score was defined as a clinically important response, the findings were in favour of typical drugs in the short term (RR, 1.14; 95% CI, 1.01 to 1.28) and equivocal in the long term (RR, 0.86; 95% CI, 0.74 to 1.00; risk difference, –0.10; 95% CI, –0.21 to 0.00). No clear differences were seen between treatment groups in terms of relapses in specific symptoms (psychosis, hallucinations).

TABLE 49 *Intramuscular ziprasidone versus intramuscular haloperidol: immediate term (1 week)*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early				
Any reason	Brook 1998 (132) Swift 1998 (306)	8/90 38/206	8/42 36/100	0.50 (0.35 to 0.72)
Lack of efficacy – immediate term	Brook 1998 (132) Swift 1998 (306)	1/90 0/206	3/42 0/100	0.16 (0.02 to 1.45)
Any adverse event	Brook 1998 (132)	41/90	25/42	0.77 (0.55 to 1.07)
Side-effects				
Akathisia	Brook 1998 (132) Swift 1998 (306)	19/296	27/142	0.34 (0.20 to 0.59)
Dystonia	Brook 1998 (132) Swift 1998 (306)	13/296	15/142	0.42 (0.20 to 0.85)
EPS	Brook 1998 (132) Swift 1998 (306)	5/296	31/142	0.08 (0.03 to 0.19)
Use of anticholinergic medication	Brook 1998 (132)	13/90	20/42	0.30 (0.17 to 0.55)
Dizziness	Swift 1998 (306)	35/206	13/100	1.31 (0.72 to 2.36)
Gastrointestinal problems	Swift 1998 (306)	59/206	8/100	3.58 (1.78 to 7.20)
Hypertonia	Swift 1998 (306)	5/206	12/100	0.22 (0.08 to 0.62)
Insomnia	Swift 1998 (306)	32/206	12/100	1.29 (0.70 to 2.40)
Anxiety	Swift 1998 (306)	32/206	13/100	1.19 (0.66 to 2.17)
Headache	Swift 1998 (306)	35/206	8/100	2.12 (1.02 to 4.41)
Pain at injection site	Swift 1998 (306)	22/206	2/100	5.34 (1.28 to 22.26)

n, *number of events*; N, *number of participants in group*

TABLE 50 *Ziprasidone versus haloperidol: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving study early – any reason: short term	Goff 1998 (90)	38/73	8/17	1.04 (0.89 to 1.21)
	Study 128-115 (163)	Commercial-in-confidence: data removed		
	Study 128-301 (235)	Commercial-in-confidence: data removed		
	Study NY-97-001 (572)	Commercial-in-confidence: data removed		

n, *number of events*; N, *number of participants in group*

TABLE 51 *Ziprasidone versus haloperidol: dichotomous outcomes – 26 weeks or longer*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state				
No clinically important response (PANSS negative subscale)	Hirsch 1999 (301)	95/148	114/153	0.86 (0.74 to 1.00)
Relapse of positive symptoms – hallucinations	Hirsch 1999 (301)	9/148	12/153	0.78 (0.34 to 1.79)
Relapse of positive symptoms – psychosis	Hirsch 1999 (301)	8/148	4/153	2.07 (0.64 to 6.72)
Leaving study early – any reason	Hirsch 1999 (301)	38/148	36/153	1.08 (0.94 to 1.25)
	Study 128-108 (599)	Commercial-in-confidence: data removed		
Any adverse event	Hirsch 1999 (301)	114/148	130/153	0.91 (0.81 to 1.01)
Side-effects				
Cardiovascular problems – dizziness	Hirsch 1999 (301)	6/148	10/153	0.62 (0.23 to 1.66)
Gastrointestinal problems	Hirsch 1999 (301)	31/148	15/153	2.14 (1.20 to 3.79)
Agitation	Hirsch 1999 (301)	11/148	10/153	1.14 (0.50 to 2.60)
Akathisia	Hirsch 1999 (301)	7/148	25/153	0.29 (0.13 to 0.65)
Extrapyramidal	Hirsch 1999 (301)	2/148	7/153	0.30 (0.06 to 1.40)*
Hypertonia	Hirsch 1999 (301)	3/148	11/153	0.28 (0.08 to 0.99)
Unspecified movement disorders	Hirsch 1999 (301)	22/148	62/153	0.37 (0.24 to 0.56)
Tremor	Hirsch 1999 (301)	9/148	15/153	0.62 (0.28 to 1.37)
Insomnia	Hirsch 1999 (301)	24/148	27/153	0.92 (0.56 to 1.52)
Somnolence	Hirsch 1999 (301)	20/148	13/153	1.59 (0.82 to 3.08)
Anxiety	Hirsch 1999 (301)	11/148	11/153	1.03 (0.46 to 2.31)
Asthenia	Hirsch 1999 (301)	12/148	8/153	1.55 (0.65 to 3.69)
Depression	Hirsch 1999 (301)	9/148	11/153	0.85 (0.36 to 1.98)
Dry mouth	Hirsch 1999 (301)	4/148	8/153	0.52 (0.16 to 1.68)
Headache	Hirsch 1999 (301)	9/148	16/153	0.58 (0.27 to 1.27)

n, *number of events*; N, *number of participants in group*

* *Risk difference, –0.02 (95% CI, –0.04 to 0.00)*

Leaving study early

The numbers leaving the studies early in the long term were similar in both treatment groups (RR, 1.08; 95% CI, 0.94 to 1.25). In the immediate term, participants receiving ziprasidone in injectable form were less likely to leave the study early than those receiving haloperidol (RR, 0.50; 95% CI, 0.35 to 0.72), but no difference was seen in the short term (RR, 1.04; 95% CI, 0.89 to 1.21). Heterogeneity was seen in the result for 'leaving the study early due to lack of efficacy' (chi-squared = 13.40; $p = 0.02$); the source of this was unclear.

Side-effects

There were no clear differences between ziprasidone and haloperidol for 'any adverse event' in either the immediate term (RR, 0.77; 95% CI, 0.55 to 1.07), the short term (RR, 0.94; 95% CI, 0.88 to 1.01), or the long term (RR, 0.91; 95% CI, 0.81 to 1.01).

ECG data was reported in one study (Hirsch 1999[292]), although four studies contained statements that ECG was recorded. Hirsch 1999 reported that no clinically relevant changes in ECG were seen in either group, and that no participant had a Q-Tc interval greater than 500 ms or an increase in Q-Tc interval of 20% or more.

In the immediate-term intramuscular studies, ziprasidone was significantly less likely than haloperidol to be associated with akathisia (RR,

0.34; 95% CI, 0.20 to 0.59), dystonia (RR, 0.42; 95% CI, 0.20 to 0.85), EPS (RR, 0.08; 95% CI, 0.03 to 0.19; risk difference, –0.20; 95% CI, –0.27 to –0.13), use of anticholinergic medication (RR, 0.30; 95% CI, 0.17 to 0.55) or hypertonia (RR, 0.22; 95% CI, 0.08 to 0.62). Ziprasidone was significantly more likely to be associated with gastrointestinal problems (RR, 3.58; 95% CI, 1.78 to 7.20), headache (RR, 2.12; 95% CI, 1.02 to 4.41) and pain at the injection site (RR, 5.34; 95% CI, 1.28 to 22.26).

In the short term, ziprasidone was significantly less likely than typical antipsychotic drugs to be associated with dystonia (RR, 0.30; 95% CI, 0.17 to 0.52), akathisia (RR, 0.37; 95% CI, 0.26 to 0.52), any EPS (RR, 0.32; 95% CI, 0.21 to 0.47, risk difference, –0.13; 95% CI, –0.18 to –0.08), use of benztropine (RR, 0.42; 95% CI, 0.35 to 0.50) or hypertonia (RR, 0.46; 95% CI, 0.28 to 0.75). Asthenia (RR, 2.37; 95% CI, 1.24 to 4.53) and insomnia (RR, 1.47; 95% CI, 1.01 to 2.14) seemed to occur significantly more with ziprasidone than with haloperidol. Heterogeneity was seen in the results for dystonia (chi-squared = 3.06; $p = 0.08$), somnolence (chi-squared = 5.91; $p = 0.015$) and use of benztropine (chi-squared = 4.78; $p = 0.092$), hence these results should be treated with caution.

In the long term, ziprasidone was associated with significantly less akathisia (RR, 0.29; 95% CI, 0.13 to 0.65) and unspecified movement disorders (RR, 0.37; 95% CI, 0.24 to 0.56) than haloperidol but with significantly more gastrointestinal problems (RR, 2.14; 95% CI, 1.20 to 3.79).

Similar weight gain was reported for ziprasidone and haloperidol groups (Hirsch 1999[292]), with women gaining slightly more weight (0.8 kg in the ziprasidone group and 0.9 kg in the haloperidol group) than men (0.3 kg in each group). Too few data were available for these results to be included in the analysis.

Pfizer Study NY-97-001: commercial-in-confidence data removed.

Ziprasidone versus amisulpride

Commercial-in-confidence data removed, including table.

Ziprasidone versus olanzapine

Commercial-in-confidence data removed, including tables showing dichotomous and continuous outcomes.

Ziprasidone versus risperidone

Commercial-in-confidence, data removed, including tables showing results for both the short and the long term.

Sensitivity analysis

All the included studies had > 25% attrition so a sensitivity analysis was not possible.

Publication bias

Because of the small numbers of studies within each outcome comparison, it was not possible to construct funnel plots to assess the likelihood of publication bias in this review.

Rare or long-term events

No non-randomised studies of rare or long-term events with ziprasidone were found that met the inclusion criteria for this review.

Other systematic reviews

No new systematic reviews of ziprasidone were found.

Chapter 12

Zotepine: effectiveness

Numbers and characteristics of included RCTs

New RCTs

Two new RCTs were submitted for this review by the manufacturers of zotepine: Knoll CTR 4002, 2000 (commercial-in-confidence); Welch 1996 (Study BPI1202, commercial-in-confidence).[295] Another new RCT was identified from the literature searches – Fischer 1999.[296] Data extraction sheets for these trials can be found in appendix 2.

Old RCTs

The original review was of ten RCTs: Barnas 1987,[297] Cooper 1999a,[298] Cooper 1999b,[299] Dieterle 1991,[300] Fleischhacker 1989,[301] Klieser 1996,[302] Meyer-Lindberg 1996,[108] Petit 1996,[303] Sarai 1987,[304] Wetzel 1999.[305] Data extraction sheets for these trials can be found in appendix 3.

Total RCTs

All 13 included trials were both randomised and double-blind. One was sponsored by Klinge Pharma, eight had company employees from Knoll Pharmaceuticals as named authors, and one appeared to be undertaken by independent researchers (Sarai 1987[304]).

There were 180 participants in Klieser 1996,[302] 159 in Cooper 1999a[298] and 126 in Petit 1996.[303] Power calculations were reported in Cooper 1999a, Cooper 1999b[299] and Petit 1996; in the latter it was stated '…so that a difference between treatment groups of 8.2 points could be detected in the change from baseline to endpoint in the BPRS total scores…'. In Cooper 1999a, an 8.8 change in mean BPRS total scores was used and, in Cooper 1999b, a difference in recurrence rates between groups from 20% to 50% could be detected with 90% power and 5% significance. There were 40 participants in Dieterle 1991,[300] 94 in Sarai 1987,[304] 108 in Fischer,[296] 50 in Meyer-Lindenberg 1996,[108] 40 in Fleischhacker 1989,[301] 30 in Barnas 1987[297] and 41 in Wetzel 1991.[305]

Commercial-in-confidence data removed.

Duration

Most trials were of very short duration, lasting between 6 and 8 weeks; one lasted for 26 weeks but only met the inclusion criteria for the outcome 'leaving study early'.

Commercial-in-confidence data removed.

Interventions

Four placebo-controlled trials were identified (Cooper 1999a,[298] Fischer 1999,[296] Welch 1996,[295] Cooper 1999b[299]). In four studies, haloperidol was used as the drug of comparison, in one study chlorpromazine was used (Cooper 1999a), in two perazine (Dieterle 1991;[300] Wetzel 1991[305]), and in one thiothixene (Sarai 1987[304]). In Meyer-Lindenberg 1996,[108] zotepine was compared with clozapine, while in Klieser 1996,[302] six groups were used, one using risperidone at two dose levels, one using clozapine, one remoxipride and one haloperidol. Doses of zotepine ranged from 75 to 450 mg. Haloperidol was used in low doses in Barnas 1987[297] (mean 4.2 mg daily) but in Fleischhacker 1989 and Petit 1996, doses over 10 mg daily were used. Thiothixene at 15–60 mg daily was used in Sarai 1987, and in Meyer-Lindenberg 1996, the control group was allocated 150–450 mg of clozapine daily. In Klieser 1996, risperidone, 4 or 8 mg, clozapine, 400 mg, remoxipride, 400 mg, or haloperidol, 15 mg, daily were used. In Dieterle 1991, perazine, mean dose 348 mg daily, was used, while in Wetzel 1991, perazine, 150–900 mg daily.

Commercial-in-confidence data removed.

Participants

Participants in 12 trials met operationalised diagnoses of schizophrenia as defined either by DSM[66] or ICD criteria. An inclusion criterion in Cooper 1999a[298] was a baseline score of 4 on the CGI and, in Cooper 1999b,[299] a baseline score of 3, with a history of recurrence of illness within the last 18 months. In Meyer-Lindenberg 1996,[108] only those who had previously not responded to at least 3 weeks of treatment with two conventional antipsychotic drugs at effective doses. In Petit 1996,[303] only those with a baseline score of 4 on the CGI were included. In Sarai 1987,[304] those who were 'overshadowed by lack of spontaneity' were included; those at advanced stages of schizophrenia, with psychomotor

excitement, in sedated states, hallucinating, deluded or with sleep disturbances were excluded. Participants in Fischer 1999[296] were those with predominantly negative symptoms.

Most participants in the included studies were in hospital, including all those in the Barnas 1987[297] and Petit 1996[303] trials. Small proportions of those in the other studies were attending outpatient departments.

Commercial-in-confidence data removed.

Outcomes

The definition of improvement consisted of an analysis of variance of BPRS or CGI scores in two trials (Fleischhacker 1989,[301] Meyer-Lindenberg 1996[108]). Kaplan–Meier survival analysis of time-to-recurrence was used in Cooper 1999b,[299] while in Cooper 1999a[298] the mean change in BPRS scores was used, although endpoint scores were supplied by the trialists. In Klieser 1996[302] and Wetzel 1991,[305] endpoint BPRS scores were given, while it was unclear how graphs had been used in Dieterle 1991[300] and no details were given. However, in both Barnas 1987[297] and Sarai 1987,[304] a binary report of 'improved or not' from their measurements of BPRS and CGI was provided. A 50% improvement in BPRS scores was used as a measure of improvement in Petit 1996.[303]

As most participants were hospitalised there were no data relating to outcomes such as admission.

Quality of included studies

In three trials, Cooper 1999a,[298] Cooper 1999b[299] and Sarai 1987,[304] adequate concealment of allocation was reported. In the other nine trials, it was not clear exactly how randomisation had been undertaken.

Adequate precautions for blinding of treatment were clearly described in eight trials (Barnas 1987,[297] Cooper 1999a,[298] Cooper 1999b,[299] Dieterle 1991,[300] Fleischhacker 1989,[301] Petit 1996,[303] Sarai 1987,[304] Wetzel 1991[405]). None of the included trials tested the adequacy of the blindness of those rating outcomes.

In the placebo trials, 62% of patients left early (data from 3/4 studies). In comparison with typical antipsychotic drugs, about one-third of participants left before completion. In comparisons with other atypical antipsychotic drugs, it was only possible to ascertain how many left early in one study (Meyer-Lindenberg 1996[108]) – 34%; this resulted in the randomisation being broken and reporting being on matched pairs. In the Cooper 1999b[109] and Meyer-Lindenberg 1996 studies, attrition was > 50% (as specified in the protocol), so only data for the outcome 'leaving study early' were entered into this review. The reasons for leaving early were given in the Cooper 1999b trial but exactly why people decided to leave or were excluded from other studies was not explicit. In nine trials, data were analysed on an ITT basis using last observation carried forward or there was a statement to that effect. This practice may well overestimate the treatment effect. The Meyer-Lindenberg 1996 trial reported on only those controlled, matched pairs remaining in the trial. In Fleischhacker 1989,[301] only outcomes that reached significance were reported.

Commercial-in-confidence data removed.

Zotepine versus placebo

The proportions of individuals leaving studies early were high in both groups; however, fewer of those taking zotepine left studies early than those on placebo, with 58% of those on zotepine leaving early from the three trials that reported this outcome compared with 69% on placebo. Nevertheless, all other results within this comparison should be viewed with this in mind and, it is suggested, with great caution.

Only four trials compared zotepine with placebo, of which two only contributed to the outcome 'leaving study early' as they had > 50% loss to follow-up.

The results are summarised in *Tables 52* and *53*.

Global/mental state

For the outcome 'no important clinical response by 8 weeks' and using last observation carried forward, a statistically significant result in a 20% mean reduction in BPRS endpoint scores was reported in Cooper 1999a[298] in favour of zotepine over placebo (RR, 0.44; 95% CI, 0.27 to 0.72; risk difference, –0.34; 95% CI, –0.52 to –0.16).

Behaviour changes

For the outcomes of agitation, hostility and nervousness, none of the results reached statistical significance, although all favoured those taking zotepine.

TABLE 52 *Zotepine versus placebo: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Mental state: no response (20% reduction in BPRS)	Cooper 1999a (106)	14/53	32/53	0.44 (0.27 to 0.72)
Agitation	Cooper 1999a (106)	20/53	27/53	0.74 (0.48 to 1.14)
Hostility	Cooper 1999a (106)	20/53	27/53	0.74 (0.48 to 1.14)
Nervousness	Cooper 1999a (106)	22/53	28/53	0.79 (0.52 to 1.18)
Leaving study early				
Any reason	Cooper 1999a (106)	19/53	25/53	0.80 (0.70 to 0.92)
	Cooper 1999b (121)	43/63	49/58	
	Study BPI1201 (288)	Commercial-in-confidence: data removed		
Lack of efficacy	Cooper 1999a (106)	6/53	16/53	0.50 (0.38 to 0.66)
	Cooper 1999b (121)	4/63	9/58	
	Study BPI1201 (288)	Commercial-in-confidence: data removed		
Any adverse event	Cooper 1999a (106)	43/53	23/53	1.87 (1.34 to 2.61)
Side-effects				
Akathisia	Cooper 1999a (106)	20/53	27/53	0.74 (0.48 to 1.14)
Dyskinesia	Cooper 1999a (106)	24/53	30/53	0.80 (0.55 to 1.17)
Needing additional anticholinergic medication	Cooper 1999a (106)	23/53	28/53	0.82 (0.55 to 1.22)*
Insomnia	Cooper 1999a (106)	21/53	31/53	0.68 (0.45 to 1.01)
Somnolence	Cooper 1999a (106)	37/53	25/53	1.48 (1.06 to 2.07)
Constipation	Cooper 1999a (106)	21/53	26/53	0.81 (0.52 to 1.24)
Asthenia	Cooper 1999a (106)	24/53	27/53	0.89 (0.60 to 1.32)
Increased saliva	Cooper 1999a (106)	22/53	25/53	0.88 (0.57 to 1.35)
Liver function abnormalities	Cooper 1999a (106)	22/53	26/53	0.85 (0.56 to 1.29)
Pain	Cooper 1999a (106)	24/53	26/53	0.92 (0.62 to 1.38)
Weight gain	Cooper 1999a (106)	24/53	25/53	0.96 (0.64 to 1.45)

n, *number of events*; N, *number of participants in group*

* *Risk difference, –0.09 (95% CI, –0.28 to 0.10)*

TABLE 53 *Zotepine versus placebo: continuous outcomes – up to 26 weeks*

Comparison or outcome	Included studies	Treatment group		Control group		WMD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Pulse rate	Cooper 1999a	53	83.80 (11.00)	53	81.90 (8.90)	1.90 (–1.91 to 5.71)
Body weight (kg)	Cooper 1999a	53	73.00 (14.40)	53	71.30 (13.10)	1.70 (–3.54 to 6.94)

N, *number of participants in group*

Leaving study early

Any reason by 8–26 weeks

Fewer individuals taking zotepine left studies early than those on placebo, with 58% (191/331) of those on zotepine leaving and 69% (128/184) on placebo. This result reached statistical significance when the results of the three studies were pooled (RR, 0.80; 95% CI, 0.70 to 0.92), giving an overall rate of attrition of 62%.

Lack of efficacy by 8–26 weeks

For those who were withdrawn or withdrew from the studies giving the reason 'lack of efficacy', pooled results reached statistical significance in favour of zotepine (RR, 0.50; 95% CI, 0.38 to 0.66).

Side-effects

Any adverse event

More people taking zotepine had an adverse event than those on placebo (RR, 1.87; 95% CI, 1.34 to 2.61).

Movement disorders

None of the results reached significance for the outcomes of akathisia, dyskinesia and needing anticholinergic medication.

Sleep problems

Fewer of those taking placebo experienced somnolence than those taking zotepine (RR, 1.48; 95% CI, 1.06 to 2.07), while those taking zotepine suffered less insomnia, although this last result did not reach statistical significance.

Gastrointestinal problems

Fewer people taking zotepine suffered constipation but the result did not reach significance.

Other side-effects

None of the results reached significance for the outcomes of asthenia, increased salivation, laboratory test abnormality, liver function abnormalities and pain.

Pulse rate

Patients taking zotepine ended the study with an elevated pulse rate. When compared with baseline, those taking zotepine started with a lower mean rate (79.5; SD, 9.7), while those on placebo had a higher mean rate (84.9; SD, 11.4). The result did not reach significance.

Weight changes

The ITT analysis belies the fact that no-one on placebo reported weight gain as a side-effect, although five individuals on zotepine did. Because ITT analysis has been undertaken assuming the worst outcome (i.e. weight gain) for those who left the study early, the higher numbers leaving the placebo group meant that in this analysis more of those in the placebo group appeared to have experienced weight gain. Whether this is true or whether more people in the zotepine group gained weight was unclear. This is the reason that outcomes should be reported for all trial participants. For continuous data on weight change, the result did not reach significance.

Zotepine versus typical antipsychotic drugs

The results are summarised in *Tables 54* and *55*.

Global effect

In Barnas 1987,[297] the result for CGI scores that did not reach significance were dichotomised (RR, 0.5; 95% CI, 0.11 to 2.33; risk difference, –0.13; 95% CI, –0.42 to 0.15). The outcome of needing to prescribe additional antipsychotic medication was also reported in Dieterle 1991,[300] Sarai 1987[304] and Wetzel 1991.[305] It was difficult to know how to classify this outcome and understand exactly what the results meant.

Mental state

For the outcome 'no important clinical responses by 4–12 weeks', a cut-off point on the overall BPRS change score that was considered to be clinically important was pre-specified in four trials (Barnas 1987,[297] Cooper 1999a,[298] Petit 1996,[303] Sarai 1987[304]). On summation, statistical significance was found in favour of zotepine (RR, 0.77; 95% CI, 0.65 to 0.92; risk difference, –0.15; 95% CI, –0.24 to –0.05). However, heterogeneity was seen in this result (chi-squared = 7.19; $p = 0.066$), so it should be viewed with caution.

Zotepine may have been more effective in relieving negative symptoms than typical antipsychotic treatments, as indicated by the SANS scores that were in favour of zotepine (see appendix 9; WMD –8.66; 95% CI, –16.93 to –0.39).

Behavioural changes

Two studies recorded the mental state outcome of anxiety, with or without irritability (Petit 1996,[303] Sarai 1987[304]). In both, this outcome was reported as a side-effect. Heterogeneous data (using either fixed or random effects) suggested that there was a higher incidence of anxiety, with or without irritation, in the control groups. The reviewers were unclear where to present these findings as they related to mental state but were labelled as

TABLE 54 *Zotepine versus typical antipsychotic drugs: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Global state: not improved (CGI)	Barnas 1987 (30)	2/15	4/15	0.50 (0.11 to 2.33)
Mental state: no response	Barnas 1987 (30)	5/15	9/15	0.77 (0.65 to 0.92)
	Cooper 1999a (106)	14/53	29/53	
	Petit 1996 (126)	47/63	53/63	
	Sarai 1987 (94)	24/48	24/46	
Anxiety and/or irritation	Petit 1996 (126)	27/63	33/63	0.92 (0.67 to 1.27)
	Sarai 1987 (94)	16/48	13/46	
Hostility	Cooper 1999a (106)	20/53	25/53	0.80 (0.51 to 1.25)
Nervousness	Cooper 1999a (106)	22/53	28/53	0.79 (0.52 to 1.18)
Leaving study early – any reason	Barnas 1987 (30)	6/15	8/15	0.82 (0.64 to 1.05)
	Cooper 1999a (106)	19/53	25/53	
	Dieterle 1991 (40)	8/20	12/20	
	Petit 1996 (126)	25/63	30/63	
	Sarai 1987 (94)	10/48	7/46	
	Wetzel 1991 (41)	2/20	3/21	
Cognition not improved (Syndrome Short Test)	Klieser 1996 (65)	4/20	28/45	0.32 (0.13 to 0.80)*
Any adverse event	Dieterle 1991 (40)	11/20	9/20	1.02 (0.92 to 1.12)
	Knoll ZT4002 (125)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	46/63	50/63	
	Sarai 1987 (94)	39/48	37/46	
Side-effects				
ECG abnormalities	Sarai 1987 (94)	3/48	2/46	1.44 (0.25 to 8.21)
Tachycardia	Sarai 1987 (94)	8/48	2/46	3.83 (0.86 to 17.11)
Anorexia	Sarai 1987 (94)	12/48	8/46	1.44 (0.65 to 3.19)
Constipation	Cooper 1999a (106)	21/53	27/53	0.98 (0.76 to 1.25)
	Knoll ZT4002 (125)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	30/63	32/63	
	Sarai 1987 (94)	14/48	9/46	
Nausea	Sarai 1987 (94)	10/48	8/46	1.20 (0.52 to 2.77)
Akathisia	Barnas 1987 (30)	7/15	13/15	0.73 (0.58 to 0.93)
	Cooper 1999a (106)	20/53	26/53	
	Fleischhacker 1989 (40)	5/20	7/20	
	Petit 1996 (126)	25/63	37/63	
	Sarai 1987 (94)	10/48	8/46	
Dyskinesia	Knoll ZT4002 (125)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	26/63	34/63	0.79 (0.56 to 1.12)
	Sarai 1987 (94)	4/48	4/46	
Dystonia	Barnas 1987 (30)	6/15	11/15	0.47 (0.24 to 0.93)
	Fleischhacker 1989 (40)	1/20	4/20	
Gait disturbance	Sarai 1987 (94)	5/48	5/46	0.96 (0.30 to 3.09)
Needing additional antiparkinsonian medication	Barnas 1987 (30)	8/15	13/15	0.65 (0.54 to 0.77)
	Klieser 1996 (65)	6/20	25/45	
	Petit 1996 (126)	42/63	62/63	
Parkinsonism	Sarai 1987 (94)	7/48	5/46	1.34 (0.46 to 3.93)
Restlessness	Sarai 1987 (94)	15/48	11/46	1.31 (0.67 to 2.54)
Rigidity	Barnas 1987 (30)	8/15	11/15	0.63 (0.40 to 0.98)
	Fleischhacker 1989 (40)	4/20	13/20	
	Sarai 1987 (94)	7/48	6/46	

continued

***TABLE 54* contd** *Zotepine versus typical antipsychotic drugs: dichotomous outcomes – up to 26 weeks*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
***Side-effects* contd**				
Tremor	Barnas 1987 (30)	7/15	12/15	0.65 (0.44 to 0.95)
	Fleischhacker 1989 (40)	4/20	7/20	
	Knoll ZT4002 (128)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	6/63	7/63	
	Sarai 1987 (94)	9/48	11/46	
Insomnia	Cooper 1999a (106)	21/53	25/53	0.81 (0.66 to 1.01)
	Knoll ZT4002 (125)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	34/63	37/63	
	Sarai 1987 (94)	20/48	29/46	
Lassitude	Sarai 1987 (94)	13/48	11/46	1.13 (0.57 to 2.27)
Sleepiness	Sarai 1987 (94)	13/48	8/46	1.56 (0.71 to 3.41)
Somnolence	Cooper 1999a (106)	36/53	28/53	1.29 (0.94 to 1.76)
Asthenia	Cooper 1999a (106)	24/53	28/53	0.95 (0.65 to 1.39)
	Knoll ZT4002 (125)	6/59	4/66	
Dry mouth	Barnas 1987 (30)	6/15	10/15	1.13 (0.84 to 1.54)
	Knoll ZT4002 (125)	Commercial-in-confidence: data removed		
	Petit 1996 (126)	30/63	32/63	
	Sarai 1987 (94)	10/48	2/46	
Dizziness	Sarai 1987 (94)	6/48	7/46	0.82 (0.30 to 2.26)
Headache	Sarai 1987 (94)	7/48	5/46	1.34 (0.46 to 3.93)
Hyperhydrosis	Barnas 1987 (30)	7/15	8/15	0.88 (0.43 to 1.80)
Increased salivation	Cooper 1999a (106)	22/53	28/53	0.79 (0.52 to 1.18)
Liver function abnormalities	Barnas 1987 (30)	12/15	8/15	1.09 (0.87 to 1.38)
	Cooper 1999a (106)	22/53	26/53	
	Fleischhacker 1989 (40)	12/20	6/20	
	Petit 1996 (126)	30/63	32/63	
	Sarai 1987 (94)	5/48	2/46	
Nasal congestion/obstruction	Sarai 1987 (94)	7/48	2/46	3.35 (0.73 to 15.31)
Pain	Cooper 1999a (106)	24/53	27/53	0.89 (0.60 to 1.32)

n, *number of events*; N, *number of participants in group*

[*] *Risk difference, –0.42 (95% CI, –0.65 to –0.20)*

TABLE 55 *Zotepine versus typical antipsychotic drugs: continuous outcomes – up to 26 weeks*

Comparison or outcome	Included studies	Treatment group		Control group		MD (95% CI)
		N	Mean (SD)	*N*	Mean (SD)	
Pulse	Cooper 1999a	53	83.80 (11.00)	52	85.10 (10.30)	–1.30 (–5.38 to 2.78)
Body weight (kg)	Cooper 1999a	53	73.00 (14.40)	52	74.30 (11.40)	–1.30 (–6.26 to 3.66)

N, *number of participants in group*

side-effects. The trialists did not make explicit whether they considered that zotepine failed to control the natural anxiety of the study participants or whether the experimental compound caused the anxiety. Hostility and nervousness as side-effects were reported in Cooper 1999a[298] and, while the outcome favoured zotepine, no significance was found.

Leaving study early – any reason

The numbers leaving studies early were 32% (70/219) in the zotepine group and 39% (85/218) in the comparator groups (RR, 0.82; 95% CI, 0.64 to 1.05).

Side-effects

Any adverse event

In four studies (Knoll CTR4002, Dieterle 1991,[300] Petit 1996,[303] Sarai 1987[304]), data on 'any adverse event' were reported. No differences were found between zotepine, haloperidol and thiothixene.

Cardiovascular problems

Abnormal ECG results for those taking zotepine were reported in two studies (Petit 1996,[303] Sarai 1987[304]), although details were given in only one (Sarai 1987: RR, 1.44; 95% CI, 0.25 to 8.21). In the same study, more tachycardia was reported in the zotepine group than in the thiothixene group (RR, 3.83; 95% CI, 0.86 to 17).

Gastrointestinal problems

There were few data and these did not suggest differences between zotepine and either haloperidol or thiothixene for the outcomes of anorexia, constipation, or nausea.

Movement disorders

Zotepine produced less akathisia (RR, 0.73; 95% CI, 0.58 to 0.93), dystonia (RR, 0.47; 95% CI, 0.24 to 0.93), tremor (RR, 0.65; 95% CI, 0.44 to 0.95) and rigidity (RR, 0.63; 95% CI, 0.40 to 0.98) than other drugs. The finding for akathisia contained heterogeneity (chi-squared = 7.04; df = 3), mostly as a result of inclusion of data from Sarai 1987,[304] in which the comparison drug was thiothixene. The removal from the results of data for a drug not prone to cause movement disorders, increased the result in favour of zotepine. Rates of dyskinesia, gait disturbance, parkinsonism and restlessness gave no suggestion of a differential effect of zotepine and the comparator drugs. The suggestion that zotepine caused fewer movement disorder side-effects than typical antipsychotic drugs may be supported by the data on use of additional antiparkinsonian medication. Pooled results from Barnas 1987,[297] Klieser 1996[302] and Petit 1996[303] found in favour of zotepine (RR, 0.65; 95% CI, 0.54 to 0.77).

Commercial-in-confidence data removed.

Sleep problems

There was no suggestion that differences existed between zotepine and either haloperidol or thiothixene for the outcomes of insomnia, lassitude, sleepiness or somnolence.

Other side-effects

Asthenia, dry mouth or an increase in salivation, dizziness, headache, hyperhydrosis, nasal congestion and pain were equally prevalent in both groups. Heterogeneity was noted in the result for dry mouth (chi-squared = 9.44; $p = 0.024$), hence this result should be viewed with caution. Five studies reported the incidence of abnormal liver function tests. None of these abnormalities were stated to be serious but they were slightly more common in the zotepine group (RR, 1.09; 95% CI, 0.87 to 1.38).

Pulse rate

Continuous data for pulse rates were reported in one study (Cooper 1999a[298]); while the outcome favoured zotepine, no significance was found.

Weight increase

This outcome was only reported in one study (Cooper 1999a[298]). The mean weight of those on zotepine at endpoint was less than those on chlorpromazine but this did not reach any level of significance and was reported using last observation carried forward. The chlorpromazine group also started off at a higher level (chlorpromazine: mean weight at baseline, 72.9 kg; SD, 12; zotepine: 70.6 kg; SD, 14.2). In one trial (Petit 1996[303]), a weight gain in those taking zotepine was reported but not the variance of this gain.

Change in cognition

More individuals on zotepine improved, as measured by the Syndrome Short Test, than did those on haloperidol (RR, 0.32; 95% CI, 0.13 to 0.80).

Sensitivity analysis

When only those studies in which zotepine was compared with haloperidol were included in the analysis, there was no longer any significant difference between the zotepine-treated and haloperidol-treated groups for the mental state response outcome (RR, 0.84; 95% CI, 0.70 to 1.01).

Zotepine versus atypical antipsychotic drugs

Two studies were included in this part of the review (Klieser 1996,[302] Meyer-Lindenberg 1996[108]). In the Meyer-Lindenberg 1996 study, zotepine was compared with clozapine in a group of individuals whose illnesses were moderately unresponsive to drug treatments. Few data were available from this trial for this review. The Klieser 1996 study was a comparison of two doses of risperidone, clozapine, remoxipride and haloperidol against zotepine. Here, haloperidol was excluded and, for continuous outcomes, only the data for risperidone, 8 mg, were compared with zotepine. The control groups experienced significantly less movement disorders than those on zotepine. It was disappointing that the two studies did not present more data that were either clinically meaningful or hypothesis generating.

The results are summarised in *Table 56*.

Global state
No data were available on global outcomes such as 'response'.

Mental state
No data were available on mental state clinical effectiveness outcomes.

Leaving study early – any reason
As far as the data showed, zotepine was as acceptable as clozapine for this group of individuals (RR, 1.43; 95% CI, 0.65 to 3.15).

Side-effects
For the dichotomous outcome of needing less antiparkinsonian medication, statistical significance was found for the other three atypical drugs against zotepine (RR, 2.88; 95% CI, 1.22 to 6.78; risk difference, 0.20; 95% CI, –0.01 to 0.40).

Changes in Cognition Short Test
This scale was used in one study (Klieser 1996[302]); significance was not found.

Sensitivity analysis

When studies with > 25% attrition (Barnas 1987,[297] Cooper 1999a,[298] Dieterle 1991,[300] Petit 1996[303]) were excluded from the analysis, the following changes were seen in the results. The rates of response in zotepine-treated and typical antipsychotic-treated groups were no longer different (RR, 0.97; 95% CI, 0.67 to 1.40) and there was no longer any significant difference in BPRS scores. The risks of akathisia and needing antiparkinsonian medication were no longer significantly different between groups (RR, 0.97; 95% CI, 0.52 to 1.83; RR, 0.54; 95% CI, 0.26 to 1.11, respectively) but the risk of abnormal liver function tests was higher for zotepine than for typical antipsychotic drugs (RR, 2.10; 95% CI, 1.04 to 4.23).

Publication bias

Time constraints meant that it was not possible to construct funnel plots to assess the likelihood of publication bias in this review.

Rare or long-term events

No non-randomised studies of rare or long-term events with zotepine were identified that met the inclusion criteria for this review.

Other systematic reviews

Butler and colleagues[306] included 15 RCTs in a meta-analysis of the efficacy of zotepine.

TABLE 56 *Zotepine versus atypical antipsychotic drugs: dichotomous outcomes*

Comparison or outcome	Included studies (number of participants)	Treatment group *n/N*	Control group *n/N*	RR (95% CI)
Leaving the study early – any reason	Meyer-Lindenberg 1996 (50)	10/25	7/25	1.43 (0.65 to 3.15)
Cognition – not improved (Syndrome Short Test)	Klieser 1996 (135)	4/20	33/115	0.70 (0.28 to 1.75)*
Additional antiparkinsonian medication required	Klieser 1996 (135)	6/20	12/115	2.88 (1.22 to 6.78)

n, *number of events*; N, *number of participants in group*

* *Risk difference, –0.09 (95% CI, –0.28 to 0.11)*

BPRS and improvement scale scores were considered specifically. The results showed a greater reduction in BPRS for zotepine compared with placebo and typical antipsychotic drugs but not with clozapine. Exclusion of high-dose zotepine studies from the meta-analysis did change the results. The authors stated that heterogeneity did not reach a significant level; the results were similar to those reported here.

Wighton and colleagues[307] conducted a meta-analysis of seven RCTs to investigate the efficacy of zotepine in treating acute negative symptoms, as measured on the SANS scale. The authors reported that the test for homogeneity was not significant. The mean change in SANS score was greater with zotepine when compared with placebo and typical antipsychotic treatments. Details of the literature search undertaken for the meta-analysis were lacking and it did not appear to be comprehensive.

Chapter 13

Cost-effectiveness

In this chapter the published economic literature with respect to drug treatments for schizophrenia is reviewed and described, followed by the results of our own economic model using the most recent, up-to-date cost and effectiveness data. Following this, the strengths and weaknesses and the results of economic models submitted by industry are considered and, finally, the results of the three approaches are compared to assess concordance or disagreement between the different methods of appraising the economic evidence.

Systematic review

Included studies

From 52 records found in the literature search, 31 were included in the cost-effectiveness review. A list of the included studies is presented in appendix 12. Data extraction sheets for these studies can be found in appendix 6.

Excluded studies

Once the full papers had been seen, 21 studies were excluded. Eight were cost-analyses only (no effectiveness data),[21–27,882] four were non-systematic reviews,[28–30,333] one was in Spanish,[31] two reported costs only in terms of hospitalisations[32,33] and seven were excluded because of lack of data on costs or outcomes.[35,37–40,334] A list of excluded studies is presented in appendix 12.

Study methodology

All 31 papers that met the inclusion criteria included an economic assessment of the treatment of schizophrenia with antipsychotic medication. The 23 studies based on clinical trials were classified according to the sources of evidence (see *Table 57* – note that the key to the classification was presented in *Table 1*).[34,36,115,148,170,309–315,317,319,320,327–329,331,332,335–337]

Eight modelling studies were identified that used data from a variety of sources (*Table 58*). Four were Markov models, three were deterministic models and one used stochastic modelling methods. The type of evidence had no effect on the study conclusions.

The main characteristics of the included studies are presented in appendix 12. In ten studies, risperidone was compared with typical antipsychotic drugs or with pre-risperidone initiation, while in six risperidone was compared with the other market leader, olanzapine. Olanzapine was also compared with conventional antipsychotic treatments in six studies. None of the studies were included in which amisulpride, quetiapine,

TABLE 57 *Included empirical studies by type of evidence*

	I	II	III
A	Tunis 1999[315] Blieden 1998[313] Gregor 2000[328] Hamilton 1998[36] Johnstone 1998[148] Edgell 2000[170]	Essock 2000[335] Rosenheck 1998[115]	
B	Obenchain 1999[320]	Hammond 1999[327]	Coley 1999[314] Kasper 2000[329] Loos 2000[331] Martin 2000[332]
C		Drew 1999[311] Sacristan 1998[34]	Percudani 1999[309] Duchesne 1999[336] Bille 1999[337]
D		Chinchilla 1998[319]	Galvin 1999[312] Schiller 1999[310] Finley 1998[317]

TABLE 58 *Model-based economic evaluations*

Study	Model type
Palmer 1998[316]	Markov model
Launois 1998[321]	Markov model
Iskedjian 1999[325]	Deterministic model
Byrom 1998[324]	Deterministic model
Davies 2000[308]	Stochastic model
Almond 2000[326]	Markov model
Oh 1999[323]	Deterministic model
De Hert 2000[330]	Semi-Markov model

zotepine or ziprasidone were considered; however, a study in which sertindole was compared with olanzapine and haloperidol was included (Launois, 1998[321]). Clozapine was compared with conventional treatment in two studies (Essock 2000,[335] Rosenheck 1998[115]).

A cost-effectiveness framework was used in most studies, using a range of measures of effect. In Coley 1999,[314] readmission rates and changes in treatment were used to compare risperidone and perphenazine with haloperidol; in Blieden 1998,[313] clinical outcomes commonly used to assess interventions for mental illness were used – BPRS, Hamilton Depression Scale, Negative Symptoms Scale, QLS. In three studies a cost–utility framework was used (Iskedijian 1999,[325] Davies 2000,[308] Oh 1999[323]). In Rosenheck 1998,[115] a 0–1 worst health–good health scale analogous to QALYs was developed using four standard assessment instruments; however, these do not represent utilities.

Validity of included studies

The validity of the included studies was assessed using the instrument described in appendix 12. This was intended to highlight the methods used in each of the studies, not as a scoring system. The validity assessment scores are presented in appendix 12.

Summary of costs and outcomes

Differences in the methodology and outcomes reported meant that it was not feasible to combine the results of the included studies in a meta-analysis. The main results from the included studies are summarised in appendix 12. Not all studies attempted to combine costs and effects: for those that did, the results are shown in *Table 59*.

In all studies, atypical antipsychotic drugs were found either to be a dominant treatment option or

TABLE 59 *Results from studies that formally combined costs and outcomes*

Study	Synthesis of costs and outcomes
Tunis 1999[315]	Savings per one interval (point) of improvement (olanzapine versus haloperidol) = $1632.50 for physical health factor, $5654.74 for mental health factor
Palmer 1998[316]	Using all measures of effect, olanzapine versus haloperidol is cost saving, as is olanzapine versus risperidone
Obenchain 1999[320]	ICER = –$563 per year per responder day for olanzapine compared with haloperidol
Launois 1998[321]	Sertindole versus haloperidol: France (1), sertindole dominates; France (2), sertindole more effective, more costly; Germany, sertindole dominates; Great Britain, sertindole more effective but more costly Sertindole versus olanzapine: France (1), sertindole dominates; France (2), sertindole dominates; Germany, sertindole dominates; Great Britain, sertindole dominates
Johnstone 1998[148]	ICER = –$575 for olanzapine compared with haloperidol
Davies 2000[308]	**Truncated normal distribution:** chlorpromazine (all doses) versus chlorpromazine (lower dose), chlorpromazine (all dose) dominates; haloperidol (all dose) versus chlorpromazine (all dose), haloperidol (all dose) dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol dominates; risperidone versus chlorpromazine (lower dose), £109,935; olanzapine versus chlorpromazine (all dose), olanzapine dominates **Triangular distribution:** chlorpromazine (lower dose) versus chlorpromazine (all dose), chlorpromazine (lower dose) dominates; haloperidol (all dose) versus chlorpromazine (all dose), haloperidol dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol (all dose) dominates; haloperidol (lower dose) versus chlorpromazine (all dose), haloperidol (lower dose) dominates; risperidone versus chlorpromazine (all dose), £34,241; olanzapine versus chloropromazine (all dose), olanzapine dominates
De Hert 2000[330]	Risperidone versus olanzapine, 4512.46 Euro (CWMST)

CWMST, time with minimal symptoms and toxicity

to produce incremental benefits that were worth the extra costs (i.e. they were a relatively cost-effective treatment option). However, the uncertainty surrounding the definition of an acceptable cost per QALY was highlighted in Davies 2000,[308] which meant that it was not feasible to draw conclusions as to whether treatment with atypical antipsychotic drugs represented value for money.

Summary of review results

It was not possible to synthesise the results of the economic evaluations in the form of a pooled analysis. Hence, a qualitative description of the main study findings was undertaken. The types of studies and principal results for each of the evaluations are described in appendix 12. The main conclusions relating to the cost-effectiveness of antipsychotic treatments and their comparators are summarised in *Table 60*.

Comparison with the results of the original review

In the original systematic review, three papers were identified that met the initial screening criteria. These studies all involved an economic assessment of the treatment of schizophrenia with antipsychotic medication. In two evaluations (Rosenheck 1997,[105] 1999,[340]), data from the same trial were reported, so they were treated as one study. Overall, both evaluations reported a potential economic advantage for olanzapine or clozapine when compared with haloperidol. In both, improvements were found in the patient outcomes of symptoms and quality of life. However, there were no statistically significant differences in long-term symptom ratings or quality-of-life scores for olanzapine.

Economic model

Effectiveness data used in the model

Data from both Cochrane reviews and the updated systematic review were used. When estimates were not available from these sources, data were derived from the published literature.

Probabilities of events

Because of inconsistency in the measurement and reporting of events, only adverse events that were irreversible or life threatening were included in the analysis, that is: EPS, tardive dyskinesia, hepatic dysfunction, agranulocytosis and NMS. It is likely that other events were indirectly included if they were severe enough to lead to discontinuation of therapy.

The base-case probabilities, defined by a normal distribution, are presented in appendix 12. There were too few trials in which rates of specific events were reported to estimate SDs or minimum and maximum values for tardive dyskinesia, NMS, hepatic dysfunction and agranulocytosis. These events were not assigned a distribution in the model.

Use of health and social services and associated unit costs

Data relating to the use of health and social services associated with the various management strategies and events are presented in appendix 12. The probability of inpatient admission for initiation of therapy was estimated from a trial of day and inpatient therapy for those with acute psychiatric illness, in which nearly half the patients had schizophrenia.[341]

The mean length of stay and SD for individuals who had an inpatient admission was estimated from the national Hospital Episode Statistics for those with schizophrenia.[342] A normal distribution was applied to this estimate.

The proportion of day-case admissions was taken from the study by Creed and colleagues[341] described above. Use of community-based services as required was calculated as 365 days minus the length of the inpatient stay, for initial therapy, change of therapy and relapse.

The unit costs associated with resources are presented in *Table 61*. The means and SDs for costs of inpatient stay and outpatient visits were estimated from national hospital costs data.[342] These were assigned a normal distribution. The costs of day-case visits were estimated from published data on the costs of day-hospital attendance.[343] This was assigned a triangular distribution, with most-likely, minimum and maximum values.

QALYs

Two economic evaluations of antipsychotic therapy have used linear analogue, standard gamble and time trade-off techniques to estimate the utility associated with alternative health state scenarios for patients with schizophrenia.[18,20] This model used the utility estimates generated by Glennie[18] (see appendix 12) as these estimates appeared more conservatively in favour of typical antipsychotic drugs and were determined by seven patients with schizophrenia, unlike those of Chouinard and Albright[20] who used psychiatric nurses to rate preferences. However, slightly higher utility values were estimated for clozapine

TABLE 60 *Conclusions about drug comparisons*

Comparison	Studies	Results
Atypical versus typical antipsychotic drugs		
Risperidone versus haloperidol	Coley 1999[314] Oh 1999[323] De Hert 2000[330] Galvin 1999[312] Iskedijian 1999[325]	All show risperidone less costly than haloperidol and more cost-effective
Risperidone versus chlorpromazine	Galvin 1999[312]	Results suggest patients had fewer general symptoms and lower costs while receiving atypical antipsychotic drugs, implying that atypical drug was dominant
Clozapine versus haloperidol	Galvin 1999[312] Rosenheck 1999[340]	Results suggest patients had fewer general symptoms and lower costs while receiving atypical antipsychotic drugs
Clozapine versus chlorpromazine	Galvin 1999[312]	Results suggest patients had fewer general symptoms and lower costs while receiving atypical antipsychotic drugs
Clozapine versus conventional treatment	Essock 2000[335]	Clozapine demonstrated cost-effectiveness on some measures of effectiveness
Sertindole versus haloperidol	Launois 1998[321]	Sertindole dominated in France (1) and Germany. It was associated with higher costs but increased effectiveness in France (2) and Great Britain (ICER not calculated)
Olanzapine versus haloperidol	Tunis 1999[315] Hamilton 1998[36] Johnstone 1998[338] Palmer 1998[316] Obenchain 1999[320] Davies 2000[308] Almond 2000[326]	Olanzapine more cost-effective than haloperidol
Atypical versus typical antipsychotic drugs	Byrom 1998[339]	Atypical antipsychotic drugs associated with increased effectiveness and lower costs
Atypical antipsychotic drugs: historical comparison		
Risperidone versus before-risperidone	Finley 1998[317] Chinchilla 1998[319] Schiller 1999[310] Hammond 1999[337]	Reduced costs and better outcomes associated with risperidone, implying that risperidone was dominant
Olanzapine versus before-olanzapine	Sacristan 1998[34]	Patients incurred higher costs but outcomes better with olanzapine treatment
Clozapine versus before-clozapine	Drew 1999[311] Blieden 1998[313] Percudani 1999[309]	Decreased total costs associated with clozapine; increased efficacy and fewer side-effects suggest that clozapine is dominant
Atypical versus atypical antipsychotic drugs		
Risperidone versus olanzapine	Palmer 1998[316] Kasper 2000[329] Loos 2000[331] Martin 2000[332] De Hert 2000[330] Almond 2000[326] Bille 1999[337] Duchesne 1999[336] Edgell 2000[170]	Three of six reported olanzapine more costly than risperidone; however, olanzapine considered to increase effectiveness at reasonable cost. In Edgell study, olanzapine dominated risperidone. In Bille and Duchesne studies, risperidone more cost-effective than olanzapine
Sertindole versus olanzapine	Launois 1998[321]	Sertindole dominated olanzapine in France, Germany and Great Britain

TABLE 61 *Unit costs associated with resources*

Resource	Unit cost (£)		
	Mean	Minimum	Maximum
Patient care			
Inpatient day[a]	160.86	0	378.36
Outpatient visit[a]	121.5	38	205
Day case[b]	53	42	66
Community services[b]	27.55	17	51.2
Antipsychotic drugs			
Chlorpromazine daily	0.29	0.20	0.37
Haloperidol daily	0.45	0.24	0.72
Risperidone daily	3.23	2.57	3.90
Clozapine daily	4.02	2.68	5.36
Olanzapine daily	4.35	1.74	6.96
Quetiapine daily	4.24	3.77	4.71
Zotepine daily	2.29	1.43	3.15
Ziprasidone daily	Commercial-in-confidence: data removed		
Amisulpride daily	3.00	2.00	4.00
Sertindole daily	3.05	1.22	3.66
Other drugs			
Anticholinergic drugs daily	0.06		
Beta adrenergic blocker (propanol, 40 mg) daily	0.02		
Anticonvulsant drug (valproate, 1 g) daily	0.29		

[a] *Chartered Institute of Public Finance and Accountancy (CIPFA)*[342]
[b] *Personal Social Sciences Research Unit (PSSRU)*[343]

than for atypical antipsychotic drugs, which may favour any comparisons between the atypical drugs and clozapine.

The study by Glennie[18] only produced utility ratings for clozapine, chlorpromazine, risperidone and haloperidol; hence, the utility ratings associated with scenarios for olanzapine, quetiapine, zotepine, amisulpride, ziprasidone and sertindole were presumed to be the same as for risperidone. In order not to totally discount the values produced by Chouinard and Albright,[20] these were used to determine the lower bound of the CI in the Monte Carlo simulation, rather than the Glennie values, whose original CIs appeared narrow.

The quality-adjusted life-days of events derived from the model are presented in appendix 12, with an indication of the utility estimates to which a distribution was fitted in the simulation.

Expected costs and outcomes

The simulated expected costs and outcomes from the model are shown in *Table 62*. The estimates of the probability of patients switching their initial therapy would suggest that ziprasidone and amisulpride were the most effective and olanzapine, zotepine and quetiapine were the least effective, as more patients required a change in initial therapy. The other comparators, chlorpromazine, haloperidol, clozapine, risperidone and sertindole, fell somewhere in the middle. However, inspection of the CIs in *Table 61* shows the relatively high degree of uncertainty that surrounded the point estimates of effect and cost.

The expected costs and QALYs for each of the evaluated drugs are also shown in *Table 62*.

In *Table 63*, the drug comparisons that were dominant are shown (i.e. the drug was less costly and more effective), together with the incremental cost-effectiveness ratios (ICERs) for the non-dominant comparisons according to their cost per QALY (ICERs and CIs are also presented in appendix 12). The CIs were calculated using standard parametric assumption, suggested by Willan and O'Brien;[344] however, it was noted that this approach was likely to yield conservative CIs for the ICER, with an interval wider than the nominal 95% level. The results for chlorpromazine and haloperidol should be interpreted with some degree of caution because, as noted earlier, estimates of treatment effect for these two drugs were not derived from the systematic review but were simply taken from the control arms of the trials of atypical antipsychotic drugs.

Given that the choice of treatment was between atypical compounds, then the least expensive was olanzapine, although, again, an inspection of the CIs for both costs and effects showed some uncertainty associated with its use. Zotepine gave the second lowest costs and higher QALYs than olanzapine. Ziprasidone was an alternative to zotepine that appeared to be more effective at a reasonable cost. However, given the level of uncertainty within the analyses, although ziprasidone appeared to dominate amisulpride, the cost and QALY CIs were wide and these differences were not statistically significant; thus amisulpride could be seen as a reasonable alternative to ziprasidone. The remainder of the atypical antipsychotic drugs fell in between these extremes in terms of costs and QALYs.

TABLE 62 *Expected costs and outcomes of therapy (normal distribution)*

Comparator	Expected costs (95% CI) £	Expected QALYs (95% CI)	Probability of switching initial therapy
Chlorpromazine			
1st line	12,534 (12,502 to 12,567)	0.57 (0.569 to 0.572)	0.22
2nd line	9,870 (9,858 to 9,882)	0.65 (0.644 to 0.649)	
3rd line	9,868 (9,856 to 9,880)	0.64 (0.643 to 0.646)	
Final line	9,947 (9,935 to 9,960)	0.65 (0.649 to 0.653)	
Haloperidol			
1st line	13,238 (13,198 to 13278)	0.55 (0.582 to 0.557)	0.25
2nd line	10,478 (10,484 to 10933)	0.61 (0.607 to 0.612)	
3rd line	10,499 (10,479 to 10519)	0.61 (0.61 to 0.615)	
Final line	10,724 (10,702 to 10745)	0.63 (0.627 to 0.632)	
Clozapine			
1st line	13,475 (13,430 to 13520)	0.55 (0.547 to 0.552)	0.24
2nd line	10,909 (10,884 to 10933)	0.62 (0.619 to 0.625)	
3rd line	10,898 (10,875 to 10922)	0.62 (0.620 to 0.625)	
Final line	10,963 (10,941 to 10990)	0.63 (0.623 to 0.629)	
Olanzapine			
1st line	10,802 (10,743 to 10860)	0.42 (0.415 to 0.422)	0.46
2nd line	9,057 (9,018 to 9095)	0.48 (0.475 to 0.483)	
3rd line	9,028 (8,989 to 9067)	0.48 (0.472 to 0.480)	
Final line	9,055 (9,017 to 9095)	0.48 (0.475 to 0.483)	
Quetiapine			
1st line	11,579 (11,532 to 11625)	0.44 (0.441 to 0.446)	0.39
2nd line	9,545 (9,517 to 9573)	0.50 (0.501 to 0.507)	
3rd line	9,563 (9,535 to 9591)	0.51 (0.50 to 0.509)	
Final line	9,548 (9,520 to 9576)	0.50 (0.501 to 0.507)	
Zotepine			
1st line	11,840 (11,802 to 11878)	0.52 (0.514 to 0.518)	0.32
2nd line	9,483 (9,463 to 9502)	0.58 (0.577 to 0.582)	
3rd line	9,489 (9,470 to 9508)	0.58 (0.578 to 0.582)	
Final line	9,512 (9,492 to 9531)	0.58 (0.578 to 0.583)	
Risperidone			
1st line	13,798 (13,749 to 13847)	0.62 (0.612 to 0.618)	0.15
2nd line	10,917 (10,891 to 10947)	0.70 (0.693 to 0.70)	
3rd line	10,919 (10,891 to 10947)	0.70 (0.692 to 0.699)	
Final line	10,990 (10,961 to 11018)	0.70 (0.699 to 0.706)	
Ziprasidone			
1st line	14,477 (14,447 to 14506)	0.66 (0.652 to 0.660)	0.08
2nd line	11,394 (11,388 to 11401)	0.75 (0.746 to 0.75)	
3rd line	11,393 (11,386 to 11399)	0.75 (0.746 to 0.75)	
Final line	11,418 (11,412 to 11423)	0.75 (0.747 to 0.751)	
Amisulpride			
1st line	15,295 (15,266 to 15325)	0.66 (0.662 to 0.665)	0.06
2nd line	11,956 (11,949 to 11963)	0.75 (0.747 to 0.75)	
3rd line	11,959 (11,951 to 11966)	0.75 (0.747 to 0.75)	
Final line	12,131 (12,123 to 12139)	0.76 (0.760 to 0.764)	
Sertindole			
1st line	12,286 (12,246 to 12327)	0.53 (0.532 to 0.537)	0.29
2nd line	9,941 (9,920 to 9963)	0.61 (0.606 to 0.611)	
3rd line	9,948 (9,927 to 9970)	0.61 (0.606 to 0.611)	
Final line	9,976 (9,948 to 9991)	0.61 (0.608 to 0.613)	

TABLE 63 *Comparison of cost-effectiveness*

Interventions that dominate		
Intervention A (dominates)	**Intervention B (is dominated)**	
Chlorpromazine	Haloperidol (1st, 2nd, 3rd, final); clozapine (2nd, 3rd, final); sertindole (2nd, 3rd)	
Haloperidol	Clozapine (final)	
Ziprasidone	Amisulpride (1st, 2nd, 3rd)	
Sertindole	Haloperidol (2nd, 3rd)	
Zotepine	Quetiapine (2nd, 3rd, final)	
Intervention A	**Intervention B (higher costs + higher effectiveness)**	**ICER**
Cost per QALY < £10,000		
Chlorpromazine	Quetiapine	8,027 (1st line); 2,166 (2nd line); 2,346 (3rd line); 2,660 (final line)
Chlorpromazine	Sertindole	9,850 (1st line); 725 (final line)
Chlorpromazine	Olanzapine	4,782 (2nd line); 5,250 (3rd line); 5,247 (final line)
Chlorpromazine	Zotepine	5,528 (2nd line); 6,316 (3rd line); 6,214 (final line)
Clozapine	Ziprasidone	7,866 (1st line); 4,850 (2nd line); 3,535 (3rd line); 3,791 (final line)
Clozapine	Risperidone	3,733 (1st line); 160 (2nd line); 2,625 (3rd line); 385 (final line)
Clozapine	Amisulpride	8,161 (3rd line); 8,984 (final line)
Olanzapine	Zotepine	8,763 (1st line); 4,260 (2nd line); 4,610 (3rd line); 4,570 (final line)
Olanzapine	Risperidone	8,454 (2nd line); 8,595 (3rd line); 8,795 (final line)
Olanzapine	Ziprasidone	8,655 (2nd line); 8,759 (3rd line); 8,751 (final line)
Olanzapine	Sertindole	6,800 (2nd line); 7,076 (3rd line); 7,084 (final line)
Quetiapine	Zotepine	3,100 (1st line)
Quetiapine	Ziprasidone	8,370 (1st line); 7,396 (2nd line), 7,625 (3rd line); 7,480 (final line)
Quetiapine	Sertindole	7,622 (1st line); 3,600 (2nd line), 3,850 (3rd line); 3,890 (final line)
Quetiapine	Amisulpride	9,644 (2nd line); 9,983 (3rd line); 9,934 (final line)
Quetiapine	Risperidone	6,860 (2nd line); 7,136 (3rd line); 7,210 (final line)
Haloperidol	Quetiapine	8,481 (2nd line); 7,200 (3rd line); 9,046 (final line)
Haloperidol	Risperidone	6,237 (1st line); 8,780 (2nd line); 7,000 (3rd line); 3,800 (final line)
Haloperidol	Ziprasidone	9,160 (2nd line); 8,127 (3rd line); 5,783 (final line)
Haloperidol	Olanzapine	9,193 (3rd line)
Ziprasidone	Sertindole	1,415 (1st line)
Risperidone	Ziprasidone	8,561 (1st line); 9,540 (2nd line); 9,480 (3rd line); 8,560 (final line)

continued

***TABLE 63* contd** *Comparison of cost-effectiveness*

Intervention A	Intervention B (higher costs + higher effectiveness)	ICER
Cost per QALY < £20,000		
Haloperidol	Olanzapine	16,835 (1st line); 14,246 (2nd line)
Haloperidol	Amisulpride	18,700 (1st line); 14,780 (2nd line); 13,272 (3rd line); 10,823 (final line)
Haloperidol	Ziprasidone	11,263 (1st line)
Haloperidol	Clozapine	12,750 (1st line)
Haloperidol	Quetiapine	16,100 (1st line)
Haloperidol	Olanzapine	11,126 (final line)
Clozapine	Quetiapine	15,541 (1st line); 11,366 (2nd line); 12,136 (3rd line); 10,884 (final line)
Clozapine	Amisulpride	15,241 (1st line); 10,470 2nd line)
Clozapine	Olanzapine	16,325 (1st line); 13,228 (2nd line); 13,357 (3rd line); 12,720 (final line)
Chlorpromazine	Zotepine	16,650 (1st line)
Chlorpromazine	Olanzapine	10,866 (1st line)
Chlorpromazine	Risperidone	17,514 (1st line); 17,516 (3rd line)
Chlorpromazine	Ziprasidone	14,815 (1st line); 15,240 (2nd line); 13,872 (3rd line); 14,710 (final line)
Chlorpromazine	Amisulpride	19,009 (3rd line); 19,854 (final line)
Olanzapine	Ziprasidone	12,700 (1st line)
Olanzapine	Risperidone	12,981 (1st line)
Olanzapine	Amisulpride	15,860 (1st line); 10,737 (2nd line); 10,855 (3rd line); 10,985 (final line)
Olanzapine	Quetiapine	17,833 (3rd line); 24,650 (final line)
Olanzapine	Sertindole	11,100 (1st line)
Quetiapine	Risperidone	11,716 (1st line)
Quetiapine	Amisulpride	15,391 (1st line)
Risperidone	Amisulpride	19,000 (final line)
Risperidone	Sertindole	15,811 (1st line); 10,844 (2nd line); 10,788 (3rd line); 11,266 (final line)
Ziprasidone	Sertindole	10,378 (2nd line); 11,115 (3rd line); 10,300 (final line)
Amisulpride	Sertindole	16,853 (1st line); 14,392 (2nd line); 14,364 (3rd line); 14,366 (final line)
Zotepine	Risperidone	17,200 (1st line); 11,950 (2nd line); 11,916 (3rd line); 12,316 (final line)
Zotepine	Amisulpride	14,547 (2nd line); 14,529 (3rd line); 14,550 (final line)
Zotepine	Sertindole	15,266 (2nd line); 15,300 (3rd line); 15,466 (final line)
Zotepine	Ziprasidone	15,247 (1st line); 11,241 (2nd line); 11,200 (3rd line); 11,211 (final line)

continued

***TABLE 63* contd** *Comparison of cost-effectiveness*

Intervention A	Intervention B (higher costs + higher effectiveness)	ICER
Cost per QALY < £40,000		
Chlorpromazine	Risperidone	20,340 (2nd line); 20,860 (final line)
Chlorpromazine	Amisulpride	20,860 (2nd line)
Amisulpride	Sertindole	20,053 (1st line)
Risperidone	Amisulpride	26,416 (1st line); 20,708 (2nd line); 20,800 (3rd line)
Zotepine	Sertindole	23,450 (1st line)
Zotepine	Amisulpride	20,452 (1st line)
Haloperidol	Zotepine	33,166 (2nd line); 33,666 (3rd line); 24,240 (final line)
Haloperidol	Clozapine	39,900 (3rd line)
Haloperidol	Sertindole	37,400 (final line)
Olanzapine	Quetiapine	24,400 (2nd line)
Clozapine	Zotepine	32,960 (1st line); 35,650 (2nd line); 35,225 (3rd line); 29,020 (final line)
Cost per QALY < £50,000		
Clozapine	Sertindole	49,350 (final line)
Haloperidol	Clozapine	43,100 (2nd line)
Haloperidol	Zotepine	46,433 (1st line)
Chlorpromazine	Amisulpride	46,016 (1st line)
Cost per QALY > £50,000		
Chlorpromazine	Clozapine	98,200 (1st line)
Clozapine	Sertindole	59,450 (1st line); 96,800 (2nd line); 95,000 (3rd line)
Ziprasidone	Amisulpride	71,300 (final line)

Although additional sensitivity analyses on individual model parameters were not carried out, a probabilistic sensitivity analysis was carried out by simultaneously accounting for the uncertainty in all the model parameters; in addition, the results did not appear to change significantly according to changes in probabilities defined in the model. The probabilities used in an earlier version of the analysis differed in some respects from those shown in appendix 12 – for example, relapse rates for olanzapine treatment had previously been taken from just one trial and estimated to be 0.91, whereas in the current version of the model the estimate used is 0.03. The conclusions regarding the cost-effectiveness of olanzapine relative to its comparators did not differ dramatically from the conclusions previously drawn, although costs were significantly lower.

Industry submissions

Company reports on cost-effectiveness issues were submitted for each of the eight atypical antipsychotic drugs. A summary of each submission is presented in appendix 12. The levels of agreement between published literature, industry submissions and the economic models conducted as part of this review are presented in *Table 64*.

TABLE 64 *Comparison of results*

Comparison	Review evidence	Industry evidence	Economic model	Comments
Risperidone versus haloperidol	Risperidone less costly and more cost-effective than haloperidol	Total medical costs $636 lower than in haloperidol group. Model-based evaluations favoured risperidone[a,b] UK model (from original study) showed first-line therapy risperidone most cost effective	Risperidone has higher costs but associated with better outcomes	Agreement between all three forms of evidence that risperidone more cost-effective than haloperidol
Risperidone versus olanzapine	3/6 studies reported olanzapine more costly than risperidone; however, olanzapine considered to increase effectiveness at reasonable cost	Incremental cost per QALY for olanzapine compared with risperidone, £859 (olanzapine submission) Risperidone more cost-effective than olanzapine based on RODOS results (risperidone submission) Review of other models and trial-based studies supported this finding	Risperidone more costly but associated with better outcomes	Disagreement between three methods and our model and one of the industry submissions suggesting that risperidone more cost-effective
Olanzapine versus haloperidol	Olanzapine more cost-effective than haloperidol	Favoured olanzapine in terms of total costs, incremental cost per life-year saved; olanzapine also dominant to first-line haloperidol, based on results of cost–utility model	Haloperidol more costly but associated with better outcomes	Considerable uncertainty in estimates of costs and outcomes for olanzapine in our model
Clozapine versus typical and atypical antipsychotic drugs	Patients appeared to have fewer general symptoms and lower costs while receiving atypical antipsychotic drugs	Discreet event simulation model concluded clozapine patients had more well days but costs to pharmacy budget increased; savings found in terms of total costs	Clozapine has higher costs but higher QALYs than olanzapine, quetiapine, zotepine and sertindole. It is dominated by chlorpromazine for all lines apart from first	Contradicting conclusions between economic model and published/industry evidence; however, unclear whether chlorpromazine used a typical comparator and not haloperidol
Sertindole versus atypical and typical antipsychotic drugs	–	Model results show sertindole more effective but more costly than risperidone, and more effective and less costly than olanzapine and haloperidol	Sertindole has higher costs than zotepine, quetiapine and olanzapine but does not give significantly better outcomes. It is unlikely to represent a cost-effective option compared with many of other atypical antipsychotic drugs. Dominated by chlorpromazine for 2nd and 3rd line but dominates haloperidol for 2nd and 3rd line therapy	Contradictory conclusions to industry submission

continued

***TABLE 64* contd** *Comparison of results*

Comparison	Review evidence	Industry evidence	Economic model	Comments
Zotepine versus typical and atypical antipsychotic drugs	–	5-year Markov model showed zotepine to be least expensive drug compared with risperidone and olanzapine, and second to haloperidol	Zotepine dominates quetiapine for all lines except first; has lower costs than risperidone, amisulpride and sertindole but also associated with lower QALYs	Agreement with estimates of cost compared with risperidone; economic model showed olanzapine had lower costs and haloperidol higher cost. Estimate of total cost dependant on items included, however
Ziprasidone versus atypical and typical antipsychotic drugs	–	Ziprasidone most cost-effective treatment option compared with haloperidol, risperidone and olanzapine	Ziprasidone dominates amisulpride for all lines except final; it has higher costs but higher QALYs than clozapine, olanzapine, chlorpromazine, risperidone, sertindole, zotepine, quetiapine and haloperidol	Agreement between industry submission and economic model conclusions
Amisulpride versus haloperidol	–	Souetre *et al.*[c] showed £545 cost difference between amisulpride and haloperidol in favour of amisulpride Amisulpride versus risperidone (AMIRIS) trial results showed total costs were £2145 less for amisulpride compared with haloperidol	Amisulpride has better outcomes but higher costs	Contradictory results: economic model showed amisulpride associated with better outcomes but slightly higher costs
Quetiapine versus haloperidol	–	Markov model showed quetiapine total costs £217 lower than haloperidol over 5 years	Haloperidol more costly but associated with better outcomes	Agreement between sources of evidence

RODOS, Risperidone Olanzapine Drug Outcomes study in Schizophrenia
[a] *Davies A,* et al. Clin Ther *1998;**20**:196–213*
[b] *Lecomte P,* et al. Value in Health *2000;**3**:1–11*
[c] *Souetre E,* et al. Encephale *1992;**18**:263–9 (in French)*

Chapter 14
Discussion

Major findings

Amisulpride

Amisulpride was more acceptable to patients with schizophrenia than placebo, as suggested by the attrition rates. This was true in both the short and the long term. Those taking amisulpride for more than 6 months were more likely to experience extrapyramidal side-effects than those taking placebo.

In the short term, fewer participants taking amisulpride left trials early than those taking typical antipsychotic drugs, which suggests that amisulpride may have been more acceptable to individuals with schizophrenia than typical antipsychotic drugs. Amisulpride seemed to be as effective as or slightly more effective than haloperidol, fluphenazine or flupenthixol in improving mental state and more effective in improving global response. Those taking amisulpride may have experienced fewer side-effects than those taking typical antipsychotic drugs and they may have experienced fewer movement disorders, daytime sleepiness and neurological side-effects. Amisulpride may also have been significantly more likely than typical antipsychotic drugs to cause weight gain in the long term.

In one trial that compared amisulpride with olanzapine, no differences were found between the two drugs in terms of effectiveness or attrition rates.

In the two trials that compared amisulpride with risperidone, the results were equivocal in terms of measures of 'response'. Individuals taking risperidone were less likely to experience 'agitation'.

Amisulpride versus ziprasidone: commercial-in-confidence data removed.

No published economic evaluations of amisulpride were found but the data submitted by the manufacturers suggested that costs for amisulpride were between £545 and £2145 less than those for haloperidol. The economic model also suggested that amisulpride was associated with marginally higher costs than haloperidol but that the increase in QALYs was about 0.13.

Clozapine

Clozapine may have been more effective than typical antipsychotic drugs in preventing relapse in patients with treatment-responsive illness, and in promoting clinical improvement in individuals with both previously treatment-responsive and treatment-resistant illness. It may also have been more acceptable in the long term, as suggested by fewer people dropping out of groups treated with clozapine than those treated with typical antipsychotic drugs. When asked directly, participants were no more satisfied with clozapine than with typical antipsychotic drugs in the short term. Higher incidences of increased salivation, drowsiness and increased temperature were seen in clozapine-treated groups, whereas a higher incidence of dry mouth or EPS was seen in groups treated with typical antipsychotic drugs. Individuals treated with clozapine in three small RCTs were no more likely to gain weight than those treated with typical antipsychotic drugs (although clinical experience did suggest that clozapine does cause more weight gain than typical antipsychotic drugs). However, compared with risperidone and olanzapine, similar numbers of those treated with clozapine gained weight and both risperidone and olanzapine showed a greater risk of weight gain when compared with typical antipsychotic drugs (see below). This may suggest that had weight gain been measured in more clozapine versus typical antipsychotic drugs trials, the result could have been different. There were no differences in the RCT evidence between clozapine and typical antipsychotic drugs in the tendency to cause fits or blood problems in the long term (blood problems were more likely with clozapine in the short term).

Clozapine was also better than typical antipsychotic drugs in promoting clinical improvement in those with treatment-resistant illness in the long term, and fewer of those taking clozapine left trials early. In the short term, in addition to the side-effects already mentioned, clozapine was less likely to cause low blood pressure, dizziness or dry mouth, and more likely to cause fits than typical antipsychotic drugs. The incidence of movement disorders in those with treatment-resistant schizophrenia was not significantly different between those

treated with clozapine and those treated with typical antipsychotic drugs.

In one small study, almost half of the clozapine-treated children and adolescents developed blood problems, so the use of clozapine in this subgroup must be undertaken with extreme caution.

Olanzapine and risperidone were no more or less beneficial than clozapine. Fewer people treated with olanzapine than with clozapine suffered nausea and vomiting, orthostatic dizziness, hypersalivation, dizziness and constipation.

Patients taking risperidone were more likely than those taking clozapine to experience EPS, dry mouth, insomnia and impotence. Individuals taking clozapine were more likely than those taking risperidone to experience fatigue, hypersalivation and tachycardia. When zotepine was compared with clozapine, no differences were seen in attrition rates.

Non-randomised studies provided inconclusive evidence that clozapine may be associated with a reduced incidence of suicide; however, one study suggested that clozapine may increase the risk of sudden death. In the highest quality, non-randomised study on mortality, no excess mortality was reported for clozapine. NMS did not appear to be more common with clozapine than with risperidone (results of one study). Recent observational studies of blood problems did not suggest an increased incidence of blood problems compared with typical antipsychotic drugs; a large increase was seen in a longer-term study but this presumably included the period before the introduction of weekly blood monitoring for clozapine-treated patients. Substantial weight gain over 12 months was reported with clozapine in one retrospective chart review.

In one database-mining study, cardiomyopathy or myocarditis was reported to be less common with clozapine than with other antipsychotic drugs, and in a retrospective controlled study, less tardive dyskinesia was observed in clozapine-treated individuals than in those treated with typical antipsychotic drugs. As the study participants were individuals with schizophrenia, and mostly with its treatment-resistant form (in keeping with clozapine's licensed indications), it was not possible to predict if the results were applicable to patients with their first psychosis.

Published economic evaluations suggested that other atypical antipsychotic drugs had lower costs and that those receiving them had fewer symptoms than those receiving clozapine or typical antipsychotic drugs. Submissions from the manufacturers of clozapine indicated that clozapine patients had greater numbers of well days but that costs to the pharmacy budget increased; however, savings in terms of total costs were found with clozapine. The economic model suggested that clozapine seemed to represent a more cost-effective option than quetiapine, olanzapine, zotepine and sertindole. Clozapine may be marketed by a generic manufacturer at a lower price in the near future, as it is now 'off patent'. If lower-priced generic forms are marketed, this will have favourable implications for cost-effectiveness; however, weekly blood monitoring will still be necessary.

Olanzapine

Individuals treated with olanzapine were less likely than those treated with placebo to leave a study early owing to lack of efficacy.

Olanzapine may be better than typical antipsychotic drugs in terms of 'response' and social functioning. Individuals treated with olanzapine needed fewer antiparkinsonian drugs than those treated with typical antipsychotic drugs and had lower incidences of blurred vision, hypersalivation, difficulty with urination, orthostatic changes, EPS, nausea and vomiting, and drowsiness. Before 6 months and after 12 months, fewer participants dropped out of olanzapine-treated groups than out of groups treated with typical antipsychotic drugs but, between 6 and 12 months, there were no significant differences in attrition rates. Olanzapine-treated patients had an increased appetite compared with those taking typical antipsychotic drugs but weight gain data showed no significant differences between groups. Relapse rates were reported in only one study, and this was excluded from the effectiveness analysis as more than 50% of participants left the study early; however, relapse rates in this study were very high.

In patients with treatment-resistant illness, olanzapine caused fewer orthostatic changes, dyskinetic movements and dry mouth than typical antipsychotic drugs.

The two RCTs of an intramuscular preparation of olanzapine contained too few data to use in the meta-analysis but the results did indicate a similar effectiveness to intramuscular haloperidol in acutely agitated people.

Olanzapine was superior to haloperidol in a subgroup of participants in one trial with schizoaffective disorder.

Olanzapine was superior to haloperidol and caused less EPS in a subgroup of participants from one trial with first-episode psychosis.

When compared with atypical antipsychotic drugs, olanzapine caused less long-term attrition, less EPS and less new 'parkinsonism' than risperidone but was associated with a greater incidence of dry mouth and was more likely to cause an increase of at least 7% in body weight at 3 months. The results for olanzapine were not significantly different from those for clozapine for all effectiveness outcomes in patients with treatment-resistant schizophrenia. Individuals taking olanzapine were less likely to experience constipation, dizziness, nausea or increased salivation than those taking clozapine.

No differences were seen between olanzapine- and amisulpride-treated participants in terms of leaving the study early or effectiveness.

Olanzapine versus ziprasidone: commercial-in-confidence data removed.

Non-randomised studies of mortality indicated that olanzapine might be associated with fewer suicide attempts than haloperidol and at an identical rate to risperidone. All-cause mortality studies did not appear to suggest any difference between sertindole, risperidone and olanzapine. A controlled prospective study found that olanzapine was significantly more likely than risperidone or haloperidol to cause weight gain (follow-up RCT data indicated a mean weight change of 6.26 kg after approximately 2.5 years). A pooled analysis of the results of three RCTs found a much lower incidence of tardive dyskinesia in olanzapine-treated patients than in haloperidol-treated patients. In one study, one case of NMS was found in 8858 patients given olanzapine.

Published economic evaluations suggested that olanzapine was more cost-effective than haloperidol; the manufacturer's submission supported this and also found that it was more effective than risperidone (however, it should be noted that the risperidone manufacturer's submission found in favour of risperidone). The economic model would suggest that haloperidol was cost-effective compared with olanzapine. However, as previously noted, the results from the typical antipsychotic drugs included in the model should be interpreted with some caution, as estimates of effect were not derived in the same way as the atypical data. The model also found that risperidone was associated with more costs but better outcomes than olanzapine.

Quetiapine

The attrition rate was high in all trials; hence, the results of this review must be treated with caution. Attrition was lower in the quetiapine group than in the placebo and typical antipsychotic drugs groups, although these results were only of borderline significance. Individuals taking quetiapine were more likely than those taking placebo to see an improvement in their mental state; however, they were also more likely to experience dizziness and a dry mouth.

Quetiapine versus placebo: commercial-in-confidence data removed.

Quetiapine did not appear to be any more or less effective than typical antipsychotic drugs but it was less likely to cause parkinsonism and akathisia, and those taking quetiapine were less likely to need antiparkinsonian medication. It may have caused significantly more constipation, sleepiness, low blood pressure and dry mouth than typical antipsychotic drugs.

When high-dose quetiapine was compared with low-dose quetiapine, a lower attrition rate was seen in the high-dose group. Patients on high-dose quetiapine were possibly more likely to improve clinically than those on low-dose quetiapine but this result was only of borderline significance. Those in the low-dose group experienced less dizziness than those in the high-dose group.

In one RCT quetiapine was compared with risperidone – quetiapine may have been more likely to improve depression and less likely to cause EPS than risperidone.

Quetiapine versus risperidone: commercial-in-confidence data removed.

In two non-randomised studies of weight change, a gain in weight of 1.38–3.83 kg was reported after 9–12 months of quetiapine treatment.

No published economic evaluations of quetiapine were found. The manufacturer's submission suggested that quetiapine total costs were £217 lower than haloperidol over 5 years. The economic model suggested that haloperidol was more costly than quetiapine but was associated with better

outcomes (possibly owing to the high attrition rates in the quetiapine studies). In comparison to other atypical antipsychotic drugs, quetiapine would seem to be no more or less cost-effective than many of the other comparators.

Risperidone

Risperidone appeared to have a greater effect than typical antipsychotic drugs in improving mental state; however, typical antipsychotic treatments have a greater effect on verbal learning skills in the long term. Patients taking risperidone were less likely to experience relapse within 1 year than those taking haloperidol. Risperidone had an advantage over haloperidol in that it had a reduced tendency to cause movement disorders, although haloperidol is particularly prone to cause these. Risperidone appeared to be more acceptable than haloperidol, as fewer people left the study early. Those taking risperidone were also less likely to experience daytime sleepiness in the long term. Risperidone did, however, make weight gain more likely than haloperidol in the short term. For risperidone versus haloperidol, the response of individuals experiencing first-episode schizophrenia was similar to that for all patients. Patients with schizoaffective disorder (data from one trial) experienced fewer extrapyramidal side-effects with risperidone than with haloperidol, with no differences between groups in terms of mental state. The responses of elderly patients with schizophrenia did not differ from those for all patients (one study).

There were too few data available from this review to guide clinical practice when considering risperidone for those with predominantly negative symptoms.

Risperidone did, however, seem to be equally acceptable as clozapine to those people with schizophrenia who were intolerant of older antipsychotic drugs but was associated with more movement disorders. Risperidone was less likely than clozapine to cause tachycardia and hypersalivation, and more likely to cause dry mouth, impotence and insomnia.

Olanzapine seemed to be more acceptable to patients than risperidone in terms of leaving studies of more than 6 months' duration early. Individuals taking olanzapine experienced fewer movement disorders than those taking risperidone, but more short-term weight gain and dry mouth. However, these studies had high attrition rates and the results should be viewed with caution.

Risperidone seemed to be less effective than amisulpride in terms of measures of 'response'. Those taking risperidone were less likely to experience agitation. There were no other differences between the two drugs in terms of side-effects.

Quetiapine may have been more effective than risperidone in improving depression. Participants taking risperidone were more likely than those taking quetiapine to experience movement disorder side-effects.

Quetiapine versus risperidone: commercial-in-confidence data removed.

Ziprasidone versus risperidone: commercial-in-confidence data removed.

The results of a non-randomised retrospective database study suggested that the all-cause mortality rate for risperidone was higher than that for olanzapine or sertindole. Pooled data from RCTs and open-label studies suggested a tardive dyskinesia rate approximately five times greater for haloperidol than risperidone. In the same study, a mean weight gain of 3.3 kg was reported after 1 year of risperidone treatment. Risperidone was reported to be associated with a rate of NMS similar to that for clozapine but approximately ten times less than that for 'other agents'.

Published economic evaluations suggested that risperidone was less costly and more cost-effective than haloperidol and the manufacturer's submission supported this – their UK model showed that, for first-line therapy, risperidone was the most cost-effective antipsychotic drug. The manufacturer's submission also found in favour of risperidone compared with olanzapine but the olanzapine submission found the opposite. The economic model suggested that risperidone had higher costs but more QALYs than haloperidol for all lines of therapy. Risperidone was found to be more costly than olanzapine but associated with better outcomes.

Sertindole

Sertindole was more likely to bring about an improvement in global state than placebo. When sertindole was compared with haloperidol, less attrition was seen in the sertindole-treated group and, at a dose of 24 mg, these patients were as likely to respond to treatment in terms of improvement as those taking haloperidol. Those taking sertindole were more likely to have a Q-Tc interval of more than 500 ms and

were also more likely to gain weight, experience postural hypotension and abnormal ejaculation, and to have a blocked nose. They were less likely to experience akathisia, hypertonia, tremor or psychiatric hospitalisation.

Sertindole non-randomised studies: commercial-in-confidence data removed.

There were no published economic evaluations of sertindole. Commercial-in-confidence data removed.

In the economic model, sertindole was found to be more effective but more costly than olanzapine, and less effective and less costly than risperidone and amisulpride.

Ziprasidone

Most of the included studies had high rates of attrition, so all results should be viewed with caution. Ziprasidone was more effective than placebo for mental state outcomes. Fewer people left the ziprasidone-treated group than the placebo group owing to lack of efficacy. Those on ziprasidone needed less additional sedation than those on placebo; they experienced more daytime sleepiness and were more likely to need antiparkinsonian medication.

Commercial-in-confidence data removed.

Individuals receiving ziprasidone as an injection in the immediate term were less likely to leave the study early than those receiving haloperidol. Ziprasidone may have caused more headache, nausea and vomiting, asthenia and insomnia than haloperidol; however, it caused less akathisia, dystonia, tremor and hypertonia. The injected form caused more pain at the injection site than the injected form of haloperidol.

Ziprasidone versus amisulpride: commercial-in-confidence data removed.

Ziprasidone versus risperidone: commercial-in-confidence data removed.

Ziprasidone versus olanzapine: commercial-in-confidence data removed.

Ziprasidone cost-effectiveness: commercial-in-confidence data removed.

Zotepine

Zotepine was more effective than placebo for mental state outcomes. Fewer people left the zotepine-treated group than the placebo group, perhaps indicating that zotepine was more acceptable than placebo. More people experienced adverse events, particularly somnolence, while taking zotepine.

When zotepine was compared with typical antipsychotic treatments, it was more effective than comparator drugs for mental state outcomes (although when studies with high attrition were removed there was no longer any difference). Negative symptom scale data favoured zotepine over typical antipsychotic drugs. Those taking zotepine experienced less akathisia, dystonia, tremor or rigidity and more tachycardia than those taking typical antipsychotic drugs, and were given less antiparkinsonian medication (although when studies with high attrition rates were removed, there were no differences between groups for akathisia or use of antiparkinsonian medication). Cognitive function was more likely to improve on zotepine than it was on haloperidol.

When zotepine was compared with clozapine and risperidone, individuals taking zotepine were more likely to need antiparkinsonian medication than those taking either of the other drugs.

There were no published economic evaluations of zotepine. The manufacturer's submission showed zotepine to be the least expensive drug compared with risperidone, olanzapine and haloperidol. The economic model showed zotepine to be the least expensive drug compared with risperidone, sertindole and amisulpride.

Volume and quality of the evidence

Number and size of trials

The included studies were generally of short duration, small (underpowered) and failed to report many outcomes in sufficient detail to allow pooling of all possible data. When this was possible, wide CIs were obtained for some outcomes of interest. This made it difficult to be certain whether there was in fact any real difference between the drug under review and its comparators, or whether they were the same in these respects. There was a poor consideration of statistical power on the part of the authors of trial reports. Just because an atypical antipsychotic drug and its comparator have not been shown to be significantly different in effect, it does not follow that they are equivalent in effect; studies that demonstrate equivalence need to be more

highly powered than those that are designed to show a difference. Thus, although many of the atypical antipsychotic drugs were not shown to be significantly different from typical antipsychotic drugs or from each other on measures of efficacy, it was not possible to say with confidence that they were as efficacious as the typical antipsychotic drugs or each other. Similarly, when atypical antipsychotic drugs were not shown to cause significantly more side-effects than placebo, this did not allow the conclusion that they did not cause any side-effects at all.

Few non-randomised studies met the inclusion criteria for rare or adverse events. Those that did rarely used a comparator group and the reviewers were able to conclude little from them.

Generalisability

Many trials were short term, the majority having a duration of only 4–8 weeks. This provided little information about the effect of new antipsychotic drugs on the symptoms of schizophrenia in the long term. The severe clozapine-related side-effect of loss of white blood cells (agranulocytosis), as well as other side-effects such as tardive dyskinesia, may occur later than the first 4–8 weeks of treatment and thus may be under-reported in short-term studies. On the other hand, deficiencies of global and social functioning caused by schizophrenia may take much longer to improve, and the beneficial effect of the antipsychotic drugs under investigation may be underestimated in short-term RCTs.

It was clear that most of the studies were 'efficacy' trials that allowed few comments on the comparative 'effectiveness' of these drugs as they might be used in routine clinical practice.

The setting also compromised the generalisability of the trials. Most of the research was undertaken in hospital and may therefore be generalisable to those with acute episodes of schizophrenia; however, the majority of patients have chronic schizophrenia and are treated with maintenance doses of antipsychotic drugs in the community.

The diagnostic criteria of the trials were in almost every case based on either DSM or ICD classification. Rigid inclusion criteria ensured internal consistency but excluded many of the patients who might receive these drugs in routine clinical practice and reduced the 'real world' external validity of the trial results. Certainly it was difficult to generalise to other psychotic patients, such as those with schizophreniform disorder or schizoaffective disorder (although nearly all the ziprasidone RCTs included individuals with schizoaffective disorder, and one risperidone trial included only those with schizoaffective disorder). Many individuals will receive antipsychotic medication for presumed schizophrenia-like disorders in the absence of 'DSM-III-R' psychotic symptoms or before exhibiting continuous disturbance for 6 months (a major DSM-III-R criterion).[66] Similarly, many will have co-existing substance abuse disorders or other co-morbid mental disorders, such as depression. The results of the review can therefore be said to be applicable to those with DSM or ICD schizophrenia. However, they cannot be assumed to be externally valid and generalisable to the large numbers of patients in routine clinical practice who fall outside the rigid DSM-III-R classification system, yet require antipsychotic medication.

Most trials were multicentre, primarily within the developed world.

Trials measured outcome using multiple rating scales not often used in clinical practice and that were sensitive to change, rather than collecting simple dichotomous outcomes. This made it difficult to judge the degree to which results could be extrapolated to real-world patients in real-world settings. For this reason, scale data have not been presented in the main body of this report.

Most trials excluded individuals who had previously been resistant to neuroleptic treatment (with the notable exception of clozapine) or participants with predominantly negative (except for amisulpride) or positive symptoms or first-episode schizophrenia (except for one trial of risperidone and one of olanzapine).

Quality of conduct and reporting of trials

Most of the trial reports were published after the CONSORT [Consolidated Standards for Reporting of Trials] statement[345] that encouraged high standards of trial reporting.

Many were published only as conference abstracts, with many methodological details missing, and the review authors were often not able to obtain these details from the trial authors. Even in full papers, details of methods of randomisation and allocation concealment were missing. Details of statistical analysis were also poor, with many trial authors not conducting either an ITT analysis or one using the last observation carried forward. This could lead to an over-optimistic picture of partici-

pants who leave the trial early; if participants have left a trial it is likely that they will stop taking their medication and their condition is then likely to deteriorate rather than to stay exactly the same. The review authors conducted an ITT analysis using the worst possible outcome for those who were lost to follow-up, wherever possible; however, missing details often meant that it was not possible. Despite the small numbers of participants in the trials, some researchers removed people from analysis post-randomisation, without indicating the original group of allocation. This made ITT analysis impossible.

The procedure by which concealment of allocation took place was seldom described. The trials usually declared only randomisation and double-blind protocol but did not report how these procedures were performed. Double-blindness might be difficult to achieve, particularly in clozapine trials, given the need for routine blood monitoring. The authors might need to demonstrate how this was achieved in the day-to-day running of the trial. The achievement of double-blindness cannot be assumed if authors fail to report how it was achieved, given such logistical difficulties. Poor reporting of randomisation may be associated with wrong estimates of effect.[187,188] This alone should encourage caution in those interpreting the results.

The authors of many papers failed to report important basic information, such as the participant groups' demographic or illness details and the numbers leaving the study early. Outcomes were frequently presented only in graphical format, and the variance of continuous data went unreported. This rendered some continuous data useless for this review and made it impossible to verify the claims of trialists.

Attrition rates were perhaps higher than those seen in routine practice, particularly considering that most participants were recruited and managed in an inpatient setting. Consequently, all the results outlined in this review were based on assumptions about missing data that may be true but were difficult to justify. This may reflect the rigidity of study protocols. The high default rates (> 25%) that are observed when a rigid trial design is imposed on routine care for schizophrenia (or any disorder) suggest that the randomised trial design should more closely replicate routine care. There was no information on the subsequent care of people leaving the trials. The appropriateness of this care might be evaluated with a more pragmatic randomised trial design.

High non-compliance rates among those taking conventional antipsychotic medications orally are generally recognised and expected in routine practice with the use of depot preparations. The relative effectiveness of oral novel antipsychotic versus oral conventional antipsychotic medication is not generalisable to the many individuals who are in receipt of depot medication. Most of the new antipsychotic compounds are not currently available in depot form. Those that have been trialed in injectable form (ziprasidone and olanzapine) seemed to be aimed at rapid sedation of acutely agitated patients rather than at long-term maintenance therapy; however, depot forms of risperidone and of olanzapine are being developed (no trials of these were found).

It was often not possible to calculate event rates for individuals having predominantly positive or negative symptoms of schizophrenia and for those experiencing their first episode of schizophrenia, again because of the small number of full trials with useful data and the inclusion of participants suffering mainly with chronic as opposed to first-episode schizophrenia.

The barely adequate reporting of allocation concealment, possible lack of double-blindness for these outcomes and unclear reasons for loss to follow-up would suggest that estimates of effect of the experimental intervention may be prone to bias.[346]

It is of particular note that the trials of atypical antipsychotic drugs included the work of Dr Borison, whose work recently came under scrutiny; it has been suggested that trials conducted by him may contain falsified data.[347] It was not possible in the timescale of this review to undertake a sensitivity analysis of the effect of excluding trials conducted by Dr Borison, but this would be interesting to undertake in the future. This is particularly relevant to quetiapine, risperidone and clozapine.

Outcomes

Outcome reporting was mainly symptom and physician oriented. Global and functional outcomes, such as dischargeability and working ability were seldom reported. Patient satisfaction was hardly ever reported and family burden was not reported at all. None of the trials reported on service utilisation, economic outcomes or quality of life, or on satisfaction with care directly.

It was disappointing that, in most trials, the acceptability of treatment was not assessed directly by questioning trial participants and their carers.

It was unfortunate that hardly any quality-of-life data were usable, as this outcome is of increasing interest to clinicians, carers and those with schizophrenia. Simple outcomes such as 'no crisis in family life', 'gaining employment', 'avoiding trouble with the police' or 'feeling that life has improved in quality' may have resulted in more comprehensible information. That such outcomes, of key importance to recipients of care, clinicians and managers/policy makers, were absent suggests that these trials were not undertaken primarily to convince these groups of the value of the new drugs.

Future research should ensure that service users are involved in design of trial methodology, outcomes assessed and questions asked, in order for the research to address issues most important to them.

Definitions of improvement differed across trials. This warranted some caution in drawing conclusions, as it was difficult to decide whether results relating to clinical improvement were comparable.

The overall measure of efficacy of trials was often dichotomised from continuous scales (BPRS, PANSS). The validity of dichotomising was, however, unclear, particularly as different trialists used different thresholds to dichotomise data (e.g. 20%, 30% and 40% reductions in PANSS were all used as thresholds). It may be possible to position threshold cut-off points so as to make results appear to favour the drug under review, when a different threshold point would show no difference between groups. Without an explanation of why a particular cut-off point was chosen, dichotomising of data from continuous scales should perhaps be viewed with caution.

In most trials, improvement was defined as a 20% reduction on the BPRS or PANSS scales. This was not likely to mark a clinically significant improvement. Both scales include a restricted range of items relating to various aspects of psychopathology (including positive and negative symptoms). Each of these individual items attracts equal weight. The validity of using a 20% reduction on this scale must be viewed with a degree of caution. It was far from clear whether a 20% reduction in scores represented an externally valid and clinically important improvement in mental state that those with schizophrenia and their clinicians would generally regard as a successful outcome. It is quite possible to record improvements in a small number of the items on these scales to achieve a 20% reduction, while still retaining the most disabling and distressing features of a schizophrenic episode. The CGI scale is different from the BPRS and PANSS. Being less focused on specific symptoms, it takes into account behavioural and social aspects of an individual's day-to-day functioning. It might be argued that by being less focussed on specific aspects of psychopathology, it represents a more valid measure of the overall impact of schizophrenia and treatment on the wider aspects of functioning and quality of life. Although being a crude and imprecise measure of clinical outcome, it is perhaps a more externally valid global measure than BPRS and PANSS.

Some trials reported efficacy as an analysis of variance from the BPRS, CGI and Nurses' Observation Scale for Inpatient Evaluation (NOSIE) endpoint scores or as a maximum percentage improvement, which did not allow the reviewers to extract and compare many data. When mean scores were reported, often no SD was given. The removal of individuals from an analysis can rarely be justified; the rates of attrition reported in this review are from trials in which participants were removed from the analysis.

Some of the outcomes classified as 'movement disorders' included monitoring the use of antiparkinsonian drugs. If those involved in the day-to-day care of the trial participants were not absolutely blinded to the treatment that a participant was receiving, it is likely that bias could occur, particularly with regard to this outcome – that is, those suspected of being on a more typical antipsychotic drug that is known to cause EPS may be more likely to receive prophylactic antiparkinsonian medication.

On the other hand, in assessing the frequency of extrapyramidal adverse effects, it must be remembered that some trialists used anticholinergic add-on medication in the control groups to alleviate neurological side-effects. To this extent the comparison would be biased in favour of the conventional antipsychotic treatments.

It would have been reassuring if the side-effect 'author-defined EPS' had been reported *a priori*. If they are defined *post hoc*, the potential for bias is considerable.

Comment must be made about what appears to be a fairly unsystematic approach to collecting data on side-effects, with few trials reporting on the tools used for collecting data. In other studies the use of a treatment-emergent symptoms checklist was suspected but this was not made clear by the authors.

Because in some trials only side-effects with a frequency of 10% or greater were reported, rare adverse effects will not have been reported. This could be important. If this policy had always been implemented rigorously in drugs trials, the agranulocytosis linked to clozapine and ocular problems associated with thioridazine would have gone unreported. Reports of other trials were equally unhelpful; adverse events were reported only when statistically significant differences occurred between groups. Hence, if a specific side-effect had similar rates of occurrence in both groups it would not have been reported.

For some drugs (e.g. sertindole, amisulpride), no more than three, and in some cases only one, trials considered the same outcome.

Data on mortality were missing from the majority of RCTs. Mortality data from non-randomised studies were, on the whole, unconvincing, being retrospective and lacking comparative data.

Industry sponsorship

Most of the included studies were sponsored by manufacturers of the more expensive atypical antipsychotic drugs. Publication bias (fewer negative studies than expected) had already been seen in the Cochrane review of risperidone versus typical antipsychotic drugs,[14] and it seems likely that the same bias may exist for the other atypical antipsychotic drugs (that is, studies that do not show a positive result for a drug tend to be withheld from the public domain).

Choice of appropriate comparator drugs and their dosage

Most trials in the review used haloperidol as the comparator drug, possibly because most trials were conducted in North America and it is a US Food and Drug Administration requirement for drug licensing that new atypical antipsychotic drugs are compared with haloperidol. Haloperidol is known to have a particularly high incidence of movement disorder side-effects. It would have added much to the debate if other low-cost conventional antipsychotic drugs, such as chlorpromazine and fluphenazine, had been compared with the new atypical antipsychotic drugs in this respect.

There have been two Cochrane reviews of typical antipsychotic drugs compared with placebo. A systematic review of chlorpromazine versus placebo[4] confirmed that chlorpromazine was effective in reducing relapse over 6 months to 2 years and in improving global state (although the placebo response rate was 40%), but was associated with sedation, acute movement disorders, parkinsonism, hypotension and weight gain. A systematic review of haloperidol versus placebo[5] confirmed that haloperidol was also effective in improving global state but was associated with dystonia, akathisia and parkinsonism. The risk of movement disorders seemed to be higher with haloperidol than with chlorpromazine but this was an indirect comparison – the two drugs have not been compared directly in a systematic review.

The doses of the drugs used in the trials are also very important. Comparator drugs may have been given at inappropriately high doses in some trials. This would be most likely to produce a high incidence of EPS in the haloperidol group and lead to bias in the result for 'movement disorders' outcomes in favour of the new drug. A low dose of an atypical antipsychotic drug may give an overly negative view of its effectiveness when compared with an appropriate dose of a comparator drug; however, a high dose of the same drug may lead to an overestimation of the incidence of side-effects compared with the appropriate dose of a comparator drug. A low dose of comparator drug would make the drug under review seem more effective in comparison, a high dose would make it appear to have fewer side-effects than the comparator drug.

The recommended UK doses of all antipsychotic drugs were taken from the *British National Formulary*, March 1999 (it has, however, been suggested that the recommended doses are not those used in practice).

Amisulpride

The recommended dose of amisulpride is 400–800 mg daily for an acute psychotic episode and 50–300 mg daily for chronic schizophrenia with predominantly negative symptoms. Thus the doses of amisulpride given in the trials seem appropriate. The recommended dose of haloperidol is between 3 and 15 mg daily for patients whose illness is not treatment-resistant. None of the trial participants had treatment-resistant

illness, so haloperidol may have been given in an inappropriately high dose in some trials (Delcker 1990,[53] Moeller 1997[57]). The recommended dose for flupenthixol is 3–18 mg daily and for fluphenazine 2.5–10 mg daily. Flupenthixol was given at an inappropriately high dose in one trial (25 mg daily: Hillert, 1994[54]) but the fluphenazine dose was appropriate. The 8 mg daily dose of risperidone given in Fleurot 1997[62] was also higher than current recommendations. Significant results were found in favour of amisulpride for 'neurological' adverse events (short term), 'at least one EPS' (short term) and leaving the study early due to adverse events, all of which were no longer significant when trials using inappropriately high doses of comparator drugs were excluded from the analysis.

Amisulpride may produce fewer extrapyramidal side-effects than typical comparator drugs but when a high dose of a comparator drug is compared with the recommended dose of amisulpride, such conclusions cannot be drawn with confidence.

Clozapine

The recommended dose of clozapine is 200–450 mg daily for acute psychosis and 150–300 mg daily as a maintenance dose. Included trials used doses of clozapine ranging from 50 mg to 900 mg daily; hence, the clozapine dose may have been inappropriately high or inappropriately low in some trials. In treatment-resistant illness the dose tended to be about 400 mg daily. The recommended doses of comparator drugs used in the included trials were as follows, with the actual dose ranges used given in parentheses: chlorpromazine, 150–300 mg daily (25–2000 mg daily); haloperidol, 3–15 mg daily (1–28 mg daily); trifluoperazine, 10 mg daily and above (20–30 mg daily); risperidone, 3–6 mg daily (3–12 mg daily); zotepine, 75–300 mg daily (225 mg daily); olanzapine, 5–20 mg daily (15–25 mg daily). Thus some of the comparator drugs may have been given at inappropriately high or low doses also.

Olanzapine

The recommended dose for olanzapine is 5–20 mg daily. Doses given in the included studies ranged from 1 mg to 25 mg daily. Thus, in some trials, inappropriately high or low doses of olanzapine may have been given. Recommended doses of comparator drugs used in included trials are as follows, with the actual dose ranges used given in parentheses: haloperidol, 3–15 mg daily (1.5–20 mg daily); clozapine, 150–450 mg daily (200–600 mg daily); chlorpromazine, 150–300 mg daily (200–1200 mg daily); fluphenazine, 2.5–10 mg daily (6–21 mg daily); risperidone, 3–6 mg daily (4–12 mg daily); amisulpride, 400–800 mg daily (150 mg daily). Thus, inappropriately high or low doses of the comparator drugs may have been given also.

Quetiapine

The recommended dose of quetiapine is 300–450 mg daily. Doses given in the trials included in this review ranged from 50 mg to 800 mg daily. Thus, in some trials, inappropriately high or low doses of quetiapine may have been used. The recommended doses of comparator drugs used in included trials are as follows, with actual dose ranges used given in parentheses: chlorpromazine, 150–300 mg daily (384 mg daily); haloperidol, 3–15 mg daily (1–16 mg daily). Thus, inappropriately high or low doses of the comparator drugs may also have been given.

Risperidone

In three trials (Chouinard 1993,[255] Marder 1994,[116] Peuskens 1995[263]), multiple fixed doses of risperidone were compared with one fixed dose of haloperidol. The multiple doses of risperidone were pooled together for the purposes of comparison. This meant pooling doses of risperidone of 1 mg or 2 mg daily that were, arguably, sub-therapeutic. Excluding these lower doses, however, did not materially change the results for the principal outcomes of interest.

In most trials, the mean daily dose of haloperidol at endpoint was 10 mg daily or less. If trials in which the dose of haloperidol at endpoint was greater than this are excluded, the beneficial effect of risperidone in causing clinical improvement is no longer statistically significant. However, the magnitude of this change is very small and is most probably attributable to loss of power as a result of excluding trials. Similarly, excluding data from those trials in which higher doses of haloperidol were given does marginally weaken the result relating to leaving trials early, making it no longer statistically significant. Again, this may well be due to loss of power rather than a substantive change in effect. Excluding the higher doses of haloperidol did not materially change the results in terms of extrapyramidal side-effects and the strong beneficial effect of risperidone over the control drug was retained.

Sertindole

The recommended dose of sertindole is 12–20 mg daily. Doses given in the trials included in this

review ranged from 8 mg to 24 mg daily. Thus an inappropriately high or low dose of sertindole may have been used in some trials. The recommended doses of the comparator drug used in the included trials are as follows, with the actual dose used given in parentheses: haloperidol, 3–15 mg daily (10 mg daily).

Ziprasidone

At present there is no recommended daily dose for ziprasidone as it does not have a UK licence. Doses used in the trials included in this review ranged from 4 mg to 200 mg daily. The recommended doses of comparator drugs used in the included trials are as follows, with the actual dose ranges used given in parentheses: haloperidol, 3–15 mg daily (2.5–40 mg daily). Thus haloperidol may have been given at an inappropriately high dose; however, the 40 mg dose was given intramuscularly to acutely psychotic patients.

Zotepine

The recommended daily dose of zotepine ranges from 75 mg to 300 mg daily. Doses given in the included trials ranged from 100 mg to 600 mg daily. Thus in some trials, an inappropriately high or low dose of zotepine may have been used. An inappropriately high or low dose of the comparator drug may also have been used. The recommended doses of comparator drugs used in the included trials are as follows, with actual dose ranges used given in parentheses: haloperidol, 3–15 mg daily (4–20 mg daily); chlorpromazine, 150–300 mg daily (200–600 mg daily); perazine (not licensed in UK), (150–900 mg daily); risperidone, 3–6 mg daily (8 mg daily); clozapine, 200–450 mg daily (150–450 mg daily); remoxipride (not licensed in UK) (400 mg daily); thiothixene (not licensed in UK) (15–60 mg daily). In one trial (Barnas 1987[297,348]), noticeably lower doses of zotepine and haloperidol were used (means: 94.4 mg daily, 4.2 mg daily, respectively) than in other trials.

Limitations of the review

Trial inclusion criteria

Cochrane reviews often only include RCTs because of their methodological rigour, and this leads to less potential for bias in the results. However, as most RCTs of atypical antipsychotic drugs were short term, the reviews contained little information about the rates of potentially serious side-effects that may occur in the long term, such as tardive dyskinesia, hepatic complications and cardiac problems. Agranulocytosis was only specifically looked for in the clozapine trials. Reports of long-term cardiac side-effects with sertindole and, more recently, with clozapine, as well as with older drugs such as thioridazine and pimozide, may indicate a more widespread side-effect among users of antipsychotic drugs but the short-term nature of most investigations made it very difficult to draw any conclusions.

It was for this reason that non-randomised studies that considered these effects were included in this review. However, as mentioned earlier, these were mostly of poor quality and not very informative.

Missing trials

The search strategy used by the Cochrane Schizophrenia Group is very comprehensive and has been supplemented by the NHS Centre for Reviews and Dissemination's own search strategy[16] and updated. However, it is still possible that some trials may have been missed. Problems with translation has meant that data from some RCTs have not yet been included in the review and the short timescale allowed for this update meant that some possibly relevant studies have not been obtained.

Publication bias

For most drugs, the reviewers aimed to test for the presence of publication bias but, unfortunately, were unable to do this since there were insufficient trials with only a limited range of sample sizes. This prevented the construction of funnel plots. However, in the risperidone review, construction of a funnel plot was possible.

The number of unpublished trials submitted by drug manufacturers was smaller than expected (19 in total), except in the case of Pfizer Ltd, who submitted 12 unpublished trials of ziprasidone. Each of the unpublished economic evaluations submitted by the manufacturers found in favour of their drug.

The finding in the risperidone review, using funnel plot analysis, that trials reporting a number of the major outcomes of interest were not evenly distributed is strongly suggestive of a bias in favour of risperidone. There are a number of potential causes of funnel plot asymmetry, including publication bias, language bias, multiple publication bias, poor methodological design among smaller trials, true heterogeneity (e.g. effect size differs according to trial size owing to intensity of intervention) and chance. This

review relied heavily upon published accounts of research comparing risperidone with conventional antipsychotic drugs (largely haloperidol) and steps were taken to avoid multiple publication and language biases. True heterogeneity did not seem to be a factor, since the larger trials did not seem to offer interventions that differed from smaller ones. Asymmetry in favour of risperidone was seen among most of the outcomes reported. The almost-uniform direction of this bias suggests that this was not a purely chance result. Publication bias is a likely explanation for the observed asymmetry.

The exact cause, magnitude and importance of the observed bias is difficult to establish and will only be determined when all the evaluations of risperidone that have been undertaken are in the public domain and available for systematic review. In the meantime, the estimates of the superiority of risperidone, or indeed of any of the other new atypical antipsychotic drugs, should be considered with this potential bias in mind. The true difference between the atypical and conventional antipsychotic drugs is likely to be smaller (or maybe larger) than the estimates given in this review.

Statistical pooling

Participants who dropped out of the trials were added into the numbers of those who experienced adverse side-effects, which could lead to overly pessimistic incidences.

Trials often dichotomised their overall measure of efficacy from continuous scales (BPRS, PANNS) but the validity of dichotomising is unclear, as previously mentioned. Cochrane review authors use dichotomised data preferentially over continuous scale data and also dichotomised scale data when possible, using threshold values suggested by trial authors. This may have biased the results of the review in favour of the atypical antipsychotic drugs, as mentioned earlier.

Interpretation of outcomes

In this review it was assumed that the numbers of people leaving trials early (the attrition rate) was a measure of the non-acceptability of the treatment; however, this may not be the case and acceptability of treatment may not influence attrition rates. In any case, it is only a proxy measure – even if acceptability of treatment does influence attrition rates, it too is probably influenced by other factors. Acceptability of treatment is always better determined by discussion with patients with schizophrenia and their carers directly.

It may not always be appropriate to pool results from typical antipsychotic drugs together for comparison with the drug of interest if the drugs vary in their propensity to cause certain effects, for example, sedation and anticholinergic side-effects. However, all typical antipsychotic drugs have been pooled together for all outcomes in this review for the sake of simplicity in presenting the data. There are drawbacks to both approaches.

Quality of existing Cochrane reviews and ease of use

The four Cochrane reviews[4,5,13,14] that had already been completed before the commencement of this review were assessed for aspects of methodological quality. All four clearly set out inclusion criteria for studies but some may have been a little too inclusive. Two of the four did not specify the primary outcomes of interest. Searching was comprehensive and it is unlikely that any published studies were missed. Quality assessment focussed on allocation concealment and it is a moot point whether studies that did not state that they were randomised but did state that they were double-blind should be included in the review (as in two of the four studies) or be listed as awaiting assessment. Other aspects of quality (including sponsorship by drug manufacturers) were often used in sensitivity analyses and, in one review > 50% attrition was used as a reason for excluding studies. Two of the four studies inappropriately used ORs as summary estimates when RRs should have been used as the event rates were high. These were converted into RRs for this review. Study details were well reported in all four reviews.

Other systematic reviews of more than one atypical antipsychotic drug

In a systematic review of four of the new atypical antipsychotic drugs,[205] quetiapine was found to be equally as likely as typical antipsychotic drugs to improve symptoms but to cause less attrition and movement disorders. Patients taking quetiapine were less likely to receive additional antiparkinsonian medication. Compared with haloperidol, negative symptoms worsened on quetiapine but, compared with chlorpromazine, were equivalent. Quetiapine was not compared with each comparator drug separately in the Cochrane review,[348a] and was found to be equivalent to comparator drugs in relieving negative

symptoms; quetiapine may also have caused less attrition than placebo but not than typical antipsychotic drugs. Movement disorders were found to occur equally in both groups in the Cochrane review. The more positive findings for quetiapine in the Leucht review[205] may be explained by the handling of data in the ITT analysis. In the Cochrane review, missing data were replaced by 'bad' outcomes; in the Leucht review the last observation was carried forward.

In the same review,[205] individuals taking risperidone were found to have improved more and be less likely to leave the study early than those taking typical drugs. Rates of adverse events and numbers receiving antiparkinsonian medication were equivalent in both groups. Patients with negative symptoms fared better on risperidone than on typical antipsychotic drugs. In the Cochrane review,[348a] however, movement disorders were found to occur less frequently in the risperidone group. Movement disorders were not considered specifically in the Leucht review – dropouts caused by adverse events were recorded, as was the use of antiparkinsonian medication. The latter outcome may be particularly prone to bias, as mentioned earlier.

The authors of another review[349] performed a comprehensive literature search, as in this review, but also included non-systematic review articles and expert opinion. Validity was assessed using the following criteria: appropriateness of inclusion and exclusion criteria; allocation concealment; blinding (patients, health professionals, data collection, data analysis); follow-up; appropriateness of outcome measures; statistical power of results. Papers were categorised according to study design and recommendations were graded from A (strong) to D (weak). Consensus was used to answer questions in those areas with no evidence. When different doses of the experimental drug were used in trials, a weighted average effect size was estimated across all doses. For some outcomes, results for all atypical antipsychotic drugs were combined.

Fewer trials of each drug were found in this review[349] than in either the original or this updated review, probably because, although the search cut-off dates were similar, we had access to the latest versions of Cochrane reviews, some of which had been updated with new trials before submission of this report. There were some differences in results for each drug: for example, the review authors[349] found that amisulpride had a small effect on negative symptoms. They reported mainly data on efficacy and tolerability (using attrition as a proxy measure) of the atypical antipsychotic drugs and did not concentrate on short-term adverse effects.

The main findings of this review[349] were:

- trials of atypical antipsychotic drugs showed considerable variability in efficacy and tolerability, when compared with conventional antipsychotic drugs, making simple combined estimates from trials of limited value; most trials were short term (6–8 weeks) and of questionable quality, thus providing limited evidence on how best to treat patients in the longer term
- analysis by drug suggested small benefits in reduced psychiatric symptoms that favoured some atypical antipsychotic drugs; however, there was inadequate information in direct randomised comparisons of atypical antipsychotic drugs to provide reliable evidence on their relative effectiveness
- there was no evidence of specific effects for atypical antipsychotic drugs upon negative and depressive symptoms; effects, when they occurred, seemed to involve all classes of symptoms equally
- there was limited evidence of improved tolerability for olanzapine compared with risperidone
- in long-term trials, the average improvement in psychiatric symptom scores attributable to atypical antipsychotic drugs was, at best, modest
- the findings in the two studies presenting net costs of care were imprecise; the net cost of prescribing atypical antipsychotic drugs in the UK setting remains uncertain and it cannot be presumed that any savings from reduced hospitalisation or use of other services will offset their higher acquisition cost
- there have been reports of suspected NMS in trials of at least one atypical antipsychotic drug currently licensed; information on the relative incidence of treatment-emergent side-effects is surprisingly limited for atypical drugs
- an analysis based on the extension phases of three randomised trials in which olanzapine and haloperidol were compared suggested a significant reduction in tardive dyskinesia in chronic patients at high risk.

The review authors[349] also used a meta-regression analysis to investigate observed heterogeneity between trials and found that overall benefits attributable to randomisation for atypical antipsychotic drugs were no longer apparent in the

model. They found that modelling chlorpromazine or haloperidol as the comparator drug gave similar results. They went on to suggest that haloperidol, 12 mg, may be as effective as the atypical antipsychotic drugs but would still cause more extrapyramidal symptoms.

However, this suggestion should only be used as a hypothesis-generating tool to guide future research and not as a recommendation for practice until good quality trials of atypical antipsychotic drugs versus haloperidol at this dose have been conducted. It should also be borne in mind that one of the major advantages claimed for the new atypical antipsychotic drugs is that they cause fewer extrapyramidal effects than typical antipsychotic drugs and, in this respect, the review supports these claims.[349]

In a systematic review[350] in which risperidone and olanzapine were compared indirectly by comparing each to haloperidol, similar results were obtained using this approach to the results from a trial in which risperidone and olanzapine were compared directly. The results of the review are not reported here as direct comparisons are preferable to indirect comparisons, and several RCTs in which olanzapine and risperidone were compared are included in this review.

How atypical are the atypical antipsychotic drugs?

Effectiveness in controlling psychotic episodes

Risperidone, amisulpride, zotepine, olanzapine and clozapine were more effective than typical antipsychotic comparators in relieving overall symptoms of schizophrenia. Quetiapine and sertindole were no more or less effective than typical antipsychotic drugs in alleviating the overall symptoms of psychosis in schizophrenia.

Ziprasidone: commercial-in-confidence data removed.

Negative symptoms

The effects of the new atypical antipsychotic drugs on negative symptoms were not addressed in most trials, which is surprising given the claims made by many of the manufacturers for efficacy with regard to these symptoms. In the amisulpride trials, negative symptoms were specifically considered but no significant differences were found between amisulpride and typical antipsychotic drugs.

Amisulpride versus ziprasidone: commercial-in-confidence data removed.

Clozapine was found to be more effective than typical antipsychotic drugs in improving negative symptoms in those whose illness was resistant to conventional antipsychotic treatment. Zotepine also seemed to be more effective on negative symptoms than typical antipsychotic drugs. Olanzapine, quetiapine, risperidone, sertindole and ziprasidone did not appear to be any more effective in relieving negative symptoms than typical antipsychotic drugs.

The difficulty in differentiating negative symptoms from movement disorders, such as slowness and poverty of movement, may bias results in favour of the new antipsychotic drugs over haloperidol, especially when haloperidol is used at relatively high doses.

Attrition

In general, fewer individuals in the atypical antipsychotic drug groups (except those for ziprasidone and zotepine) left trials early than those in the typical antipsychotic drug groups, which suggests that atypical antipsychotic drugs were more acceptable.

Side-effects

Movement disorders

All of the new antipsychotic drugs do, indeed, seem to cause fewer movement disorder side-effects than typical antipsychotic treatments, although issues such as dose or definition and reporting of symptoms (see above) limit the confidence that can be placed in these results.

An analysis based on extension phases of three RCTs of olanzapine versus haloperidol suggested that significantly less tardive dyskinesia occurred with olanzapine (7.1%) than with haloperidol (16.2%) in chronic patients at high risk.
A 1-year trial of risperidone versus haloperidol demonstrated no significant differences in rates of occurrence of tardive dyskinesia.[351] In a 6-week trial, there were no differences in rates of tardive dyskinesia between individuals taking amisulpride and those taking haloperidol. The results from non-randomised studies also indicated that risperidone caused significantly less tardive dyskinesia than haloperidol.

Sedation

Clozapine increased daytime sleepiness (somnolence) or drowsiness compared with typical drugs. Olanzapine, amisulpride, sertindole and perhaps

risperidone led to less somnolence or drowsiness than in those treated with typical comparator drugs, and the other atypical antipsychotic drugs were no more or less sedating than the typical antipsychotic drugs with which they were compared.

Autonomic effects

Side-effects such as increased salivation, increased temperature and rhinitis (blocked nose) were seen in both the clozapine- and sertindole-treated groups. The opposite effect was seen in the quetiapine group, that is, increased incidence of dry mouth. Olanzapine was associated with fewer autonomic effects than typical antipsychotic drugs. The other atypical antipsychotic drugs did not cause either more or fewer autonomic side-effects than their typical antipsychotic comparators.

Gastrointestinal effects

Atypical antipsychotic drugs were not significantly better or worse than typical antipsychotic drugs in terms of rates of nausea and vomiting, except for ziprasidone, which caused more nausea and vomiting, and olanzapine, which caused less nausea and vomiting.

Weight gain

In RCTs, amisulpride, risperidone and sertindole were found to cause weight gain. It has been suggested that weight gain impacts negatively on the quality of life of those with schizophrenia but this information is based on a telephone survey that was not rigorous in design.[352]

In non-randomised studies, sertindole seemed to cause more weight gain than haloperidol. Because of poor reporting or reporting of skewed data, it was difficult to quantify the average weight gain in the two groups, olanzapine and typical antipsychotic drugs. For olanzapine, weight gain was consistently greater than for the typical antipsychotic drugs. Risperidone, amisulpride and clozapine were also linked with weight gain compared with typical antipsychotic drugs. From the few data available, no difference between groups was suggested in ziprasidone or zotepine RCTs. Quetiapine-treated patients gained weight in non-controlled studies.

In one Cochrane review,[4] chlorpromazine was also found to cause significant weight gain compared with placebo whereas in another Cochrane review,[5] haloperidol was not.

Two reviews on antipsychotic drugs and weight gain were published recently – one sponsored by Pfizer Ltd (the manufacturer of ziprasidone)[353] and one conducted at the Maudsley Hospital.[354] In the first review, the following weight changes were found at 10 weeks: clozapine 4.45 kg; olanzapine 4.15 kg; sertindole 2.92 kg; risperidone 2.10 kg; ziprasidone 0.04 kg. There were too few data to evaluate quetiapine at 10 weeks and zotepine and amisulpride were not evaluated. The conventional antipsychotic drugs induced weight changes ranging from a reduction of 0.39 kg (molindone) to an increase of 3.19 kg (thioridazine). Placebo was associated with a mean weight reduction of 0.74 kg. In some cases in this review, the estimates of mean weight changes and SDs were calculated by the authors, so most results are based on assumptions. The results of the second review also indicated that all atypical antipsychotic drugs, with the exception of ziprasidone, were associated with weight increases. Clozapine was found to have the highest risk of weight gain, followed by olanzapine and quetiapine; the risk was probably lower for risperidone, sertindole and zotepine, and lower still for amisulpride. In the Cochrane reviews, risperidone was also found to cause less weight gain than olanzapine, and zotepine probably less weight gain than clozapine, but it was not possible to draw any further conclusions. The Maudsley review[355] did not meet our criteria for systematic reviews – only MEDLINE was searched, and it has been shown that this may lead to a large amount of published research being missed. No inclusion criteria were reported and validity was not assessed. The data were not synthesised in a systematic way and none was given more weight than others. The trial designs included were not described but some may have been more rigorous than others.

Prolactin-related problems

Problems related to hyperprolactinaemia, such as gynaecomastia, galactorrhoea, impotence and infertility, were not reported on for most of the atypical antipsychotic drugs (with the exceptions of amisulpride, risperidone and sertindole). This would seem to reflect a lack of awareness or concern about the distressing nature of these side-effects on the part of those conducting the trials. Incidence of adverse events related to hyperprolactinaemia were reported for amisulpride, risperidone and sertindole; none of these reviews indicated a statistically significant difference from its typical antipsychotic comparators. Serum prolactin levels were sometimes reported in trials but are not reproduced here, as they are not classified as a clinical outcome. Prolactin-related problems are known to exist for many typical antipsychotic drugs.

Cardiotoxic effects

The Q-T interval, measured by ECG, is the time between ventricular depolarisation and repolarisation, and varies inversely with heart rate. The 'corrected' Q-Tc interval is calculated from formulae that incorporate correction factors for heart rate. Many factors can affect the Q-Tc interval, including eating a meal, sleeping, obesity and alcoholism. Prolongation of the Q-Tc interval has also been observed in trained athletes. A variety of medical conditions are associated with prolongation of the Q-Tc interval, such as electrolyte disturbances, cardiac disease, hypothyroidism and hypoglycemia. Some drugs have been shown to prolong the Q-Tc interval, including antibiotics, antihistamines, antidepressants and antipsychotics. Prolongation of the Q-Tc interval has been linked with ventricular arrhythmias including Torsade de pointes – a rare, usually self-limiting but potentially life-threatening, ventricular arrhythmia. Ventricular arrhythmia may present as heart palpitations and syncope, and has been linked with seizures and sudden death.

At least two atypical antipsychotic drugs have been noted to have potentially fatal effects on cardiac conductance. Sertindole was eventually withdrawn from the UK market (except for patients who were already stabilised on the drug) in 1999, and a long-term follow-up study of clozapine recipients reported cardiomyopathy or myocarditis in approximately 3 per 1000 physically healthy young adults. However, in non-randomised studies of mortality for both drugs, no excess rates of cardiac death compared with other antipsychotic drugs have been reported.

Of the typical antipsychotic drugs, thioridazine has also been associated with problems of cardiac conductance and is now only recommended for use under specialist supervision. Use of pimozide is only recommended if an annual ECG is carried out.

In many trials cardiac conductance was not measured as an outcome, so the effects of other atypical (or typical) antipsychotic drugs on this outcome cannot be stated with any certainty. Even if ECG changes are measured, sudden cardiac death is a relatively rare outcome and long-term follow-up would be required to gain an accurate picture of the event rate. There is certainly cause for concern over this outcome and further research is needed before the possibility of sudden cardiac death can be ruled out for any of the antipsychotic drugs.

Head-to-head comparisons of atypical antipsychotic drugs

When atypical antipsychotic drugs are compared with each other, the following differences are seen.

Amisulpride versus ziprasidone: commercial-in-confidence data removed.

More patients taking amisulpride than risperidone experienced 'agitation'. Fewer individuals treated with clozapine than with risperidone suffered movement disorders, impotence, dry mouth or insomnia. Fewer of those treated with olanzapine than with clozapine suffered nausea and vomiting, orthostatic dizziness, hypersalivation and constipation. More individuals on clozapine compared with olanzapine or risperidone suffered fatigue, nausea and vomiting, excess salivation, tachycardia, orthostatic dizziness, constipation or leucocytosis. Olanzapine caused more weight gain and dry mouth than risperidone but fewer movement disorders. Quetiapine may have been more likely to improve depression than risperidone.

Quetiapine versus risperidone: commercial-in-confidence data removed.

Zotepine is perhaps more likely to cause movement disorders than clozapine or risperidone. Amisulpride may be more effective than risperidone in terms of 'response'.

Ziprasidone versus olanzapine: commercial-in-confidence data removed.

Ziprasidone versus risperidone: commercial-in-confidence data removed.

Economic evaluation

Systematic review

Both the original and the updated reviews concluded that the use of atypical antipsychotic drugs, although associated with increased acquisition costs, reduced the level of use of healthcare resources, namely hospital services. This means that the total cost of care is reduced when treatment with atypical antipsychotic drugs is initiated. The atypical antipsychotic compounds also seemed to be associated with better outcomes, in terms of QALYs.

This would suggest that initiation of atypical antipsychotic therapy for patients who are not responding to typical antipsychotic drug therapy is worthwhile and should be encouraged. In terms

of choosing between the different atypical antipsychotic compounds there is less evidence. There were comparisons between olanzapine and risperidone, which suggested that, despite its higher acquisition cost, olanzapine was worthwhile. On the other hand, a comparison between olanzapine and sertindole showed the latter to be dominant (i.e. produced lower costs and was more effective). However, uncertainty regarding cost and outcomes data led many authors to be cautious about interpreting the results of evaluations with confidence.

Economic model

The decision model presented here used probabilistic simulation analysis to incorporate uncertainty in the estimates of event rates, resource use and unit costs. It concluded that haloperidol, olanzapine, quetiapine and zotepine were inferior in terms of cost-effectiveness to chlorpromazine, clozapine, risperidone, ziprasidone, amisulpride and sertindole. However, the uncertainties associated with most of the costs and effects made it difficult to be completely certain that any observed differences in point estimates of costs and effects did actually exist.

There were a number of issues related to the data and analyses, which meant that the results are uncertain. First, the analyses were exploratory in nature. Some of the data used were taken from studies that yielded 'statistically significant' results only after a number of different comparisons. Thus, some of these results may have been chance findings. Furthermore, many data used in the model were subject to a range of uncertainties or based on relatively small sample sizes. For instance, some of the utility estimates used were derived from a sample of seven patients, which is clearly far from satisfactory.

The results are, in some respects, similar to published evaluations, in that the model suggests that haloperidol, despite having relatively low acquisition costs, is not more cost-effective than a number of atypical antipsychotic drugs with greater acquisition costs.

In terms of differences between the atypical antipsychotic drugs, on the basis of unpublished effectiveness and cost data, ziprasidone seems to be cost-effective but, on the basis of published data and the fact that it does not have a UK licence, it does not present a cost-effective prescribing option at present.

Overall

Three approaches were used in this appraisal to evaluate the cost-effectiveness of drugs for the treatment of schizophrenia. For some comparisons all three methods were in agreement (see *Table 64*). For example, the published evidence, the confidential submissions from industry and the results from the model agreed that risperidone was more cost-effective than haloperidol. Furthermore, the results from the model also suggested that a number of other atypical antipsychotic treatments were more cost-effective than haloperidol. There was, however, some degree of disagreement between the published data and our own analyses. This was largely caused by the inclusion of chlorpromazine as an appropriate comparator in the model. Once this drug was included, the results of the model did not suggest any additional benefit associated with the use of atypical antipsychotic drugs in terms of a reasonable cost per QALY. This clearly contradicts the findings of the systematic review of economic evaluations, which found atypical antipsychotic treatments to be more cost-effective. As noted previously, the systematic review was not designed to identify chlorpromazine and haloperidol trials and, hence, estimates of effect for these two drugs were taken from the control arms of the atypical antipsychotic drug trials. The estimates that are currently used in the model are unlikely, therefore, to represent an unbiased estimate of effect; hence, it is proposed that for each line of therapy the decision should be between different atypical antipsychotic drugs, but not between atypical and typical antipsychotic drugs.

Ziprasidone: commercial-in-confidence data removed.

The aim of an ongoing clinical trial (the CUtLASS Trial[356]) is to assess the cost–utility, based on quality of life, of atypical versus conventional antipsychotic drugs over a 1-year period. The results should be available in late 2003 and should add considerably to the cost-effectiveness evidence base for atypical antipsychotic drugs.

Psychosocial treatments for schizophrenia

Comprehensive care for schizophrenia involves not only drug treatments but also the provision of ongoing support, valid information and, when appropriate, therapies or rehabilitative strategies. A review of Cochrane reviews of psychosocial

treatments for schizophrenia[357] came to the following conclusions.

- Individual psychoeducational interventions can decrease the risk of relapse, although the mechanism by which this is achieved is unclear.
- Family intervention (a supportive, educational and, perhaps, therapeutic interaction with the family of people with schizophrenia) decreases the risk of relapse. However, this decrease was most marked with early studies undertaken by pioneers of the technique.
- The evidence suggests that cognitive behavioural therapy may decrease relapse and readmission rates and may also improve a patient's mental state.
- Assertive community treatment (ACT) reduces hospital admissions and time spent in hospital by nearly 50%. ACT teams could prove particularly useful in environments where psychiatric inpatient care is at a premium.
- The care programme approach (case management) may help health and social services keep in contact with patients, and may serve useful administrative functions, but ACT is required to keep those who are severely mentally ill out of hospital.
- The whole area of non-pharmacological treatments for individuals with schizophrenia is under-researched. Well-designed, generalisable RCTs are needed. These should involve those seen in everyday practice and measure meaningful outcomes, including adverse effects.
- A realistic trial of the effectiveness of antipsychotic drugs should probably include adjuvant psychosocial treatments as well.

Chapter 15
Conclusions

Evidence for the effectiveness of the new atypical antipsychotic drugs compared with older drugs is, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population of those with schizophrenia. Evidence for the effectiveness of the new atypical antipsychotic drugs compared with each other is still limited. Evidence for the cost-effectiveness of the new atypical antipsychotic drugs in the UK compared with each other and with older drugs is also limited. Thus, all conclusions are based on limited evidence and should be treated with caution.

There is no evidence on the effectiveness of the atypical antipsychotic drugs compared with typical antipsychotic drugs for those with concurrent substance abuse problems or comorbid mental illness, such as depression. There are few implications for those with related disorders such as schizoaffective and schizophreniform disorders.

More useful research is urgently needed: long-term trials involving large numbers of people, less rigid inclusion criteria and outcomes that are relevant to patients with schizophrenia and their carers should all be of primary concern. Less rigid, more pragmatic trial protocols may help both to decrease attrition rates from the trial and to increase the generalisability of the results. Outcomes related to sexual side-effects are particularly poorly reported at present.

The available evidence suggests that risperidone, quetiapine, sertindole, amisulpride, zotepine, olanzapine and clozapine are as effective or more effective in relieving overall symptoms of schizophrenia, and clozapine and risperidone in preventing relapse, than typical antipsychotic drugs.

Ziprasidone: commercial-in-confidence data removed.

Patients with predominantly negative symptoms were considered in few trials. Clozapine was more effective than typical drugs in improving negative symptoms in those with treatment-resistant illness. There was weaker evidence to suggest that zotepine may have more effect on negative symptoms than typical antipsychotic drugs. Both these findings were derived from scale-based data that may not be clinically relevant.

Ziprasidone versus amisulpride: commercial-in-confidence data removed.

All new atypical antipsychotic drugs do appear to cause fewer movement disorder side-effects than typical antipsychotic drugs.

Individuals with schizophrenia may find the new atypical antipsychotic drugs more acceptable than typical antipsychotic drugs as, in general, fewer of them left trials early (except for zotepine and ziprasidone).

Clozapine is more effective than typical antipsychotic drugs in treating those whose illnesses have not previously responded to treatment.

In one trial of risperidone in first-episode schizophrenia, participants responded similarly to all those with schizophrenia for all the major outcomes of interest. In one report of a subgroup with first-episode psychosis in a trial of olanzapine versus haloperidol, olanzapine was found to be more effective and caused less EPS than haloperidol; however, the quality of the report was poor. There is no evidence relating to the other antipsychotic drugs in first-episode illness. Informed choice should be used if possible. When this is not possible, there may be a case for using atypical antipsychotic drugs as these may be more acceptable to those with schizophrenia; however, this is not clear and more research is urgently needed. The economic model suggests that either olanzapine or chlorpromazine (depending on what is an acceptable cost per QALY) are more cost-effective treatments for first-episode patients, compared with haloperidol; however, because of the small number of trials including patients with first-episode psychosis, these results should be interpreted with caution.

In one trial of risperidone versus haloperidol for those with schizoaffective disorder, no difference was found between groups with regard to mental state but risperidone was associated with fewer movement disorder side-effects than haloperidol.

In a subgroup of another trial of olanzapine versus haloperidol in people with schizoaffective disorder, olanzapine was found to be significantly more effective than haloperidol in improving mental state.

Serious and potentially fatal cardiac side-effects have been noted with at least two atypical antipsychotic drugs (sertindole, which has now been withdrawn in the UK and, more recently, clozapine) and two typical antipsychotic drugs (pimozide and thioridazine). Any future research on the typical or atypical antipsychotic drugs should include data on cardiac effects.

Daytime sleepiness (somnolence) or drowsiness may occur more frequently in those given clozapine than in those given typical antipsychotic drugs. Olanzapine, amisulpride, sertindole and, perhaps, risperidone may cause less somnolence. There was no evidence to suggest that the other atypical antipsychotic drugs were any more or less sedating than their typical counterparts. Autonomic side-effects may occur more frequently in those given clozapine or sertindole, and less frequently in those given quetiapine or olanzapine than in those given typical antipsychotic drugs.

Amisulpride, risperidone and sertindole seem to cause more weight gain than typical antipsychotic drugs. The evidence for clozapine and olanzapine was equivocal: RCT evidence was based on a small numbers of participants and showed no difference in risk from typical antipsychotic drugs, but non-randomised studies showed an increased risk of weight gain. Quetiapine-treated patients showed an increased risk of weight gain in non-controlled studies. There is some evidence that this side-effect is more important to those with schizophrenia than had been previously assumed, and it also has serious public health implications. Future research should look specifically at the effects of antipsychotic drugs on weight.

The lack of good quality long-term evidence for most antipsychotic drugs means that anyone taking them should be carefully monitored for potentially serious adverse effects.

Non-randomised studies were, in general, of poor quality; their results suggest that atypical antipsychotic drugs are not associated with excess mortality compared with other psychiatric drugs, and may reduce suicidality (particularly clozapine).

Both the original and the updated cost-effectiveness review concluded that, although associated with increased acquisition costs, the use of atypical antipsychotic drugs reduced the utilisation of healthcare services, namely hospital services. This means that the total cost of care is reduced when treatment with atypical antipsychotic drugs is initiated. Uncertainty regarding cost and outcomes data led many authors to be cautious about interpreting the results of evaluations with confidence.

The main conclusion that can be drawn from the economic model is that, given the uncertainty that exists about the validity of the clinical data for typical antipsychotic drugs and what is an acceptable cost/QALY, it is not possible to reach any definite conclusions as to whether the additional costs and benefits represent value for money.

Apart from clozapine for those with treatment-resistant illness, no single new atypical antipsychotic drugs stands out as being more effective than any of the others. They all seemed to have slightly different side-effect profiles, which may vary in importance to those with schizophrenia and their carers.

Implications for practice and factors guiding decisions

Because of methodological flaws (including very great losses to follow-up) or under-reporting in the primary data, any implications for practice are based on limited evidence. Individuals with treatment-resistant illness or predominantly negative symptoms are often excluded from trials, as are the elderly, those with learning disabilities, and many others with schizophrenia who may also have comorbid depression or substance abuse disorders.

The long-term cardiac and hepatic side-effects of most atypical antipsychotic drugs are, as yet, unknown. Careful monitoring of all those taking any antipsychotic drug is important. For individuals with pre-existing cardiac or liver problems, antipsychotic drugs should only be administered under close supervision.

If the illness is chronic, then there seems to be little to choose between any typical or atypical antipsychotic drugs except on the issues of leaving the trial early and side-effects, such as parkinsonism.

Ziprasidone: commercial-in-confidence data removed.

No firm implications can be drawn regarding the effect of new antipsychotic drugs on agitation, hostility and withdrawal.

The effectiveness of clozapine in comparison to conventional antipsychotic drugs in hospitalised, adult patients is well established. Clozapine is effective in treatment-resistant illness.

The short-term risks–benefits of quetiapine are not much different from those of classical antipsychotic drugs and, like other atypical antipsychotic drugs, quetiapine has not been shown to be effective in treating negative symptoms; however, it does cause fewer movement disorder side-effects.

Risperidone does appear to have some advantages over haloperidol, in terms of limited alleviation of symptoms and side-effects profile. It may also be more acceptable to those with schizophrenia, perhaps because of decreased sedation, despite a tendency to increase weight more than conventional medications. Little is known from trials about long-term effects.

Risperidone does seem broadly similar to olanzapine in its ability to relieve symptoms of schizophrenia, but has a greater tendency to cause extrapyramidal side-effects. This should be considered alongside a reduced tendency to cause weight gain compared with olanzapine. Although risperidone is a cheaper alternative to clozapine, there are insufficient data to suggest that it is as effective as clozapine for those with treatment-resistant illness.

Sertindole, 20 mg daily, seems more antipsychotic than placebo. It was better tolerated than haloperidol and produced few movement disorders. However, it has also been shown to cause cardiac anomalies, weight gain, rhinitis and problems with sexual functioning. The cardiac problems were evident even within poorly reported trials and the drug has now been withdrawn for those not already stabilised on it; however, compared with olanzapine or risperidone, no differences were reported in non-randomised studies of mortality.

The few data that are currently available suggest that ziprasidone is as clinically effective and acceptable as haloperidol for those with schizophrenia. It is less likely than haloperidol to cause movement disorders but may cause more nausea and vomiting. The injected form of the drug may cause more pain at the site of injection than haloperidol.

Zotepine is clinically effective and acceptable for those with schizophrenia in the short term. It may have an effect on the negative symptoms of schizophrenia and it is less likely to cause movement disorders than typical antipsychotic drugs. Further studies are needed to clarify its effect on negative symptoms, using a pragmatic and clinically meaningful way of assessing this outcome over longer periods, before any implications for practice are considered. There appears to be no strong advantage in taking zotepine over any other atypical antipsychotic medication at present.

First-episode schizophrenia

The current review can provide little guidance on whether atypical, rather than conventional antipsychotic drugs should form the first-line treatment for schizophrenia.

The evidence base to support the choice of antipsychotic drug for first-line and first-episode treatment of schizophrenia is limited. Only two trials, one of risperidone and one of olanzapine, included those with first-episode psychosis; thus it is not possible to suggest which drugs should be given to this group of patients. However, both risperidone and olanzapine did seem to be more effective than haloperidol.

An informed choice should be made if possible, however; many individuals with first-episode schizophrenia are in acute distress and too ill to enter into discussion when they first enter care. It has also been suggested that the first experience of antipsychotic drugs for someone with schizophrenia is very important in determining future compliance with medication and long-term prognosis.

If atypical antipsychotic drugs are more acceptable to those with schizophrenia than typical antipsychotic drugs, then there may be a case for prescribing atypical antipsychotic drugs to first-episode patients and, perhaps, changing the drug later when an informed discussion can take place. However, it is not clear from the evidence in this review that atypical antipsychotic drugs really are more acceptable than typical antipsychotic drugs. Fewer people leave studies early in atypical than in typical antipsychotic groups but this may be for any number of reasons (most probably, unblinding of trial investigators) rather than reflecting acceptability of treatment. Only in one trial of clozapine were participants directly questioned about drug acceptability, and neither clozapine nor haloperidol was favoured.

Patients with treatment-resistant illness (and those with mainly negative symptoms)

Clozapine has been shown to be effective in treatment-resistant illness and in those with negative symptoms. The other atypical antipsychotic drugs do not appear to be any more effective than typical antipsychotic drugs in these groups, although the results for olanzapine and zotepine are unclear.

Few suggestions can be made at this stage about the advantages or disadvantages of prescribing one atypical antipsychotic drug over another atypical antipsychotic medication, except in the case of clozapine for treatment-resistant illness in patients with predominantly negative symptoms. All the other drugs have differing side-effect profiles, which may vary in importance to individual patients.

Recommendations for further research

Conduct of trials (methodology)

Whether new atypical antipsychotic drugs are more effective than other low-cost conventional neuroleptic drugs, such as chlorpromazine and trifluoperazine, has yet to be proven.

Large randomised, long-term, community-based trials are required, in which global outcomes are measured, such as social functioning, satisfaction with treatment, ability to live and work in the community, and compliance, as well as smaller trials of groups of patients needing special attention.

Newer atypical antipsychotic drugs are considered to be effective on negative symptoms and, to rule out the effect of comorbid depression, this should be evaluated using separate rating scales of mood disorders.

The reasons for discontinuation should be reported in detail. The occurrence or lack of deaths and serious or life-threatening adverse effects, such as agranulocytosis, should routinely be reported. ITT analysis should be undertaken and reported in sufficient detail to allow the reader to be sure that it is, in fact, what took place. Last observation carried forward (for continuous data) or other methods should be used to include patient data for as many participants as possible in the endpoint data analysis. Again, the numbers should be reported.

Outcomes

There is a compelling need for an internationally agreed set of standardised outcomes for schizophrenia trials.

Weight gain is a common side-effect that has, in the past, been poorly reported, making it difficult to pool data from trials. Future research should collect data on body weight in a usable form. Tardive dyskinesia is also a very common side-effect that usually develops in the long term; hence, it is often not reported in RCTs, which tend to be conducted over shorter periods. It would be very useful to have good quality data from long-term RCTs on this common side-effect, so that a realistic estimate could be made of its relative occurrence rate for all new atypical and typical antipsychotic drugs.

Other important side-effects that are often poorly reported or overlooked completely are those relating to hyperprolactinaemia (such as gynaecomastia, galactorrhoea, impotence and infertility) and changes in cardiac conduction. Cardiac conduction effects can be fatal and have been noted in at least two new antipsychotic drugs (sertindole, now been withdrawn in the UK, and clozapine) and in two older drugs (pimozide and thioridazine). This is enough to raise concern about all antipsychotic drugs and all future trials of these drugs should include data on cardiac function – a potentially very serious, albeit rare, complication.

Reporting of trials

Clear and strict adherence to the CONSORT statement[345] for all outcomes would have resulted in this review being more informative. Protocols for trials are now acceptable as publications in their own right.[358] Appropriate power calculations, the proposed selection of participants, randomisation process and its concealment, and recording of outcomes could be presented and clearly described. Better reporting of randomisation, allocation concealment and blinding procedures would lend extra value to the results of these trials.

Final reports should present a table of baseline characteristics of those in each group to reassure readers that the groups were similar, and should give reasons for every post-randomisation loss to follow-up. Clinically useful and understandable outcomes (binary and, if required, continuous) should be presented and an ITT analysis undertaken.

Those undertaking reviews are often unaware of the extent to which research goes unpublished, and will never be sure that they are in possession of all of the

available research evidence. The importance of this is that much unpublished work relates to smaller-scale trials that do not favour new treatments or give negative results. Statutory legislation requiring prospective registration of research trials may be the only solution to the problem of publication bias.[359] Furthermore, there should be a requirement on the part of those who undertake research (published or unpublished) to make all data available to those undertaking systematic reviews.[360]

The use of specific trial identifiers within multiple publications would greatly decrease confusion over identification of the source trial.

Data should preferably be presented in tables with means and SDs, including the actual numbers of patients studied. Although the data change between baseline and endpoint stages would be informative, endpoint scores would be preferred in order to make interstudy comparisons more accessible.

The presentation of continuous data should make clear the number of participants, mean, and SD.

If *p*-values are used, exact values should be reported as well as the test employed. If data are presented graphically, exact numbers should also be reported.

Independent research

Funding that is as free of conflicts of interest as possible is justified. (In two trials in which olanzapine was compared with risperidone, the company sponsoring the research found in favour of their product.)

An independent research group may be more easily able to use a modification of an RCT that is more acceptable to patients with schizophrenia.

Head-to-head comparisons of atypical antipsychotic drugs

It is disappointing that the small number of existing trials did not present more data that were either clinically meaningful or hypothesis generating. More trials are clearly needed to compare the advantages and disadvantages of each atypical antipsychotic drug with its competitors. Trials should be of longer durations to determine the effects of a drug on both acute symptoms and chronic illness, together with its impact on an individual's life. A large, long-term pragmatic trial of the two market leaders, risperidone and olanzapine, using outcomes chosen by and relevant to service users, would be of great interest, as would a similar comparative trial of zotepine and clozapine in those with treatment-resistant illness and/or with negative symptoms. Trials of all atypical antipsychotic drugs (beginning with the two market leaders) in first-episode schizophrenia should provide information valuable for practice decisions. Concurrent prospective economic evaluations are required to inform the cost implications (costs and potential savings) of these drugs in clinical practice; the results of the ongoing CUtLASS trial on the cost-effectiveness of atypical versus conventional antipsychotic drugs are eagerly awaited.

First-episode schizophrenia

Future research should evaluate not only the effectiveness and safety of atypical antipsychotic drugs in first-episode schizophrenia but also alternative approaches to initial therapy (including emergency treatment), such as low-dose antipsychotic treatment and concurrent short-term use of benzodiazepines, as well as best practice in nursing care on the ward or in the home, to allow optimum dosage of antipsychotic treatments. As for all recommended research, this should include real-world populations with diagnostic uncertainty and comorbidity, and users' experiences and views should be recorded.

Real patients

RCTs are also needed on the effects of atypical antipsychotic drugs in children and the elderly, and the effectiveness and safety of using more than one antipsychotic drug simultaneously (common practice in the UK, even though not recommended). Research is also required into whether differences in gender or ethnicity influence response to antipsychotic drugs, and the impact of adjunctive psychosocial treatments on the effectiveness of antipsychotic treatment.

Informed choice/best-fit medication

As each of the atypical antipsychotic drugs has a different range of side-effects and benefits, which may vary in importance to service users, and since, as with all drugs, individuals may respond to the same drug in different ways, studies that explore the approach of informed choice or best fit would be valuable. Future systematic reviews of this topic should include trials that allowed clinician-determined switching of medication within the time frame of the study, in reaction to poor response or serious side-effects. The effects of an informed choice approach on patient compliance, relapse, self-esteem and quality of life (as well as on cost-effectiveness) should also be evaluated.

Acknowledgements

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

The authors would like to thank the members of the expert advisory panel (see below) for their useful advice and constructive comments on the draft protocol and report.

They would also like to thank Nerys Woolacott, Marie Westwood and Carol Forbes, who assisted with the selection of studies and data extraction, and Caroline Horwood, Vanda Castle and Sally Cunningham for secretarial support.

Our thanks are also due to the Cochrane Schizophrenia Group, who provided enormous input to the review in terms of advice, location of studies and all aspects of the review process.

External advisory panel

The external reviewers were selected from a range of backgrounds and their role was to read and comment on a near-final draft of the document. They are not responsible for the final report, which may not reflect their views.

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A-M Bagnall	Lead reviewer responsible for producing the final update of the review and for writing the report. Involved in the selection of trials and in the extraction and synthesis of data
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L Ginnelly	Responsible for the cost-effectiveness section of the document; involved in selection of studies, data extraction, report writing and updating of the economic model
J Glanville	Devised search strategy and carried out literature searches; wrote the search methodology sections of the report
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We look forward to hearing from you.

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ISSN 1366-5278