Early Intervention for psychosis (Review)

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TABLE OF CONTENTS

[Intervention Review]

Early Intervention for psychosis

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ABSTRACT

Background

Proponents of early intervention have argued that outcome might be improved if more therapeutic efforts were focused on the early stages of schizophrenia or on people with prodromal symptoms. Early intervention in schizophrenia has two elements that are distinct from standard care: early detection and phase-specific treatment. Both elements may be offered as supplements to standard care, or may be provided through a specialised early intervention team. Early intervention is now well established as a therapeutic approach in America, Europe and Australasia, but it is unclear how far early detection, phase-specific treatments, and the use of early intervention teams are underpinned by evidence of effectiveness.

Objectives

To evaluate the effects of: (a) early detection; (b) phase-specific treatments; and (c) specialised early intervention teams in the treatment of people with prodromal symptoms or first episode psychosis.

Search strategy

We searched CINAHL (1982-2002), The Cochrane Controlled Trials Register (November 2001), The Cochrane Schizophrenia Group Register (July 2003), EMBASE (1980-2002), MEDLINE (1966-2002), PsycINFO (1967-2002), reference lists and contacted the European First Episode Network (2003). For the 2006 update we searched the Cochrane Schizophrenia Group's register.

Selection criteria

We included all randomised controlled trials designed to prevent progression to psychosis in people showing prodromal symptoms, or to improve outcome for people with first episode psychosis. Eligible interventions, alone and in combination, included early detection, phase-specific treatments, and care from specialised early intervention teams. We accepted cluster-randomised trials but excluded non-randomised trials.

Data collection and analysis

We reliably selected studies, quality rated them and extracted data. For dichotomous data, we estimated relative risks (RR), with the 95% confidence intervals (CI). Where possible, we calculated the number needed to treat/harm statistic (NNT/H) and used intention-to-treat analysis (ITT).

Main results

We included seven studies with a total of 941 participants. Six studies were small with numbers of participants ranging between 56 and 83, and one study randomised 547 people. None of the studies had similar interventions and therefore they were analysed separately. One small Australian trial (n=59) was concerned with a phase-specific intervention (low dose risperidone and cognitive behavioural therapy) for people with prodromal symptoms. This group were significantly less likely to develop psychosis at a six month follow up than people who only received care from a specialised team which did not involve phase-specific treatment (n=59, RR 0.27 CI 0.1 to 0.9, NNT 4 CI 2 to 20). This effect was not significant at 12 month follow up (n=59, 1 RCT, RR 0.54 CI 0.2 to 1.3). A UK-based study (EDIE) randomised 60 people with prodromal symptoms, to cognitive behavioural therapy (CBT) or a monitoring group. Only two outcomes were reported: leaving the study early and transition to psychosis, both sets of data were non-significant. A Chinese trial used a phase-specific intervention (family therapy) plus out patient care trial for people in their first episode of psychosis and found reduced admission rates care compared with those who received only outpatient care (n=83, RR 0.28 CI 0.1 to 0.6, NNT 3 CI 2 to 6). The applicability of this finding was, however, questionable. One Dutch study (n=76) comparing phase-specific intervention (family therapy) plus specialised team with specialised team for people in their first episode of schizophrenia found no difference between intervention and control groups at 12 months for the outcome of relapse (n=76, RR 1.05 CI 0.4 to 3.0). The large Scandinavian study (n=547) allocated people with first episode schizophrenia to integrated treatment (assertive community treatment plus family therapy, social skills training and a modified medication regime) or standard care. Global state outcome GAF significantly favoured integrated treatment (n=419, WMD -3.71 CI -6.7 to -0.7) by one year, but by two years data were non-significant. Rates of attrition were significantly lower (n=547, RR 0.59 CI 0.4 to 0.8, NNT 9 CI 6 to 18) for integrated treatment by one and two year follow-up. PRIME (USA) was the only double blind study and allocated people with prodromal symptoms to olanzapine or placebo. No significant differences were found between olanzapine and placebo in preventing conversion to psychosis by about 12 months (n=60, RR 0.58 CI 0.3 to 1.2). Clinical Global Impression change scores 'severity of illness' were equivocal by 12 months. Scale of Prodromal Symptoms (SOPS) scores were also equivocal and the PANSS, total, positive and negative outcomes were non-significant. There were no significant differences between the olanzapine and placebo group on adverse effects rating scales - SAS, BAS and AIMS scores; Weight gain was significantly higher in the olanzapine group (n=59, WMD 7.63 CI 4.0 to 11.2) by 12 months. Finally one more Australian study included people in their first episode of psychosis who were acutely suicidal and allocated people to phase-specific cognitively orientated therapy or standard care. Outcome data for leaving the study early and suicide were equivocal.

Authors' conclusions

We identified insufficient trials to draw any definitive conclusions. The substantial international interest in early intervention offers an opportunity to make major positive changes in psychiatric practice, but making the most of this opportunity requires a concerted international programme of research to address key unanswered questions.

PLAIN LANGUAGE SUMMARY

Early Intervention for psychosis

Schizophrenia typically begins in young adulthood and may lead to disability that lasts a lifetime. The onset of psychosis is usually preceded by a period of non- psychotic symptoms, known as prodromal symptoms. The symptoms of full-blown schizophrenia include hallucinations, delusions, disordered thinking, and emotional withdrawal. There is some evidence that a delay in receiving adequate treatment reduces the chances or the extent of recovery.

In broad terms, early intervention has two objectives: the first is to prevent the onset of schizophrenia in people with prodromal symptoms; the second is to provide effective treatment to people in the early stages of schizophrenia, with the goal of reducing the ultimate severity of the illness. Early intervention services are now widespread in America, Europe, and Australia.

We sought to review all trials that involved early intervention for people with prodromal symptoms, or a first episode of psychosis. We identified seven studies, most were underpowered and at present we have insufficient data to draw any definitive conclusions, although further trials are expected.

BACKGROUND

Schizophrenia and other functional psychoses cause enormous suffering for individuals and their families. They are also a leading cause of healthcare expenditure, accounting for 7.8% (£947,000,000) of NHS expenditure on inpatient beds in 1992/3 (NHS Executive 1996). Despite new medications and the development of community care, about one third of people with schizophrenia have a poor long-term outcome (Mason 1997). An overview of studies investigating outcomes has shown that people with schizophrenia have a one-year relapse rate of 15% to 35%, rising to 80% within five years (Larsen 1998). Achievement of full remission becomes less likely after each relapse, and about 10% of sufferers eventually commit suicide (Wiersma 1998).

Until recently, the orthodox approach to treating schizophrenia was to concentrate therapeutic resources on those people who developed severe and chronic disabilities (McGorry 1999). This approach has been challenged by proponents of early intervention, who have argued that greater investment of resources in the early stages of the disorder might substantially reduce the numbers of people developing chronic disabilities (Wyatt 1991). This argument has been strengthened by the observation that there may be an association between various outcome parameters and the duration of untreated psychosis (the time from the development of the first psychotic symptom to the receipt of adequate drug treatment) (Norman 2001). This has led to the proposition that untreated psychosis may be "toxic" and that early intervention might prevent irreversible harm (Sheitman 1998).

Early intervention in psychosis has two elements that are distinct from standard care: early detection and phase-specific treatment. Early detection may be defined as either the identification of people thought likely to develop psychosis (i.e. those who display "prodromal" symptoms, but have never been psychotic (Schaffner 2001)) or the identification of people who are already psychotic, but have not yet received adequate treatment (Wyatt 2001). Phase-specific treatments are defined as treatments (psychological, social, or physical) that are especially targeted at people in the prodrome or early stages of schizophrenia (Miller 1999). Phase-specific treatments may be directed at preventing progression to psychosis (in people with "prodromal" symptoms), or at promoting recovery (in people who have recently experienced their first episode of psychosis).

Early detection and phase-specific treatments may be provided as supplements to standard psychiatric care, or they may be provided by means of a specialised early intervention team (Garety 2000). Such teams provide care exclusively to people who have prodromal symptoms or are in early stages of schizophrenia (Edwards 2000).

The arguments in favour of early intervention have been so persuasive that early intervention teams are well-established in America, Europe and Australasia (Edwards 2002). Recently the UK government announced its intention to set up 50 early intervention teams in England to provide specialised care to all young people with a first episode of psychosis (DoH 2000). It remains unclear, however, how far these service developments are underpinned by evidence of effectiveness. There is particular concern over the ethics of early intervention with prodromal patients, when the benefits of early detection and treatment are unclear, and there is no certainty that they will go on to develop psychosis (Rosen 2000).

OBJECTIVES

To evaluate the effects of early intervention in the treatment of early psychosis.

The two specific objectives were to determine:

1. The effects of early detection and treatment of people with "prodromal" symptoms, in terms of:

1.1 prevention of progression to full blown psychosis

1.2 clinical and social outcomes

1.3 process variables and costs.

2. To determine the effects of early detection and treatment of people in their first episode of psychosis, in terms of:

2.1 clinical and social outcomes

2.2 prevention of relapse and

2.3 process variables and costs

2.4. reduction in duration of untreated psychosis.

"Treatment" was defined as including both phase-specific treatments and care from a specialised early intervention team.

The review was not concerned with evaluating the accuracy of methods of predicting who was likely to develop psychosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials. We accepted cluster randomised trials and listed non-randomised trials in the 'Excluded Studies' section.
In broad terms these two types of trial were included in this review:
-

1. Trials to prevent the development of psychosis
These studies involved treatments and/or methods of management that are given to people who are believed to be showing prodromal (pre-psychotic) symptoms and are therefore considered at high risk of developing psychosis. The primary aim of such studies was to prevent progression to psychosis, and invariably the interventions they offered were combined with some method of early detection of people at risk.
2. Trials to improve outcome in first episode psychosis
These studies involved treatments and/or methods of management designed for people in the early stages of psychosis. The primary aim of such studies was to improve the long term outcome. Early detection might be offered in addition to the treatments, with the aim of ensuring that the treatment was offered as early as possible after the onset of psychosis.

Types of participants

1. For trials to prevent the development of psychosis we included people who were judged by the trialists to be in a prodromal phase of psychosis, on the basis of showing prodromal symptoms (however defined).
2. For trials to improve outcome in first episode psychosis, we included people who were in their first episode of psychosis, or were in the process of recovering from their first episode. People with psychosis were defined as those presenting with any combination of delusions, hallucinations or thought disorder, or those who had been given a diagnosis of schizophrenia or schizophrenia-like disorder, bipolar disorder (manic episode) or depression with psychotic features.
We excluded trials where the majority of participants were suffering from a learning disability or an organic psychosis, or where more than 10% had experienced a previous psychotic episode. We did not exclude anyone for reasons such as age or type of psychosis (for example, affective psychosis). We excluded trials that included people who had had more than one episode of psychosis.

Types of interventions

In trials of early intervention there are many possible combinations of intervention and control condition. This depends on: the type of participant (prodromal or first episode); whether the trial involved early detection (which could involve the whole sample or just the treatment group); the type of intervention (phase-specific or specialised team); the nature of any phase-specific intervention (cognitive therapy, family therapy etc); and the type of control (no treatment, standard psychiatric care, care from a specialised team but not phase specific intervention, etc.). In this section the most likely combinations of intervention and control conditions are listed for trials to prevent the development of psychosis and trials to improve outcome in first episode psychosis.
1 Trials to prevent the development of psychosis.
These trials require prodromal patients, and since such patients do not normally present to psychiatric services, the trials therefore require some form of early detection to be applied to the whole sample. The intervention may consist of: phase-specific interventions (medication, psychological treatment or other), or care from a specialised team (which might offer phase-specific interventions). The control condition may consist of no treatment, or standard psychiatric care, or care from a specialised team (in which case the intervention will consist of care from a specialised team plus a phase specific intervention). The various types of intervention and control condition are described in more detail below.
1.1 Phase-specific intervention
In the context of preventing psychosis, phase-specific interventions are discrete treatments including medication regimes, which have been specifically developed for use in patients experiencing prodromal symptoms. A phase-specific intervention could be offered by an individual therapist or provided in the context of receiving care from a specialised team (see 1.2 below). More than one phase-specific intervention might be offered at the same time (eg: medication regime and cognitive therapy).
1.2 Care from a specialised team
In the context of preventing psychosis this is defined as a multidisciplinary psychiatric team, specialising in the treatment of patients with prodromal symptoms. Such a team would normally provide comprehensive psychiatric care to its patients and would be an alternative, rather than an addition to standard psychiatric care. In the context of a trial it is likely that any specialised team would also offer phase specific interventions.
1.3 Control conditions
In the context of preventing psychosis, the common control conditions are: no treatment; non-specific supportive therapy or care from a specialised team (which did not offer phase-specific treatments to prevent onset of psychosis).
2. Trials to improve outcome in first episode psychosis
The intervention may consist of: early detection; phase-specific interventions (medication, psychological treatment or other) or care from a specialised team (which might offer phase-specific interventions). The control condition may consist of standard psychiatric care or care from a specialised team (in which case the intervention will consist of care from a specialised team plus a phase specific intervention). A "no treatment" control group is not an ethically acceptable option in first-episode psychosis trials. The various types of intervention and control condition are described in more detail below.
2.1 Early detection
In trials to improve outcome in first episode psychosis it is possible to use early detection as an intervention applied to the treatment group alone, this is in contrast to the situation in trials designed to prevent psychosis (see 1. above) where early detection must be applied to both treatment and control groups, The theoretical basis for using early detection as an intervention is that shortening the duration of untreated psychosis in itself improves outcome.

In trials where early detection is the intervention being tested, the unit of randomisation must be a cluster (e.g. general practices or catchment areas), since it is not possible to individually randomize patients who have not yet been diagnosed.

2.2 Phase-specific intervention

In the context of improving outcome in first episode, phase-specific interventions are discrete treatments and include medication regimes, which have been specifically developed for use in the early stages of psychosis. A phase-specific intervention can be offered by an individual therapist or provided in the context of receiving care from a specialised team (see 1.2 below). More than one phase-specific intervention might be offered at the same time (eg medication regime and cognitive therapy).

2.3 Care from a specialised team

In the context of improving outcome in first episode, this is defined as a multi-disciplinary psychiatric team, specialising in the treatment of patients with first episode psychosis. Such a team would normally provide comprehensive psychiatric care to its patients and is an alternative, rather than an addition to standard psychiatric care. In the context of a trial it is likely that any specialised team would also offer phase specific interventions.

2.4 Control conditions

In the context of improving outcome in first episode, the common control conditions are standard care, or care from a specialised team (which does not offer the phase-specific intervention being provided in the treatment arm of the trial). Standard care would be the normal service for people with severe psychiatric illness in the region where the trial took place, and would normally consist of out-patient follow up, medication, and support form a community mental health team, but would not involve any phase-specific treatment or specialised team.

3. Excluded interventions

We considered treatment with low doses of neuroleptic medication (atypical or standard) a phase-specific intervention if given to prevent progression to psychosis, or in the context of a medication protocol designed specifically for treating patients in their first episode of psychosis. However, simple comparisons of atypical neuroleptic medication versus standard neuroleptics in first episode patients were beyond the scope of this review.

Types of outcome measures

Primary outcomes

For trials to prevent the development of psychosis (i.e. prodromal participants) the primary outcomes were:

1. General

1.1 Converting to psychosis during follow-up period

For trials to improve the outcome of first episode psychosis the outcomes were:

1. General

1.1 Relapse - as defined by each study or re-admission during follow-up

Secondary outcomes

For trials to prevent the development of psychosis (i.e. prodromal participants) the secondary outcomes were:

1. General
1.1 Overall functioning
1.2 Duration of hospital stay
1.3 Relapse - as defined by each study
1.4 Re-admission
1.5 Loss to follow up
1.6 Satisfaction with treatment - participant/carer
1.7 Remaining in contact
2. Mental state
2.1 General symptoms
2.2 Specific symptoms
2.2.1 Positive symptoms (delusions, hallucinations, disordered thinking)
2.2.2 Negative symptoms (avolition, poor self-care, blunted affect)
2.2.3 Mood - depression
3. Behaviour
3.1 General behaviour
3.2 Specific behaviours (e.g. aggressive or violent behaviour)
3.2.1 Social functioning
3.2.2 Employment status during trial (employed/unemployed)
3.2.3 Occurrence of violent incidents (to self, others or property)
4. Adverse effects
4.1 General
4.2 Specific
4.2.1 Death (suicide and non-suicide)
4.2.2 Movement disorders (extrapyramidal side-effects, specifically tardive dyskinesia and
neuroleptic malignant syndrome)
4.2.3 Sedation
4.2.4 Dry mouth
5. Economic
5.1 Cost of care
6. Quality of life
6.1 No substantial improvement in quality of life

For trials to improve the outcome of first episode psychosis the secondary outcomes were:

1. General
1.1 Overall functioning
1.2 Duration of hospital stay
1.3 Loss to follow up
1.4 Satisfaction with treatment - participant/carer
1.5 Remaining in contact with services
2. Mental state
2.1 General symptoms
2.2 Specific symptoms

2.2.1 Positive symptoms (delusions, hallucinations, disordered thinking)
2.2.2 Negative symptoms (avolition, poor self-care, blunted affect)
2.2.3 Mood - depression
3. Behaviour
3.1 General behaviour
3.2 Specific behaviours (e.g. aggressive or violent behaviour)
3.2.1 Social functioning
3.2.2 Employment status during trial (employed/unemployed)
3.2.3 Occurrence of violent incidents (to self, others or property)
4. Adverse effects
4.1 General
4.2 Specific
4.2.1 Death (suicide and non-suicide)
4.2.2 Movement disorders (extrapyramidal side-effects, specifically tardive dyskinesia and
neuroleptic malignant syndrome)
4.2.3 Sedation
4.2.4 Dry mouth
5. Economic
5.1 Cost of care

Search methods for identification of studies

Electronic searches

1. Electronic search for update (March 2006)
We searched The Cochrane Schizophrenia Group Trials Register (July 2003 to March 2006) using the phrase:
[early* in title, abstract or keywords of REFERENCE] or [Early* in intervention or 'prodromal or early*' in HealthCare Condition of STUDY]
This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).
2. Details of previous searches
We generated a list of relevant papers from our personal databases. On the basis of the indexing of these papers, we developed the following searches:
2.1 Electronic searches
2.1.1 We searched The Cochrane Schizophrenia Group's Register (July 2003) using the following phrase:
[Early* in intervention or 'prodromal or early*' in Health Care Condition of STUDY] or [early* in title, abstract or keywords of REFERENCE]
2.1.2 We searched CINAHL (1982 to November 2002, Ovid online) using the following phrase:
1. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/
2. exp Paranoid Disorders/
3. (schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((CHRONIC$ or SEVER$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 or 2 or 3 or 4
6. ((risk$ adj3 schiz$) or (screen$ adj3 schiz$)).mp.
7. ((duration or length) adj3 untreat$).mp.
8. ((first or initial or primary) adj3 (admission$ or hospital$ or episod$ or breakdown$)).mp.
9. (early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp.
10. (delay$ adj3 treat$).mp.
11. (" (DUP) " or premorbid$ or prodrom$).mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 5
14. (animal not human).mp.
15. 13 not 14
2.1.3 We searched The Cochrane Controlled Trials Register (November 2001) using the following phrase:
1. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/
2. exp Paranoid Disorders/
3. (schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((CHRONIC$ or SEVER$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 or 2 or 3 or 4
6. ((risk$ adj3 schiz$) or (screen$ adj3 schiz$)).mp.
7. ((duration or length) adj3 untreat$).mp.
8. ((first or initial or primary) adj3 (admission$ or hospital$ or episod$ or breakdown$)).mp.
9. (early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp.
10. (delay$ adj3 treat$).mp.
11. (" (DUP) " or premorbid$ or prodrom$).mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 5
14. (animal not human).mp.
15. 13 not 14
2.1.4 We searched Embase (1966 to November 2002, Ovid online) using the following phrase:
1. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp

SCHIZOPHRENIA, PARANOID/
2. exp Paranoid Disorders/
3. (schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((CHRONIC$ or SEVER$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 or 2 or 3 or 4
6. ((risk$ adj3 schiz$) or (screen$ adj3 schiz$)).mp.
7. ((duration or length) adj3 untreat$).mp.
8. ((first or initial or primary) adj3 (admission$ or hospital$ or episod$ or breakdown$)).mp.
9. (early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp.
10. (delay$ adj3 treat$).mp.
11. (" (DUP) " or premorbid$ or prodrom$).mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 5
14. (animal not human).mp.
15. 13 not 14

2.1.5 We searched Medline (1966 to November 2002, Ovid online) using the phrase:

1. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/
2. exp Paranoid Disorders/
3. (schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((CHRONIC$ or SEVER$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 or 2 or 3 or 4
6. ((risk$ adj3 schiz$) or (screen$ adj3 schiz$)).mp.
7. ((duration or length) adj3 untreat$).mp.
8. ((first or initial or primary) adj3 (admission$ or hospital$ or episod$ or breakdown$)).mp.
9. (early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp.
10. (delay$ adj3 treat$).mp.
11. (" (DUP) " or premorbid$ or prodrom$).mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 5
14. (animal not human).mp.
15. 13 not 14

2.1.6 We searched PsychINFO (1872 to November 2002, Ovid online) using the following phrase:

1. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/
2. exp Paranoid Disorders/
3. (schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((CHRONIC$ or SEVER$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 or 2 or 3 or 4
6. ((risk$ adj3 schiz$) or (screen$ adj3 schiz$)).mp.
7. ((duration or length) adj3 untreat$).mp.
8. ((first or initial or primary) adj3 (admission$ or hospital$ or episod$ or breakdown$)).mp.
9. (early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp.
10. (delay$ adj3 treat$).mp.
11. (" (DUP) " or premorbid$ or prodrom$).mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 5
14. (animal not human).mp.
15. 13 not 14

Searching other resources

1. Reference lists

We inspected reference lists of all identified trials and reviews for additional trials.

2. Personal contact

We contacted experts in the field within the European First Episode Network (2003) to identify unpublished trials.

Data collection and analysis

1. Selection of studies

We (MM and AL) searched The Cochrane Schizophrenia Groups register. Working independently we examined the papers identified from the search strategy. We discarded obviously irrelevant publications and retained only those in which some form of early intervention service had been compared against a control treatment and obtained copies of papers relating to relevant trials. Once these papers had been obtained, we decided whether the trials were eligible. We resolved any disagreements by discussion. For the 2006 update we (MM and JR) independently inspected citations. Where disagreement occurred, we sought to resolve this by discussion, or where doubt remained, we acquired the full article for further inspection. Once we had obtained the full articles we independently decided whether they met the review criteria. We resolved any disagreements that occurred by discussion, and when

this was not possible we added trials to the list of those awaiting assessment until we acquired further information.

2. Assessment of methodological quality

We assessed the methodological quality of included trials in this review using the criteria described in the Cochrane Handbook (Higgins 2005) and the Jadad scale (Jadad 1996). The former is based on the evidence of a strong relationship between allocation concealment and direction of effect (Schulz 1995). We allocated non-randomised studies (of early detection only, see above) to Category C. We performed a sensitivity analysis excluding trials in randomisation Category C, and trials with a follow up rate of less than 80%. The categories are defined below:

A. Low risk of bias (adequate allocation concealment)

B. Moderate risk of bias (some doubt about the results)

C. High risk of bias (inadequate allocation concealment). For the purpose of the analysis in this review, we excluded trials if they met the Cochrane Handbook criteria A or B.

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:

1. Was the study described as randomised?

2. Was the study described as double-blind?

3. Was there a description of withdrawals and drop outs?

Each item receives one point if the answer is positive. In addition, a point can be deducted if either the randomisation or the blinding/masking procedures described are inadequate. For this review we used a cut-off of two points on the Jadad scale to check the assessment made by the Handbook criteria. However we did not use the Jadad Scale was to exclude trials.

3. Data management

3.1 Data extraction

We (MM, AL) independently extracted and entered trial data into RevMan twice, cross-checking for consistency. An initial analysis included all trials meeting inclusion criteria, whilst a second sensitivity analysis excluded all but the highest quality trials (Category A and B). For the 2006 update we (MM and JR) independently extracted and entered data into RevMan, cross-checking again for consistency. Where disputes arose, we attempted to resolve these by discussion. When this was not possible and further information was needed to resolve the dilemma, we did not enter the data, and added this outcome of the trial to the list of those awaiting assessment.

3.2 Incomplete data

We excluded data where more than 50% of participants were lost to follow up (except for outcomes relating to numbers lost to follow up). For the sensitivity analysis, we excluded data if they could not be analysed on an intention to treat basis.

4. Data analysis

4.1 Binary data

For binary outcomes we calculated an estimate of the relative risk (RR) and its 95% (fixed effect) confidence intervals (CI). Where possible, we also calculated the number needed to treat (NNT) statistic. If heterogeneity was found (see section 5) we used a random effects model.

4.2 Continuous data

4.2.1 Skewed data: Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from the finite number zero, the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution, Altman 1996); (c) if a scale started from a positive value (such as PANSS which can have values from 30-210) the calculation described above in (b) was modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score.

4.2.2 Summary statistic: For continuous outcomes we estimated a weighted mean difference (WMD) (fixed effect) between groups. Again, if heterogeneity was found (see section 6) we used a random effects model.

4.2.3 Valid Scales

Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore we only included continuous data from rating scales were if the measuring instrument had been described in a peer-reviewed journal.

4.2.4 Conversion to a common metric

To facilitate comparison between trials, we converted variables (such as days in hospital) that could be reported in different metrics (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

4.2.5 Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficient of their clustered data and to adjust for this by accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but will adjust the data for the clustering effect. We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC)

[Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC was not reported, it was assumed to be 0.1 (Ukoumunne 1999).
Where cluster studies were appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies was possible using the generic inverse variance technique.
5. Investigation for heterogeneity
Firstly, we undertook consideration of all the included studies within any comparison to judge clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. This was supplemented employing, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 75%, we interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency was high, we did not summate data, but presented the data separately and investigated reasons for heterogeneity.
6. Addressing publication bias
We would have entered data from all included studies into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).
7. General
Where possible, we entered data in RevMan so that favourable outcomes for early intervention were displayed on the left of the line of no effect.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
1. Excluded studies
There are currently 58 excluded studies. Thirty-four were not randomised. Of these excluded studies seven were descriptions of services, fourteen were incorporated before and after designs. The other thirteen non-randomised studies were a mix of quasi-experimental designs (i.e. involving contemporaneous controls, from another service or geographical area), studies without any control group, or the control group was not relevant, and one study used an inadequate method of allocation whereby participants were only admitted to the study when space was available. Of the excluded randomised studies, seven involved participants with a mixture of first and second episode psychosis (Craig 2004b, Jolley 2003, Kavanagh 2004, Lenior 2003, Power 2004, SOCRATES-UK and Tarrier 2004). We will include these studies in subsequent updates of this review if separate data can be obtained on just those participants with first episode psychosis. Fourteen studies involved the use of medication only, without any special protocols for people in their first episode. We excluded other randomised studies because comparison groups were not relevant, or as in the case of one study, because there was no usable data available.
2. Awaiting Assessment
Seventy-two studies are awaiting assessment, forty-seven are only referred to in conference abstracts which provide insufficient information for the purposes of study classification. Twelve studies require translation, (ten Chinese, one French, one Polish). We are currently seeking further information from authors of ten studies; two studies have not yet been obtained, and one study is in press. We are writing to authors for additional information, but in later versions of this review studies we will ultimately exclude studies where data is unobtainable.
3. Ongoing studies
We are awaiting data from the Bechdolf-FETZ study which is a multicentre, randomised trial evaluating cognitive behavioural therapy for people with prodromal symptoms.
4. Included studies
We included seven randomised studies involving 941 participants. Two studies were single blind (EDIE-UK and LifeSPAN-Australia). The PRIME-USA study used a double blind design. The OPUS-Scandinavia and PACE-Australia studies did not use double or single blind methods. Linszen-Amsterdam and Zhang-Suzhou did not report if blinding were used. Three trials (PACE-Australia, EDIE-UK and PRIME-USA were concerned with preventing the onset of psychosis and four (LifeSPAN-Australia, Linszen-Amsterdam, OPUS-Scandinavia, and Zhang-Suzhou) were concerned with improving outcome in first episode psychosis. One study (PACE-Australia) randomised people with prodromal symptoms (phase-specific intervention, low dose risperidone and cognitive behavioural therapy plus specialised team versus specialised team). EDIE-UK included 60 people with prodromal illness who were described as being at a ultra high risk of developing first episode psychosis. Participants were randomised to either cognitive behavioural therapy (CBT) or a monitoring group. PRIME-USA is a double blind randomised controlled trial for people in the prodromal phase of psychosis. The trial compares the effects of olanzapine versus placebo in preventing or delaying conversion from the prodromal phase to active psychosis. LifeSPAN-Australia is a randomised controlled trial of a phase-specific brief individual cognitively orientated therapy for people in the first episode of psychosis who have suicidal ideas. Linszen-Amsterdam was a phase-specific intervention (family therapy) plus specialised team versus specialised team; Zhang-Suzhou was also a phase-specific intervention (family therapy) plus standard care versus standard care). The OPUS-Scandinavia study included 547 people with a diagnosis of first episode schizophrenia. Participants were randomised to either integrated treatment (an assertive community treatment enhanced by better specific content via family involvement and social skill training), or treatment as usual.
4.1 Trial duration

The three trials concerned with preventing the onset of psychosis reported data for various time points, (EDIE-UK) at 12 months, (PACE-Australia) reported at six and twelve months (the first six months being the period during which the intervention was received); PRIME-USA reported data at eight weeks, 12 months (first 12 months study intervention given) and by two years (last 12 months without intervention). The four trials concerned with improving outcome of first episode psychosis also reported data at various time points. The LifeSPAN-Australia study followed people up for six months. Linszen-Amsterdam reported at 12 months following an initial three month inpatient admission. A five year follow up also took place, but data were provided for the whole sample only, not by group allocation. OPUS-Scandinavia reported data at one and two years. Zhang-Suzhou reported at 18 months.

4.2 Participants and setting

EDIE-UK recruited participants from primary care teams (general practitioners, practice nurses and psychological therapists), student counselling services, accident and emergency departments, specialist services (community drug and alcohol teams, child and adolescent psychiatry and adult psychiatry services) and voluntary sector agencies. Participants had a mean age of 21, included male and female participants who were diagnosed at ultra high risk of developing a first episode of psychosis using the Yung modified criteria. PACE-Australia recruited participants referred to the Personal Assessment and Crisis Evaluation clinic, which is also part of the EPPIC program. Participants were between 14 and 30 years of age and met one of three criteria for an 'ultra high risk' mental state (i.e. showing symptoms that meant there were highly likely to develop a full-blown psychosis in the near future, see included studies table for details). PRIME-USA recruited people from referrals and by participants responding to study advertisements; male and female participants aged between 12 and 36 years were included with a diagnosis of being at prodromal risk of developing psychosis (COPS criteria). Participants were entered into four sites (three in USA and one in Canada). LifeSPAN-Australia recruited participants from the Western region of Melbourne, Australia and is part of the EPPIC program for treating first episode psychosis, which includes an early detection and crisis assessment team. Participants were aged between 15 and 29 years, and were acutely suicidal. Linszen-Amsterdam recruited participants aged 15-26 years old who were experiencing their first episode of schizophrenia and living in close contact with parents or relatives. All participants were recruited from an adolescent clinic and had to agree to an initial three month inpatient program before randomisation. Subsequent treatment took place on an outpatient basis. OPUS-Scandinavia recruited male and female participants with a first episode of psychosis (ICD 10), with an age range between 18 and 45 years, from inpatient and outpatient departments in Denmark. Zhang-Suzhou recruited only men who had just been discharged from Suhoz Psychiatric Hospital in China, following their first admission for schizophrenia. The intervention and standard care were provided on an outpatient basis.

4.3 Study size

OPUS-Scandinavia was the only study to use a pre-study power calculation (n=547). The other trials in ascending order of size were: LifeSPAN-Australia (56), PACE-Australia (59), EDIE-UK (60), PRIME-USA (60) Linszen-Amsterdam (76) and Zhang-Suzhou (83).

4.4 Interventions

4.4.1 Trials to prevent the onset of psychosis

The Early Detection and Intervention Evaluation trial (EDIE-UK) used cognitive therapy which was limited to a maximum of 26 sessions over six months and followed the principles developed by Beck 1976. It is a problem orientated, time limited, educational therapy with the treatment sessions carried out by experienced cognitive therapists. Both control and treatment group received regular monitoring. Whilst participants (treatment and control) were not given medication, both treatment and control received elements of case management in order to resolve crises regarding social issues and mental health risk.

In the PACE-Australia study, the intervention involved prescription of low dose risperidone (1-2 mg/day) combined with modified cognitive behavioural therapy which aimed to enhance understanding and control of symptoms. Both the intervention and control groups also received case management from a PACE therapist. This involved supportive psychotherapy, assistance with accommodation and education/employment, and family support. Participants in the control and intervention groups received standard treatment if they developed psychosis, but control patients were not otherwise prescribed neuroleptics. Both groups could be prescribed anti-depressants and benzodiazepines.

The Prevention through Risk Identification Management and Education study (PRIME-USA) used a double blind design randomising participants to olanzapine 5-15 mg/day (mean 8 mg/day) or placebo for one year, and then followed-up for a further year without medication. Individual and family psychosocial interventions with supportive and psychoeducational components were available to all patients during the first year. The nature of the interventions varied across sites the four centres but efforts were made to apply their particular treatments in a uniformly. The psychosocial intervention available at the New Haven centre was modelled on the Problem Solving Training approach (D'Zurilla 1971, D'Zurilla 1986).

4.4.2 Trials to improve the outcome of first episode psychosis

In LifeSPAN-Australia the intervention group received standard clinical care plus LifeSPAN therapy which draws on the experience at EPPIC with Cognitive Orientated Therapy for Early Psychosis (COPE) and suicide manuals such as Choosing to Live and Cognitive Therapy of Suicide Behaviour. Four phases are used for the intervention, (a) initial engagement, (b) suicide risk assessment/formulation, (c) cognitive modules and (d) final closure/handover.

In Linszen-Amsterdam the intervention was behavioural family therapy for one year. Eighteen family therapy sessions were held over a 12 month period. Each family was treated by two co-ther-

apists, from a team of two psychologists and one social worker, all of whom had at least one year of experience in providing family interventions for schizophrenia. The intervention was based on the behavioural family management approach of Falloon 1984 and involved psychoeducation, communication training and development of problem solving skills. Both intervention and control groups also received care from a specialised first episode team involving individual oriented therapy consisting of maintenance medication and disease and stress management.

In OPUS-Scandinavia participants received integrated treatment or standard care. Integrated treatment is an assertive community treatment, enhanced by better specific content via family involvement and social skill training. Standard care consisted of care at a community mental health centre. All participants were offered antipsychotic drugs according to guidelines from the Danish Psychiatric Society, which recommends a low dose atypical antipsychotic strategy for first episodes of psychotic illness. Each participant was usually in contact with a physician, community mental health nurse and in some cases a social worker. In a small proportion of case standard care also included psychosocial interventions such as training in social skills or daily living activities, or supportive contacts with the family. Antipsychotics were given to both groups based on the psychiatrists clinical assessment.

Zhang-Suzhou also used family therapy, but in the form of group and individual family sessions which were delivered on an outpatient basis over the 18 month follow up period. Both intervention and control groups also received care from the outpatients department, (consisting of medication and review) but no regular appointments or community follow-ups were provided.

4.5 Outcomes

We were able to report dichotomous data on suicide, death, leaving the study early, conversion to psychosis, adverse effects, hospital admission, days in hospital, compliance with medication, antipsychotic drug use, living independently and employment. Details of rating scales that supplied usable data for this review are given below. Studies reported outcome data at eight weeks, 12 months, eighteen months and two years. Some studies reported data only as P values or statements of significant or non-significant differences, and other continuous data could not be extracted because the number of participants was missing or standard deviations were not reported. Unusable data are listed in the 'included studies' table under outcomes.

4.5.1 Global state scales

4.5.1.1 Global Assessment of Functioning - GAF (APA 1994)

This is an observer rated scale for measuring overall severity of functional impairment. GAF consists of nine behavioural descriptors. Patients are rated between 0 (most severe) and 90 (least severe) for each descriptor. PRIME-USA, PACE-Australia and OPUS-Scandinavia reported data from this scale.

4.5.1.2 Clinical Global Impression - CGI (Guy 1970)

The CGI is a three-item scale commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. The items are: severity of illness; global improvement and efficacy index. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery. PRIME-USA reported data from this scale.

4.5.2 Mental state scales

4.5.2.1 Brief Psychopathological Rating Scale - BPRS (Overall 1962)

The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms. The original scale has sixteen items, but a revised eighteen-item scale is commonly used. Scores can range from 0-126. Each item is rated on a seven-point scale varying from 'not present' to 'extremely severe', with high scores indicating more severe symptoms. In PACE-Australia the scale was used primarily to report severity of psychotic symptoms.

4.5.2.2 Positive and Negative Symptom Scale - PANSS (Kay 1987)

The Positive and Negative Symptom Scale was developed from the BPRS and the Psychopathology Rating Scale. It is used as a method for evaluating positive, negative and other symptom dimensions in schizophrenia. The scale has 30 items, and each item can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). This scale can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P) and negative symptoms (PANSS-N). A low score indicates low levels of symptoms. EDIE-UK used this scale to determine transition to psychosis. PRIME-USA reported data from the PANSS.

4.5.2.3 Scale of Psychotic Symptoms - SOPS (Miller 1999)

The SOPS scale was modelled on the PANSS scale and is designed to measure the presence/absence of prodromal states. It consists of five positive symptom items, six negative symptom items, four disorganisation symptoms items, and four general symptom items. Each has a severity rating from 0 (never, absent) to six (severe/extreme - and psychotic for the positive items). The severity of the prodromal state is based on the sum of the rating from the SOPS items and ranges between 0 and 114. PRIME-USA reported data from this scale.

4.5.2.4 Hamilton Rating Scale for Anxiety - HRSA (Hamilton 1959)

The Hamilton Anxiety Scale (HAMA) is a rating scale developed to quantify the severity of anxiety symptoms, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe). The 14 items consist of: anxious mood; tension; fears; insomnia; intellectual; depressed mood; somatic complaints (muscular); somatic complaints (sensory); cardiovascular symptoms; respiratory symptoms; gastrointestinal symptoms; genitourinary symptoms; autonomic symptoms and behaviour at Interview. Higher scores indicate greater anxiety. PACE-Australia reported data from this scale.

4.5.2.5 Hamilton Rating Scale for Depression - HRSD (Hamilton 1960)
This is an interviewer rated scale for measuring depression. It is used for quantifying the results of an interview and depends on the skill of the interviewer in eliciting the necessary information. It contains 17 variables measured on either a five point or a three point rating scale. The variables include: depressed mood; suicide; employment and loss of interest; retardation; agitation; gastrointestinal symptoms; general somatic symptoms; hypochondriasis; loss of insight and loss of weight. Higher scores indicate more severe depression. PACE-Australia reported data from this scale.
4.5.2.6 Presence of Psychosis Scale - POPS (Olsen 2006)
The Presence of Psychosis Scale (POPS), is part of the Structured Interview for Prodromal Syndromes scale (SIPS). It marks onset of psychosis by the presence of positive symptoms at the psychotic level of intensity and of sufficient frequency and duration. PRIME-USA reported data from this scale.
4.5.2.7 Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1983)
This is also an interviewer rated scale for measuring the severity of negative symptoms of schizophrenia such as alogia, affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. Items are rated on a six-point scale with higher scores indicating more symptoms. PACE-Australia reported data from this scale.
4.5.2.8 Young Mania Scale - YMS (Young 1978)
Again an interviewer rated scale, but this time for measuring the severity of symptoms of mania. Higher scores indicate more severe symptoms. PRIME-USA and PACE-Australia reported data from this scale.
4.5.3 Adverse effects
5.5.3.1 Simpson Angus Scale - SAS (Simpson 1970)
The SAS is a 10-item scale used to evaluate the presence and severity of drug-induced parkinsonian symptoms. The ten items focus on rigidity rather than bradykinesia and do not assess subjective rigidity or slowness. The scale comprises of a 10-item rating scale, each item rated on a five-point scale with zero meaning the complete absence of condition and four meaning the presence of condition in extreme. A low score indicates low levels of parkinsonism. PRIME-USA reported data from this scale,
4.5.3.2 Barnes Akathisia Rating Scale - BAS (Barnes 1989)
The Barnes Akathisia Rating Scale is a four-item scale to assess the presence and severity of drug-induced movement disorder akathisia. It is a widely used comprehensive rating scale for akathisia. Items include, restless movements that characterise akathisia, the subjective awareness of restlessness and any distress associated with the condition. These items are rated from zero (normal) to three (severe). In addition, there is an item for rating the global severity that starts from zero (absent) to five (severe). A low score indicates low levels of akathisia. PRIME-USA reported data from this scale.
4.5.3.3 Abnormal Involuntary Movement Scale - AIMS (Guy 1976)
The Abnormal Involuntary Movement Scale has been used to assess abnormal involuntary movements associated with antipsychotic drugs, such as tardive dyskinesia and chronic akathisia, as well as 'spontaneous' motor disturbance related to the illness itself. Tardive dyskinesia is a long-term, drug-induced movement disorder. However, using this scale in short-term trials may also be helpful to assess some rapidly occurring abnormal movement disorders such as tremor. Scoring consists of rating movement severity in the anatomical areas (facial/oral, extremities, and trunk) on a five point scale (0-4). A low score indicates low levels of dyskinetic movements. PRIME-USA reported data from this scale.
4.5.4 Quality of life scale
4.5.4.1 Quality of Life Scale - QLS (Heinrichs 1984)
This is a semi-structured interview administered and rated by trained clinicians. It contains 21 items rated on a seven-point scale based on the interviewer's judgement of patient functioning. Higher scores indicate better quality of life. PACE-Australia reported data from this scale.
4.5.5 Satisfaction with care
4.5.5.1 The Client Satisfaction Questionnaire - CSQ-8 (De-Wilde 2005)
The CSQ-8 is an eight item self-report of global measure of patient satisfaction with services. The CSQ is substantially correlated with treatment dropout, number of therapy sessions attended, and with change in client-reported symptoms. The CSQ-8 consists of eight items rated on a four point Likert scale. The items are concerned with quality of services received, how well services met the client's needs and general satisfaction. The total score ranges from eight to 32. Higher scores indicate greater satisfaction of the responders OPUS-Scandinavia reported data from this scale.

Risk of bias in included studies

1. Intention to treat analysis
PACE-Australia provided all outcomes on an intention to treat basis. EDIE-UK used an ITT analysis but two people originally randomised to the treatment group were subsequently omitted from the analysis because they were found to be psychotic at the time of randomisation. However, because these exclusions are not compatible with an ITT analysis of relapse, we counted such data as relapses and included these in the final analysis. PRIME-USA also used an intention to treat analysis and reported scale data as change scores rather than endpoint scores. LifeSPAN-Australia only provided dichotomous data for leaving the study early and suicide. Linszen-Amsterdam only provided data on relapse at 12 months on an intention to treat basis. OPUS-Scandinavia used an intention to treat analysis. Zhang-Suzhou reported data on number of people readmitted and compliant on an intention to treat basis, but data on mental state and overall functioning were reported only for people who were not admitted to hospital. This rendered data unusable.

2. Randomisation
All seven studies were randomised. In the OPUS-Scandinavia study participants were randomised using computer generated random numbers. In PACE-Australia randomisation was by the study co-ordinator and the method was unspecified. EDIE-UK randomised and stratified participants by gender and genetic risk. In both LifeSPAN-Australia, Linszen-Amsterdam, PACE-Australia and Zhang-Suzhou participants were "randomly assigned", but no further details were given.
3. Blinding to interventions and outcomes
Blinding of participants and clinicians proved difficult in most studies. PRIME-USA blinded the participants, investigators and dispensers to group assignment. Other studies used independent raters, some of whom were blind to allocation. PACE-Australia and OPUS-Scandinavia used raters who were independent of the study group, but were not blind to treatment allocation. In EDIE-UK single blinding was attempted for the rater, but blinding was not maintained due to participants divulging information, or using language that suggested they were receiving cognitive therapy. Zhang-Suzhou made used independent raters blind to allocation, whereas the LifeSPAN-Australia study was described as only single blind. In Linszen-Amsterdam the status of the raters was unclear.
4. Follow up
Follow up rates were: EDIE-UK at 12 months 60% follow-up; PACE-Australia 100% at 12 months; PRIME-USA at 12 months 84%, at 24 months 72%; LifeSPAN-Australia 75% at six months; Linszen-Amsterdam unclear at 12 months (though loss to follow up did not appear to be substantial); OPUS-Scandinavia at 12 months 77% follow-up and by two years 67%; Zhang-Suzhou 94% at 18 months.
5. Overall
Because of the unclear means of randomisation and the additional potential for inclusion of bias at outcome rating, we rated all studies 'Category B'; moderate risk of bias favouring the experimental intervention.

Effects of interventions

1. The search
The search strategy identified 9279 abstracts of which 184 referred to potentially eligible studies and 155 to reviews of early intervention. From these we identified 100 relevant studies, of which 43 did not meet inclusion criteria. We were able to include three studies and the remainder are awaiting assessment. For substantive descriptions of studies please see included and excluded studies tables. For the 2006 update search we identified 159 new citations and were able to include four additional studies.
Data are available for seven of the possible seventeen types of study described above under 'Types of Interventions'. For each of the seven comparisons only one trial was available, so the results section reports the findings of single trials only, without meta-analysis. Sensitivity analyses and examination of funnel plots were impossible.
2. Trials to prevent the development of psychosis
Three studies addressed the question of prevention of psychosis by interventions for patients with prodromal symptoms. Each used different interventions.
2.1 PHASE SPECIFIC INTERVENTION (OLANZAPINE) + NON SPECIFIC SUPPORTIVE THERAPY vs PLACEBO + NON SPECIFIC SUPPORTIVE THERAPY. (All data derived from one study - PRIME-USA).
2.1.1 Leaving the study early
In PRIME-USA we found the numbers of people leaving the study early by eight weeks (n=60, RR 1.29 CI 0.6 to 2.7) and also by 12 months to be equivocal (n=60, RR 1.59 CI 0.9 to 2.9).
2.1.2 Conversion to psychosis (POPS)
By about 12 months the number of people converting to psychosis were 8/31 olanzapine group and 13/29 for the placebo group, but this small difference did not reach statistically significance (n=60, RR 0.58 CI 0.3 to 1.2).
2.1.3 Global state
2.1.3.1 Clinical Global Impression (CGI)
We found the Clinical Global Impression change score 'severity of illness' to be equivocal by 12 months (n=59, WMD -0.23 CI -0.8 to 0.4).
2.1.3.2 Global Assessment of Functioning (GAF)
We also found the Global Assessment of Functioning 'current' change score by 12 months to be equivocal (n=59, WMD 2.43 CI -4.8 to 9.6).
2.1.4 Mental state
2.1.4.1 Scale of Prodromal Symptoms (SOPS)
PRIME-USA reported several outcomes as mean change scores from the SOPS at 12 months. We found the total score, positive score, negative score, disorganisation and general scores were not significantly different between the olanzapine and placebo group.
2.1.4.2 Positive and Negative Symptom Score (PANSS)
We found the PANSS total (n=59, WMD 0.48 CI -10.7 to 11.7), PANSS positive (n=59, WMD -0.57 CI -3.8 to 2.6), PANSS negative (n=59, WMD 0.52 CI -2.6 to 3.6), and the PANSS general score (n=59, WMD 0.54 CI -5.4 to 6.5) to be not significantly different for the olanzapine and placebo group.
2.1.4.3 Young Mania Rating Scale (YMRS)
We found change scores by 12 months were equivocal (n=59, WMD -0.91 CI -3.8 to 2.0).
2.1.4.4 Montgomery and Asberg Depression Rating Scale (MADRS)
We found depression change scores at 12 months were equivocal (n=59, WMD 0.68 CI -3.8 to 5.2).
2.1.5 Adverse effects
2.1.5.1 Simpson & Angus (SAS)
Extrapyramidal symptoms were found to be equivocal between the olanzapine (mean 8 mg/day, range 5-15 mg/day) and the placebo group by eight weeks (n=59, WMD 0.10 CI -0.6 to 0.8).

2.1.5.2 Barnes Akathisia Scale (BAS)
We also found change scores for akathisia to be equivocal by eight weeks (n=59, WMD 0.50 CI -0.6 to 1.6).
2.1.5.3 Abnormal Involuntary Movement Scale (AIMS)
We found Involuntary movement scores were not significantly different for those given low dose olanzapine by eight weeks compared with placebo (n=59, WMD 0.60 CI -0.3 to 1.5).
2.1.5.4 Weight change
We found the olanzapine group had a statistically significant increase in weight compared with the placebo group by 12 months (n=59, WMD 7.63 CI 4.0 to 11.2). We also found dichotomous data supported this finding with the olanzapine group having significantly more weight gain (criteria not stated) than placebo by 12 months (n=60, RR 3.55, CI 1.5 to 8.3, NNH 3 CI 2 to 11).
2.1.5.5 Cardiovascular measures
Systolic and diastolic blood pressure values were measured sitting and standing (at eight weeks), and we found all data to be not statistically significantly different between the olanzapine and placebo group. Pulse rates were also measured (standing and sitting at eight weeks) and we again found data to be equivocal. Twelve month outcome data for change in pulse rates (sitting) did significantly favour the placebo group (n=58, WMD 8.31 CI 0.5 to 16.1), with the assumption that a lower pulse rate indicated an improvement. However, this significant finding was not replicated for pulse data recorded whilst standing, with data being non-significant.
2.1.5.6 Treatment emergent adverse events (CoStart terms)
Somnolence, increased appetite, anxiety, nervousness, asthenia, joint disorder, abnormal thoughts were all equivocal by eight weeks. We found weight gain to be significantly higher in the olanzapine group (n=60, RR 10.29, CI 1.4 to 74.8, NNH 4 CI 2 to 70) by eight weeks compared with placebo.
2.1.5.7 Fatigue
We found participants experiencing fatigue were significantly higher in the olanzapine group compared with the placebo control (n=60, RR 8.42 CI 1.1 to 62.4, NNH 4 CI 2 to 211).
2.2 PHASE SPECIFIC INTERVENTION (COGNITIVE BEHAVIOURAL THERAPY) + NON-SPECIFIC SUPPORTIVE THERAPY vs NON SPECIFIC SUPPORTIVE THERAPY
(All data derived from one study - EDIE-UK)
2.2.1 Leaving the study early by 12 months
We found the numbers of people leaving the study early were similar for both CBT (11/37) and control group (7/23) with no significant differences.
2.2.2 Transition to psychosis
The number of people who became psychotic during 12 months of observation were not significantly different for the CBT and monitoring groups (n=60, RR 0.50 CI 0.2 to 1.7).
2.3 PHASE SPECIFIC INTERVENTION (RISPERIDONE + COGNITIVE BEHAVIOURAL THERAPY) + SPECIALISED TEAM vs SPECIALISED TEAM. (All data for this comparison are derived from a single study -PACE-Australia)
2.3.1 Leaving the study early
No participants were lost to follow up at 12 months in either treatment or control group (n=59, 1 RCT, RR not possible to estimate, Risk Difference 0.00 CI -0.06 to 0.06).
2.3.2 Progression to psychosis (primary outcome)
We found that participants with prodromal symptoms who received the intervention were significantly less likely to have developed psychosis at the six month follow up than controls (n=59, RR 0.27 CI 0.1 to 0.9, NNT 4 CI 2 to 20). This effect was no longer statistically significant by 12 months (n=59, RR 0.54 CI 0.2 to 1.3).
2.3.3 Global state
PACE-Australia used the GAF to rate overall functioning. At 12 months data were skewed with no statistical differences found between the phase-specific intervention plus specialised team and the group receiving care from a specialised team (n=59, WMD 0.00 CI -5.2 to 5.2).
2.3.4 Mental state
There were no differences between intervention and control groups at six or 12 month follow up on any of the measures of mental state, but confidence intervals were generally wide. The BPRS results at both six and 12 months were equivocal and considerably skewed (n=59, WMD at 6 months -0.50 CI -2.3 to 1.3; WMD at 12 months 0.70 CI -1.0 to 2.4). This also applied to the SANS negative symptoms scores (n=59, WMD at six months -4.6 CI -12.7 to 3.5; WMD at 12 months -0.80 CI -7.9 to 6.3). Ratings of anxiety, depression and mania all had wide confidence intervals and data were skewed. No findings were statistically significant, either at six or 12 months.
2.3.5 Quality of life
We found no significant differences between intervention and control groups at six or 12 month follow up on the quality of life measure (QLS). However, confidence intervals were wide (n=59, WMD at 6 months -1.40 CI -13.6 to 10.8; WMD at 12 months 0.80 CI -10.2 to 11.8). Data were not skewed.
3. Trials to improve outcome in first episode psychosis.
3.1 PHASE-SPECIFIC INTERVENTION (COGNITIVE BEHAVIOURAL THERAPY for SUICIDALITY) + SSPECIALSED TEAM vs SPECIALISED TEAM (all data are from a single study LifeSPAN-Australia)
3.1.2 Leaving the study early
We found the number of people leaving the study early by six months were not significantly different between the LifeSpan therapy group and those receiving standard care (n=56, RR 2.02 CI 0.7 to 5.7).
3.1.3 Suicide
Two people died from suicide during the six month study; one from each intervention group.
3.2 PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + SPECIALISED TEAM vs SPECIALISED TEAM
3.2.1 Relapse (primary outcome).
In Linszen-Amsterdam we found no difference between intervention and control groups at 12 months for the outcome of relapse

but confidence intervals were wide (n=76, RR 1.05 CI 0.4 to 3.0).
3.3 PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + STANDARD CARE vs STANDARD CARE (All data derived from one study -Zhang-Suzhou)
3.3.1 Leaving the study early
In Zhang-Suzhou we found only five people in a study of 83 participants were lost by 18 months. There was no difference in the number of people lost for the two groups but confidence intervals were wide (n=83, RR 1.46 CI 0.3 to 8.3).
3.3.2 Admitted to hospital
We found that participants receiving the intervention were significantly less likely to be admitted to hospital at 18 months than people allocated to the standard care control group (n=83 RR 0.28 CI 0.1 to 0.6, NNT 3 CI 2 to 6).
3.3.3 Not compliant with medication
In both groups most people were compliant with medication. We found no significant difference in the number of people not compliant with medication at 18 months follow up, although confidence intervals were wide the data suggested a trend favouring the intervention (n=83, RR 0.57 CI 0.3 to 1.0).
3.4 SPECIALISED TEAM vs STANDARD CARE (all data derived from one study - OPUS-Scandinavia)
3.4.1 Leaving the study early
We found the numbers of people leaving early by one year were significantly lower in the integrated treatment group (n=547, RR 0.59 CI 0.4 to 0.8, NNT 9 CI 6 to 18) compared with the standard care group. By two years, numbers of people leaving the study early remained significantly lower in the integrated treatment group (n=547, RR 0.64 CI 0.5 to 0.8, NNT 7 CI 6 to 14).
3.4.2 Global state
3.4.1 Global Assessment of Functioning (GAF)
We found GAF 'symptom' endpoint scores to significantly favour the integrated treatment group (n=419, WMD -3.71 CI -6.7 to -0.7) by one year. Two year outcome data were however, not significantly different. The GAF 'function' endpoint scores at 12 months were equivocal, but by two years results significantly favoured integrated treatment compared with standard care (n=369, WMD -4.03 CI -7.2 to -0.8).
3.4.3 User satisfaction
3.4.3.1 Client Satisfaction Questionnaire Score (CSQ-8)
Overall satisfaction with levels of care were significantly better for the integrated treatment group (n=419, WMD -1.90 CI -3.1 to -0.7) compared with the standard care control at 12 months and also at two years (n=369, WMD -3.20 CI -4.1 to -2.3).
3.4.4 Compliance with treatment
We found 'treatment stopped in spite of need' - measured at one year significantly favoured the integrated treatment group (n=507, RR 0.20 CI 0.1 to 0.4, NNT 9 CI 8 to 12) compared with standard care. However, by two years we did not find any statistically significant differences between the treatment and control group (n=436, RR 0.66 CI 0.3 to 1.5).
3.4.5 Death/Suicide
Two people committed suicide (one from each treatment group) during the first year of the study. Also two people died in the control group, one an accidental death and the cause of the other death could not be ascertained.
3.4.6 Service use
We found the mean number of days spent in hospital at one year and two year time points were equivocal.
3.4.7 Social outcomes
We found no significant differences in the numbers of people 'not living independently' by one year (n=507, RR 0.55 CI 0.3 to 1.2), and two year data were also non-significant. The numbers of participants who were either 'not working or in education' measured over one year showed no significant differences between the study groups, but by two years the integrated treatment group had significantly lower levels of not being in work or education (n=436, RR 0.72 CI 0.5 to 1.0, NNT 11 CI 7 to 99), compared with the control group.

DISCUSSION

1. General

Studies were undertaken in the UK, Australia, Holland, Scandinavia, USA and China. Three studies (EDIE-UK, PACE-Australia, PRIME-USA) were concerned with preventing the development of psychosis in prodromal patients and four studies evaluated interventions for improving outcome in first episode psychosis (LifeSPAN-Australia, Linszen-Amsterdam, OPUS-Scandinavia, Zhang-Suzhou). Despite the comprehensive search, the results of this review are based on just seven studies, six of which have small sample sizes (mean average n=65, range 56-83). OPUS-Scandinavia was the exception with over 500 people randomised and was the only study to use a power calculation. Additionally, all seven studies used different interventions or controls and therefore could not be pooled for meta-analysis. These limitations are a source of uncertainty in our results. However, the substantial number of studies awaiting assessment may provide more data in the next few years.

2. Quality of design and follow up of included studies

All studies were randomised, although in terms of allocation concealment, the quality of included studies was acceptable but not good, since precise details of the method of randomisation were lacking for most studies. One study (EDIE-UK) attempted to blind raters, but this proved difficult and was not adequately maintained as participants 'divulged' sufficient information to inform the rater which treatment participants were receiving. Zhang-Suzhou and LifeSPAN-Australia also used raters who were blind to group allocation but they did not report whether allocation concealment was maintained. One study (PRIME-USA) did however use double blind methodology made possible by both groups

receiving the same psychosocial intervention with the variable being medication (olanzapine or placebo) which was easier to blind for than non-pharmaceutical interventions. OPUS-Scandinavia, Linszen-Amsterdam and PACE-Australia used independent raters not blinded to treatment. The nature of these therapies is not suited to the raters being blind to treatment allocation and where this was attempted (as with EDIE-UK) it proved difficult to maintain throughout the study.

In two trials (Linszen-Amsterdam, Zhang-Suzhou) key data were presented in a way that did not permit an intention to treat analysis on most outcomes. Rates of follow-up were particularly good in two trials (PACE-Australia, Zhang-Suzhou) and unclear (but probably acceptable) in one (Linszen-Amsterdam). Numbers of people lost to follow-up was not excessive in the other trials, but not good - EDIE-UK 70%, PRIME-USA 65%, OPUS-Scandinavia 77% and LifeSPAN-Australia 75%. One study did find significant differences in follow-up rates between treatment and controls (OPUS-Scandinavia), the effects of this unclear but may have had an impact on the findings of this review. A substantial omission from six of the seven trials was an attempt to capture the perspective of service users and their carers, by, for example, using satisfaction scales.

3. Trials to prevent the development of psychosis

3.1 PHASE SPECIFIC INTERVENTION (OLANZAPINE) + NON-SPECIFIC SUPPORTIVE THERAPY vs PLACEBO + NON SPECIFIC SUPPORTIVE THERAPY - PRIME-USA.

3.1.1 Leaving the study early

Attrition rates were not significantly different, although slightly more people did leave the olanzapine group by 12 months, but overall total attrition (65% by 12 months) were relatively low.

3.1.2 Conversion to psychosis

Olanzapine did not alter the numbers of people converting to psychosis over 12 months when compared with placebo. This study was randomised a total of 60 people and we think this number is probably too small to detect a treatment affect.

3.1.3 Global state

Clinical Global Impression 'severity of illness' and the Global Assessment of Functioning 'current' change scores were both non-significant. Data were limited by study size and larger groups may well have produced a different outcome.

3.1.4 Mental state

We did not find any significant outcome data from the SOPS scale over during 12 months of evaluation and the PANSS, YMRS and MADRS scores were also equivocal indicating that no real change in mental state occurred over a 12 month period for the olanzapine and placebo group.

3.1.5 Adverse effects

Extrapyramidal symptoms were not more frequent in the olanzapine group compared with the placebo group (SAS, BAS and AIMS), even though olanzapine dosage levels were within the lower end of the normal dose range.

3.1.6 Other adverse effects

Olanzapine did produce a statistically significant increase in weight compared with the placebo group. This limited data supports other recent reports of olanzapine's association with weight gain (Duggan 2005, Lieberman 2005). CoStart terms were also recorded and all were equivocal except for weight gain, with significantly more people gaining weight in the olanzapine group; NNH three. Cardiovascular measures were taken on blood pressure and pulse whilst sitting and standing over eight weeks with all data being equivocal. Twelve month data (sitting) pulse rates were significantly lower in the placebo group, but this may have been a chance finding since all other data were non-significant. Fatigue was higher in the olanzapine group with a NNH of four.

3.2 PHASE SPECIFIC INTERVENTION (COGNITIVE BEHAVIOURAL THERAPY) + NON-SPECIFIC SUPPORTIVE THERAPY vs NON-SPECIFIC SUPPORTIVE THERAPY- EDIE-UK

3.2.1 Leaving the study early

No differences were found for the numbers of participants leaving the study early by 12 months and as a proxy measure of treatment acceptability, CBT did not enhance or worsen compliance.

3.2.2 Transition to psychosis

The numbers of participants becoming psychotic over 12 months of observation were low and no significant differences between CBT (4/37) and the monitoring group (5/23) were found for this primary outcome.

3.3 PHASE-SPECIFIC INTERVENTION (RISPERIDONE + COGNITIVE BEHAVIOURAL THERAPY) + SPECIALISED TEAM vs SPECIALISED TEAM - PACE-Australia

3.3.1 Leaving the study early

All participants (n=59) remained in the study for one year, which is unusual for randomised trials of this length. The adherence to the study may have been due to participants being relatively well i.e. prodromal and also being cared for by a specialist team.

3.3.2 Transition to psychosis

Initial findings from this comparison suggest that a phase-specific intervention combining risperidone and cognitive behaviour therapy can delay, but not prevent the onset of psychosis. Whilst these findings are of interest, they are not definitive, as the single included trial (PACE-Australia) is substantially under-powered at the 12 month end-point. Moreover the use of a combination of

phase-specific interventions makes it unclear how far each contributes to the outcome, though a sub-analysis by the trialists suggests that risperidone makes the primary contribution.

3.3.3 Global state

GAF did not appear to have any effect on outcome in terms of global state, and again with such a small number of participants doubts will remain regarding efficacy.

3.3.4 Mental state

Delaying the onset of psychosis does not appear to have a substantial effect on medium term outcome, in terms of mental state. This could be because the trial is under powered, or it may be that the benefits of delaying onset of psychosis are less than anticipated. It is also difficult to evaluate the benefits of delaying psychosis without more information on the impact of treatment from the perspective of service users and carers.

3.3.5 Quality of life

No improvements in quality of life occurred in the early intervention group, even though they were given cognitive behavioural therapy. However, they also received risperidone which may have negated any gains in quality of life, due to its adverse effects profile.

4. Trials to improve outcome in first episode psychosis.

4.1 PHASE-SPECIFIC INTERVENTION (COGNITIVE BEHAVIOURAL THERAPY for SUICIDALITY) + SPECIALISED TEAM vs SPECIALISED TEAM - LifeSPAN-Australia

4.1.2 Leaving the study early

LifeSPAN therapy did not affect the numbers of people leaving the study early over six months, larger sample sizes and perhaps longer study time may have produced less equivocal data.

4.1.3 Suicide

Two people committed suicide, one in each group and the study size is too small to determine whether LifeSPAN therapy can reduce suicide.

4.2 PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + SPECIALISED TEAM vs SPECIALISED TEAM. Linszen-Amsterdam.

4.2.1 Relapse

Adding family therapy to care from a specialised team did not affect relapse rates, but Linszen-Amsterdam was substantially under powered, so that no definitive conclusions can be drawn. An unusual characteristic of the trial was that all participants had to consent to a three-month inpatient admission before randomisation. This may have limited the ability of the intervention to show an effect by excluding any differences in relapse rates occurring in the first three months after onset. It also limits applicability of findings to other early intervention services, which tend to be oriented towards reducing or avoiding admissions, rather than extending them (Edwards 2002).

4.3 PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + STANDARD CARE vs STANDARD CARE - Zhang-Suzhou

4.3.1 Leaving the study early

Retention of study participants over 18 months of care was good, with only 6% being lost to follow-up; the phase specific intervention with family therapy did not prove either a benefit or hindrance to study attrition.

4.3.2 Readmitted to hospital

These data suggest that family therapy in addition to standard care reduced readmission rates and possibly helped compliance. Unfortunately other outcome data were not presented on an intention to treat basis and are impossible to use. The main limitation of this trial was the particular nature of the standard care given, which appeared to be a low-key form of outpatient treatment, with little continuity and no community follow up. This makes it difficult to be certain how far the reduced admission rate in the intervention group was a non-specific effect of substantially increased contact with patients and their families, rather than a particular effect of family therapy. No data were available on how far the finding of fewer admissions was accompanied by improvements in outcome, or service user and carer satisfaction.

4.3.3 Compliance with medication

Family therapy did not appear, from limited participant numbers, to improve treatment compliance and larger sample sizes are needed to evaluate this outcome.

4.3 SPECIALISED TEAM vs STANDARD CARE -OPUS-Scandinavia

4.3.1 Leaving the study early

Integrated treatment significantly reduced the numbers of people leaving the study early by 12 months (NNT 9) and as a proxy measure of treatment acceptability was found to be more acceptable than placebo. By two years attrition rates were still significantly favouring integrated treatment (NNT 7). It appears participants were prepared to remain in treatment longer when care was given from a specialist team, which for people with psychosis is an important outcome.

4.3.2 Global state

Global Assessment of Functioning 'symptom' scores significantly favoured integrated treatment by 12 months, but this was not sustained and two year data were equivocal; GAF 'function' scores

were equivocal at 12 months, but by two years did significantly favour integrated treatment. These outcomes seem to confound each other and more research is needed to adequately determine if this form of care can indeed improve global state.

4.3.3 User satisfaction

Participants were significantly more satisfied with services in the integrated treatment group by 12 months, and this was sustained over two years. This result does fit with the positive findings for retention rates in the integrated treatment group.

4.3.4 Compliance with treatment

Overall, participants in the integrated care group were more compliant with treatment and outpatient visits than the standard care group. This effect was seen over one and two year time points suggesting integrated treatment is more acceptable to people with first episode psychosis than the standard care available to the control group. Again this result is consistent with attrition and user satisfaction outcomes.

4.3.6 Death/Suicide

Two people died from suicide, one person from each group.

4.3.7 Service use

We did not find any significant differences in the mean number of days per month participants spent in hospital and integrated treatment offered no advantages compared with the control group in terms of reducing the need for hospital care. Unfortunately, no data were reported on relapse. Relapse is a primary outcome for this review and an important measure of treatment efficacy for people with first episode psychosis, clinicians and health care managers.

4.3.8 Social outcomes

We did not find integrated treatment to have any significant affect on participant's ability to live independently over one and two year assessments. Integrated treatment did significantly improve participants employment and educational circumstances with 'not employed or in education' being lower by two years (NNT 11). However one year data were non-significant suggesting that two years of care are needed before benefits are obtained, although more data is needed to show this effect especially as most outcome data were not significant.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient data to make any firm recommendations for practice. However, the number of ongoing trials and studies awaiting assessment indicate this is a rapidly developing field, so it is likely that these implications for practice will become clearer and, perhaps radically different in the near future.

1. For people presenting with prodromal symptoms of psychosis.

At the moment it is not clear whether treating people presenting with prodromal symptoms of schizophrenia provides any benefits. There is insufficient data on the personal and social consequences of providing treatment to people who will not necessarily become unwell. Specialised treatment services for people with prodromal symptoms are only justified on an experimental basis.

2. For people in their first episode of psychosis

There is also little evidence to support the intervention of specialist teams for people in their first episode of psychosis. However, since such people do require treatment in some form, the ethical issues are less intense than for people presenting with prodromal symptoms. Moreover, there is also little evidence to support the 'standard care', which is the alternative to the employment of specialised first episode teams (NICE 2002). The use of first episode teams is therefore ethical even though there is not, as yet, strong evidence to support it.

There is little evidence to support the provision of phase-specific interventions to people in their first episode of psychosis. The only evidence available at present is for family therapy. Whilst this evidence is limited, it should be viewed in the broader context that family therapy is known to be effective for people with schizophrenia as a whole (Pharoah 2006). On this basis it would seem reasonable to recommend family therapy to people experiencing their first episode of psychosis, but there insufficient data to suggest that they should be given this intervention as a priority over people with established illness.

There is no evidence from clinical trials to support the benefits of early detection of patients in their first episode of psychosis.

3. For clinicians

Family intervention may be of value for people in their first episode of psychosis, as it may for people with longer established illnesses. It is important for clinicians to continue to keep up to date with this fast expanding field.

4. For policy makers

It is premature to implement wide-spread treatment programs for people with prodromal symptoms. Such treatment programs should only be implemented within the context of a well designed randomised study.

Implications for research

1. General

If CONSORT recommendations (Begg 1996, Moher 2001) had been followed by authors of the included studies and the editors

of the journals in which those reports were published, the effects of early intervention for psychoses would be more evident.

2. Specific

This review has identified a discrepancy between the global rate of growth of early intervention services and the paucity of underpinning evidence. Whilst there is a compelling theoretical case for early intervention, much of the supporting evidence is circumstantial (based on the correlation between duration of untreated psychosis and outcome) rather than definitive (based on improved outcome in clinical trials). If this discrepancy persists, the obvious risk is that, eventually early intervention will become routine practice, without its efficacy ever being definitively established.

Whilst this review has found some evidence of a growing body of research in the field, there is no room for complacency over the amount of work that needs to be done. Possible combinations of early detection, type of participant (prodromal or first episode), type of control, and type of intervention (phase-specific or specialised team) generate at least seventeen possible types of trial. So far, however, the review has identified only seven included trials which most of which are clearly under powered. The current substantial international interest in early intervention offers an opportunity to make major positive changes in psychiatric practice, but this opportunity may be missed without a concerted international programme of research to address key unanswered questions.

These key questions are:

Can phase-specific interventions prevent people with prodromal symptoms from developing psychosis and, if so, do they or their carers benefit as a result?

Can early detection reduce the duration of untreated psychosis, and if so, does this lead to improvements in outcome for service users and carers?

Are there phase-specific interventions that improve outcome for people with first episode psychosis, or for their carers?

Do specialised early intervention teams offer improvements in outcome over and above those provided by phase-specific interventions alone?

These questions give rise to two important points, which if borne in mind at the design stage, might increase the value of future trials in the field. Firstly, a phase-specific intervention should not be a priority for investigation unless it is known to be substantially different from existing interventions that are already known to be helpful to people at all stages of schizophrenia. For example, there is little point in investigating the effects of behavioural family therapy with minor modifications for first episode patients, when this intervention is known to be generally effective in schizophrenia. Phase-specific interventions ought to be given priority for evaluation only when they are substantial departures from what would be considered standard care, or where there is evidence that they are likely to be more effective when offered in the early stages of the illness.

Secondly, great care must be taken in defining the characteristics and activities of specialised early intervention teams. The complexity of 'early intervention' makes it likely that no two specialised teams will be identical. Unless the essence of an early intervention team can be adequately characterised, it is inevitable that disappointing findings will lead to arguments over whether a particular specialised team was really practising early intervention. Years of research effort can be wasted in this way. Lessons should be learned from research which has already been undertaken with other specialised psychiatric teams (such as assertive outreach teams) and fidelity scales developed as an early priority.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

EDIE-UK

Methods	Allocation: randomised, stratified according to gender and genetic risk (independent clerical worker, sealed envelopes). Blinding: single blind raters, attempts made to keep assessors blind*. Setting: community, Salford, Manchester. Inclusion criteria: based on PACE criteria, age range 16-36. Exclusion criteria: current of past receipt of antipsychotic medication. Follow-up: 1 year. Evaluation: conducted by research assistants.
Participants	Diagnosis: ultra high risk of developing 1st episode of psychosis (Yung modified criteria). N=60. Age: mean 21 years. Sex: male and female. History: not reported.
Interventions	1. Cognitive therapy: dose maximum of 26 sessions, over 6 months. N=37. 2. Monitoring control group. N=23.
Outcomes	Leaving the study early. Transition to psychosis (based on PANSS criteria). Unable to use - Mental state: PANSS (no usable data). Global state: GAF, GHQ (no usable data). Sociotropy - Autonomy Scale (no usable data). Meta-Cognitions Questionnaire (no usable data). Oxford-Liverpool Inventory of Feelings and Experiences (no usable data).
Notes	*Blinding was not adequately maintained due to participants divulging information about their therapist, or used language that suggested they were receiving cognitive therapy.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

LifeSPAN-Australia

Methods	Allocation: randomised (no further details). Blinding: single, no further details. Setting: Early Psychosis Prevention and Intervention Centre (EPPIC). Follow-up: 10 weeks and 6 months. Inclusion criteria: scoring from 4 to 7 on the expanded version of the BPRS suicidality subscore. Exclusion criteria: attended the EPPIC centre for more than one year. Evaluation: 'conducted blind to therapy'.
Participants	Diagnosis: first episode psychosis and acutely suicidal. N=56. Age: range 15-29 years. Sex: not reported. History: not reported.
Interventions	1. LifeSPAN therapy: dose 8 to 10 sessions + standard clinical care. N=31. 2. Standard care. N=25. LifeSPAN is a brief individual cognitively orientated therapy specifically designed for acutely suicidal youths with severe mental illness.
Outcomes	Leaving the study early. Death from suicide. Unable to use - Mental state: BPRS, SANS: (no usable data). Global state: GAF: (no usable data). QoL: (no usable data). Beck Hopelessness Scale: (no usable data). Self Esteem Scale: (no usable data). Self Report Problem Solving Rating Scale: (no usable data). Suicide Ideation Questionnaire: (no usable data). Suicide Intent Scale: (no usable data). Reasons for Living Inventory: (no usable data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Linszen-Amsterdam

Methods	Allocation: 'randomly assigned'. Blinding: unclear if raters blind to treatment condition. Setting: In-patient unit for adolescents, Amsterdam, Netherlands. Follow-up: 12 months (following on from initial 3 month inpatient admission), then 5 years. Inclusion criteria: first episode of schizophrenia, age 15-26, living or in close contact with parents or other relatives, Dutch speakers, no primary drug problem. Evaluation: 'independent raters'.
Participants	Diagnosis: schizophrenia. N=76. Age: mean 20.6. Sex: M 53 F 23. History: mean DUP 5.4 months.
Interventions	1. Behavioural family therapy + individual-orientated therapy. N=37. 2. Individual-orientated therapy alone. N=39.
Outcomes	Relapse. Unable to use - Mental state: BPRS: (data not reported). Compliance: (data not reported). Lost to follow up: (exact figures unclear, though no evidence of substantial loss).
Notes	First Episode Trial - care from a specialised team plus phase specific intervention versus care from specialised team. Unclear when randomisation took place, possible the inital sample size was 97, in which case not intention to treat. Five year data reported for whole sample, not by group allocation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

OPUS-Scandinavia

Methods	Allocation: randomised (computer generated random numbers, 1:1 in blocks of 6). Blinding: assessors not blind to treatment allocation, but independent of study group. Setting: multicentre, 5 centres, participants visited in their homes or other places in the community, or at their primary team members office. Exclusion criteria: taking antipsychotics for more than 12 weeks Follow-up: 1 and 2 years. Evaluations: by independent investigators, not blinded to treatment allocation.
Participants	Diagnosis: first episode schizophrenia spectrum disorder (ICD 10, codes in the F2 category). N=547. Age: range 18-45 years. Sex: M 256, F 291.

OPUS-Scandinavia (*Continued*)

	History: participants included in and outpatients who had not received antipsychotics for more than 12 weeks continuously.
Interventions	1. Integrated treatment. N=275. 2. Treatment as usual. N=272. Integrated treatment is an assertive community treatment, enhanced by better specific content via family involvement and social skill training. Treatment as usual consisted of care at a community mental health centre. All participants were offered antipsychotic drugs according to guidelines from the Danish Psychiatric Society, which recommends low dose, atypical antipsychotic strategy for 1st episodes of psychotic illness.
Outcomes	Leaving the study early. Global state: GAF. Client Satisfaction: CSQ-8. Suicide attempts. Social outcome: Social Network Schedule, not living independently; no working or in education. Service utilisation: average number of days in hospital. Compliance with treatment. Unable to use - Mental state: SAPS, SANS: (no usable data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

PACE-Australia

Methods	Allocation: simple randomisation by study co-ordinator. Blinding: independent rater, not blind. Setting: PACE clinic (Personal Assessment and Crisis Evaluation), part of EPPIC program, Melbourne, Australia. Inclusion criteria: age 14-30, living in Melbourne, met one of 3 criteria for an Ultra High Risk mental state. Follow-up: 0, 6,12 months.
Participants	Diagnosis: 'ultra high risk' of developing psychosis.* N=59. Age: mean 20. Sex: M 34, F 25. History: not reported.
Interventions	1. Specific Preventive Intervention: dose risperidone 1-2 mg/day + cognitive behavioural therapy + needs based case management + supportive psychotherapy. N=31. 2. Needs based intervention alone. N=28.

PACE-Australia (*Continued*)

Outcomes	Progressing to psychosis. Mental state: BPRS, HRSA, HRSD, SANS, YMS. Quality of Life: QLS. Overall functioning: GAF.
Notes	Prodromal Trial - Care from a specialised team plus a phase specific intervention versus care from a specialised team * Defined as either: family history of psychotic disorder & non specific symps & decrease in functioning on GAF of 30 points or more in last 12 ms, or attenuated psychotic symptoms sustained for at least 1 week, or brief episodes of psychotic symptoms not sustained beyond a week.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

PRIME-USA

Methods	Allocation: randomised. Blinding: double, pills dispensed in prepackaged packs, prelabelled by site number and sequential subject number within site. Setting: North America, 4 sites*, outpatient clinic. Inclusion criteria: age range 12-45 years. Exclusion criteria: past or current DSM-IV psychotic disorder; suffering from a psychiatric disorder that could account for the prodromal symptoms; judged to be suicidal or homicidal; prodromal symptoms due to drug or alcohol use. IQ less than 80; seizure disorders. Follow-up: one year medication with one year follow-up without medication. Evaluation: 'patient, investigator, prescriber and rater were maintained blind to group assignment throughout the study'.
Participants	Diagnosis: prodromal at risk of psychosis (SIPS, COPS). N=60. Age: range 12-36 years, mean 18 years. Sex: M 39, F 21. History: participants included those who had responded to advertisements, or were referred by clinicians.
Interventions	1. Olanzapine: dose 5-15 mg/day, mean 8 mg/day. N=31. 2. Placebo. N=29. Olanzapine was adjusted within a range of 5-15 mg/day based on the clinicians judgement. Individual and family psychosocial interventions were available. Lorazepam (max 8 mg/day) diazepam (max 40 mg/day) and chloral hydrate (max 100 mg/day) were used for agitation and/or insomnia. Benztropine mesylate or biperiden up to 6 mg/day allowed to treat EPS. Nizatidine 300-600 mg/day for weight gain, beginning towards the end of the study.
Outcomes	Leaving the study early. Progressing to psychosis: POPS scale. Mental state: PANSS, MADRS, YMRS, SOPS.

PRIME-USA (*Continued*)

	Global state: CGI-S, GAF. Adverse effects: SAS, AIMS, BAS, weight gain, vital signs, CoStart terms. Unable to use - QoL: no data. Resource utilisation: no usable data. Adverse effects: EPS (no usable data). Neurocognitive function: no data Premorbid functioning: Cannon-Spoor Premorbid Adjustment Scale.
Notes	*Yale University, New Haven, Connecticut; University of Toronto, Canada; University of North Carolina, USA; University of Carolina, Canada.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Zhang-Suzhou

Methods	Allocation: 'randomly assigned'. Blinding: not reported. Setting: psychiatric hospital, Suzhou, China. Inclusion criteria: male, just discharged after first episode for schizophrenia, no other medical conditions. Follow-up: 18 months. Evaluation: by 'attending physicians' blind to allocation.
Participants	Diagnosis: schizophrenia (Chinese Medical Association Criteria). N=83. Age: mean 23.8. Sex: all male. History: mean DUP 34.6 months.
Interventions	1. Family psychoeducation in individual and group sessions plus standard out-patient care. N=42. 2. Out-patient care. N=41.
Outcomes	Readmitted. Lost to follow-up Compliant with medication. Unable to use - Chlorpromazine equivalent dosage of medication: (not a clinical or social outcome). Mental state: Chinese BPRS (excluded readmitted patients) Overall functioning: Chinese GAS (excluded readmitted patients).
Notes	First Episode Trial - phase-specific intervention plus standard care versus standard care.

Risk of bias

Zhang-Suzhou (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

SIPS = Structured Interview for Prodromal Syndromes
COPS = Criteria of Prodromal Syndromes
DSM= Diagnostic and Statistical Manual
ICD-10= International Classification of Diseases
Rating Scales:
Mental state -
BDI = Beck Depression Inventory
BPRS = Brief Psychiatric Rating Scale
HRSA = Hamilton Rating Scale for Anxiety
HRSD = Hamilton Rating Scale for Depression
MADRS = Mongomery and Asberg Depression Rating Scale
PANSS= Positive and Negative Symptom Scale
SANS = Schedule for the Assessment of Negative Symptoms
SOPS=Scale of Prodromal Symptoms
POPS= Presence of Psychosis Scale
YMRS = Young Mania Rating Scale
YMS = Young Mania Scale
Global state -
CGI = Clinical Global Impression
GAS = Global Adjustment Scale
GAF = Global Assessment of Functioning
Adverse effects -
AIMS = Abnormal and Involuntary Movement Scales
BAS = Barnes Akathisia Scale
SAS=- Simpson & Angus
User satisfaction -
CSQ-8 = Client Satisfaction Questionnaire-8.
Others -
DUP = Duration of untreated psychosis
LOCF= Last Observation Carried Forward
PACE= Personal Assessment and Crisis Evaluation
EM = Explanatory Model scale
GSI = General Symptom Index of the SCL-90-R
IS/O = Integration/Sealing Over
QLS = Quality of Life Scale
UHR = Ultra high risk (of developing psychosis)
OLIFE =Oxford-Liverpool Inventory of Feelings and Experiences
MCQ =Meta-Cognitions Questionnaire
SAC=Sociotropy - Autonomy Scale

Characteristics of excluded studies *[ordered by study ID]*

Addington-1999	Allocation: not randomised, before and after design.
Alanen-1994	Allocation: not randomised, before and after design.
Albiston-1998	Allocation: not randomised, before and after design with historical control.
Anonymous-1987	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (pimozide versus flupenthixol) at standard doses without specific early intervention protocol.
Birchwood-1989	Allocation: not randomised, service description. Participants: not first episode patients (study of early detection of signs of relapse).
Clare-1994	Allocation: not randomised, service description. Participants: not first episode patients (study of early signs of depression in long term patients).
COPE-Melbourne	Allocation: non-randomised quasi-experimental design, controls selected from a similar location to the experimental site.
Craig 2004b	Allocation: randomised. Participants: people with 1st & 2nd episode psychosis.
Crow-1986	Allocation: randomised. Participants: people with first episode psychosis. Intervention: neuroleptic medication at standard doses versus no medication, no specific early intervention protocol.
Culberg-1998	Allocation: not randomised - before and after design with historical controls.
Davidson FutuRis	Allocation: randomised. Participants: people with early psychosis. Interventions: atypical versus conventional antipsychotic.
DeHaan-1997	Allocation: not randomised - before and after design.
Drury-2000	Allocation: randomised. Participants: not people with first episode psychosis.
Emsley 2004	Allocation: randomised. Participants: people with recent onset schizophrenia. Interventions: medication only (risperidone versus haloperidol).
Emsley-1999	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (risperidone versus haloperidol), no specific early intervention protocol.

(*Continued*)

Falloon-1992	Allocation: not randomised, no controls.
Fisher-2001	Allocation: not randomised - service description, outcome assessed by qualitative survey.
Fitzgerald-1998	Allocation: not randomised - before and after design.
Fresan-2001	Allocation: not randomised - before and after study.
Gaebel 2004	Allocation: randomised. Participants: people with first episode schizophrenia. Interventions: medication only (risperidone versus low-dose haloperidol).
Hartmann-1974	Allocation: not randomised - retrospective study.
Heydebrand 2004	Allocation: randomised. Participants: people with first episode schizophrenia. Interventions: haloperidol versus risperidone.
Jenner-2001	Allocation: not randomised - no control group. Participants: not people with first episode psychosis (adolescents, but on average in treatment for about 3 years).
Jolley 2003	Allocation: randomised. Participants: people with 1st & 2nd episode psychosis.
Kadota-1992	Allocation: not randomised - uncontrolled follow-up study of response to neuroleptic treatment.
Kauranen-2000	Allocation: not randomised - uncontrolled follow up study.
Kavanagh 2004	Allocation: randomised. Participants: people with 1st and 2nd episode psychosis.
Keefe-2000	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (olanzapine versus haloperidol) at standard doses without specific early intervention protocol.
Keshavan-1998	Allocation: not randomised - before and after study with historical control group.
Kopala 2003	Allocation: randomised. Participants: people with recent onset schizophrenia. Interventions: risperidone versus haloperidol.
Lenior 2003	Allocation: randomised. Participants: people with schizophrenia, 1st and 2nd or more episodes.

(*Continued*)

Lieberman 2005b	Allocation: randomised. Participants: people with first-episode psychosis and healthy volunteers. Interventions: medication only (haloperidol versus olanzapine).
Malla-2001	Allocation: not randomised - before and after study, no control group.
McGorry-1996	Allocation: not randomised - before and after study with historical controls.
Mosher 1975	Allocation: not randomised - allocation on "a consecutively admitted, space available basis" to "Soteria" - a small home like facility in the community which acted as an alternative to admission for patients in their first episode of schizophrenia.
Mottaghipour-2000	Allocation: not randomised, compared with a group of families of long term patients.
Opjordsmoen-2000	Allocation: not randomised - quasi-experimental design with control from another geographical area.
Parlato-1999	Allocation: non-randomised - a description of a service.
Perez 2003	Allocation: randomised. Participants: people with first episode psychosis. Interventions: medication only (olanzapine versus risperidone versus haloperidol).
Power 2004	Allocation: randomised. Participants: people with 1st and 2nd episode psychosis.
Purdon-2000	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (olanzapine versus risperidone versus haloperidol) without specific early intervention protocol.
Rund-1994	Allocation: not randomised, before and after study with historical control.
Sanger-1999	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (olanzapine versus haloperidol) without specific early intervention protocol.
Schooler 2003	Allocation: randomised. Participants: people with recent onset schizophrenia. Interventions: medication only (risperidone versus haloperidol).
SOCRATES-UK	Allocation: randomised. Participants: not first episode patients, participants could be in either first or second admission, as long as second admission within 2 years of first admission (estimated that 61/309 participants were not first episode).
Szymanski-1994	Allocation: not randomised - before and after study without control group.

(*Continued*)

Tait 2005	Allocation: stratified-cluster randomised trial. Participants: first episode psychosis. Interventions: educational intervention on detecting 1st episode psychosis versus cognitive behavioural therapy for depression. Outcomes: no usable data.
Tarrier 2004	Allocation: randomised. Participants: people with first or second episode schizophrenia.
Thomas-1979	Allocation: not randomised - no control group. Participants: not first episode patients, although all were adolescents, some were experiencing an exacerbation of chronic schizophrenia.
Turetz-1997	Allocation: not randomised - no control group. Participants: probably not first episode patients, although all participants were children, they were selected on the basis of treatment resistance and so probably not in the first episode.
Walczewski-1998	Allocation: not randomised - a quasi-experimental design, patients receiving a psychosocial treatment program were compared with a group receiving an individual treatment programme.
Wang-2000	Allocation: randomised. Participants: people with first episode psychosis. Intervention: medication only (risperidone versus clozapine) without specific early intervention protocol.
Welch-2000	Allocation: not randomised - service description.
Whitehorn-1998	Allocation: not randomised - before and after study without control.
Whitwell-2000	Allocation: not randomised - service description.
Wieneke-2000	Allocation: not randomised - service description.
Yap-2001	Allocation: not randomised - before and after study without control group.
Zhang-Wong-1999	Allocation: not randomised - prospective uncontrolled study to determine optimal dose of haloperidol.

Characteristics of ongoing studies *[ordered by study ID]*

Bechdolf-FETZ

Trial name or title	Early Recognition and Intervention Centre for Mental Crisis (FETZ).
Methods	
Participants	Diagnosis: Prodromal psychosis. N>188.

Bechdolf-FETZ (*Continued*)

Interventions	1. Cognitive behavioural therapy.
Outcomes	Psychosis.
Starting date	January 2001.
Contact information	Early Recognition and Intervention Centre for Mental Crisis (FETZ) Department of Psychiatry and Psychotherapy University of Cologne Kerpenerstrasse 62 50924 Cologne Germany e-mail: andreas.bechdolf@uk-koeln.de
Notes	

DATA AND ANALYSES

Comparison 1. PHASE SPECIFIC INTERVENTION (OLANZAPINE) + NON-SPECIFIC SUPPORTIVE THERAPY vs PLACEBO + NON-SPECIFIC SUPPORTIV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (for reasons other than psychosis)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 by eight weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.60, 2.74]
1.2 by one year	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.88, 2.88]
2 Converted to psychosis: POPS	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 over one year	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.18]
3 Global state: 1. Average total change score - by 1 month (CGI-severity of illness, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.82, 0.36]
4 Global state: 2. Average total change score - by 12 months (GAF-current, high score=good)	1	59	Mean Difference (IV, Fixed, 95% CI)	2.43 [-4.77, 9.63]
5 Mental state: 1. Average total change score - by 12 months (SOPS, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 total score	1	59	Mean Difference (IV, Fixed, 95% CI)	-2.76 [-12.03, 6.51]
5.2 positive score	1	59	Mean Difference (IV, Fixed, 95% CI)	-2.73 [-6.18, 0.72]
5.3 negative	1	59	Mean Difference (IV, Fixed, 95% CI)	0.28 [-3.02, 3.58]
5.4 disorganisation	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-2.69, 1.71]
5.5 general	1	59	Mean Difference (IV, Fixed, 95% CI)	0.18 [-1.84, 2.20]
6 Mental state: 2. Average total change score - by 12 months (PANSS, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 total	1	59	Mean Difference (IV, Fixed, 95% CI)	0.48 [-10.69, 11.65]
6.2 positive	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-3.75, 2.61]
6.3 negative	1	59	Mean Difference (IV, Fixed, 95% CI)	0.52 [-2.60, 3.64]
6.4 general	1	59	Mean Difference (IV, Fixed, 95% CI)	0.54 [-5.44, 6.52]
7 Mental state: 3. Average total change score - by 12 months (YMRS, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-3.77, 1.95]
8 Mental state: 4. Average total change score - by 12 months (MADRS, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	0.68 [-3.81, 5.17]
9 Adverse effects: 1. Average total change score - by 8 weeks (SAS, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.59, 0.79]
10 Adverse effects: 2. Average total change score - by 8 weeks (BAS, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.58, 1.58]

11 Adverse effects: 3. Average total change score - by 8 weeks (AIMS, high score=worse)	1	59	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.34, 1.54]
12 Adverse effects: 4. Average total weight change score (kg) - by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	7.63 [4.04, 11.22]
13 Adverse effects: 5. Weight gain - by 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [1.53, 8.28]
14 Adverse effects: 6. Average total change score - by 8 weeks (Cardiovascular)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 sitting systolic blood pressure	1	59	Mean Difference (IV, Fixed, 95% CI)	1.0 [-4.28, 6.28]
14.2 sitting diastolic blood pressure	1	59	Mean Difference (IV, Fixed, 95% CI)	0.70 [-4.43, 5.83]
14.3 standing systolic blood pressure	1	59	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-9.18, 3.58]
14.4 standing diastolic blood pressure	1	59	Mean Difference (IV, Fixed, 95% CI)	0.20 [-4.96, 5.36]
14.5 sitting pulse rate	1	58	Mean Difference (IV, Fixed, 95% CI)	7.20 [-1.04, 15.44]
14.6 standing pulse rate	1	57	Mean Difference (IV, Fixed, 95% CI)	3.90 [-4.87, 12.67]
15 Adverse effects: 7. Average total change score - by 12 months (Pulse, BPM)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 sitting pulse rate	1	58	Mean Difference (IV, Fixed, 95% CI)	8.31 [0.53, 16.09]
15.2 standing pulse rate	1	57	Mean Difference (IV, Fixed, 95% CI)	2.86 [-6.69, 12.41]
16 Adverse effects: 8. Treatment emergent adverse events - by 8 weeks (CoStart Term)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 somnolence	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.90, 5.59]
16.2 weight gain	1	60	Risk Ratio (M-H, Fixed, 95% CI)	10.29 [1.42, 74.79]
16.3 increased appetite	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.51, 6.80]
16.4 anxiety	1	60	Risk Ratio (M-H, Fixed, 95% CI)	4.68 [0.58, 37.68]
16.5 nervousness	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.37, 9.46]
16.6 asthenia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.74 [0.44, 31.55]
16.7 joint disorder	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.20, 4.27]
16.8 abnormal thoughts	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.25, 7.81]
17 Adverse effects: 9. Fatigue - by 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	8.42 [1.14, 62.40]

Comparison 2. PHASE SPECIFIC INTERVENTION (CBT) + NON-SPECIFIC SUPPORTIVE THERAPY vs NON-SPECIFIC SUPPORTIVE THERAPY

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - by 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.44, 2.16]
2 Transition to psychosis - by 12 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.66]

Comparison 3. PHASE SPECIFIC INTERVENTION (RISPERIDONE + CBT) + SPECIALISED TEAM vs SPECIALISED TEAM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - by 12 months	1	59	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Progression to psychosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 by 6 months	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.08, 0.89]
2.2 by 12 months	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.30]
3 Global state: Average endpoint score (GAF, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	4.20 [-2.57, 10.97]
3.2 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Mental state: 1a. Average endpoint score (BPRS psychotic symptoms -general, high score=worse, skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.25, 1.45]
4.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.25, 1.25]
4.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.99, 2.39]
5 Mental state: 1b. Average endpoint score (SANS, psychotic symptoms -negative, high score=worse, skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-9.80, 3.40]
5.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-4.60 [-12.72, 3.52]
5.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-7.87, 6.27]
6 Mental state: 2a. Average endpoint score anxiety (HRSA, high score=worse, skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-4.85, 3.45]
6.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-4.81, 2.61]
6.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	0.60 [-4.18, 5.38]

7 Mental state: 2b. Average endpoint score depression (HRSD, high score=worse, skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.51, 3.51]
7.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-4.77, 4.37]
7.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	1.20 [-3.22, 5.62]
8 Mental state: 2c. Average endpoint score mania (YMS, high score=worse, skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	0.80 [-1.38, 2.98]
8.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.46, 3.86]
8.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Quality of life: Average endpoint score (QLS, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 at baseline	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-14.12, 7.92]
9.2 by 6 months	1	59	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-13.63, 10.83]
9.3 by 12 months	1	59	Mean Difference (IV, Fixed, 95% CI)	0.80 [-10.15, 11.75]

Comparison 4. PHASE-SPECIFIC INTERVENTION (CBT for SUICIDALITY) + SPECIALISED TEAM vs SPECIALISED TEAM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - by 6 months	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.72, 5.66]
2 Suicide - by 6 months	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.05, 12.26]

Comparison 5. PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + SPECIALISED TEAM vs SPECIALISED TEAM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse by end of treatment - by 12 months	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.37, 2.98]

Comparison 6. PHASE-SPECIFIC INTERVENTION (FAMILY THERAPY) + STANDARD CARE vs STANDARD CARE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - by 18 months	1	83	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.26, 8.31]
2 Readmitted to hospital - by 18 months	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.13, 0.62]
3 Not compliant with medication	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.04]

Comparison 7. SPECIALISED TEAM vs STANDARD CARE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 by one year	1	547	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.81]
1.2 by two years	1	547	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.50, 0.82]
2 Global state: 1. Average endpoint score - by 12 and 24 months (GAF-symptom, high score= good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 by one year	1	419	Mean Difference (IV, Fixed, 95% CI)	-3.71 [-6.69, -0.73]
2.2 by two years	1	369	Mean Difference (IV, Fixed, 95% CI)	-2.51 [-5.70, 0.68]
3 Global state: 2. Average endpoint score - by 12 and 24 months (GAF-function, high score= good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 by one year	1	419	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-5.15, 0.55]
3.2 by two years	1	369	Mean Difference (IV, Fixed, 95% CI)	-4.03 [-7.23, -0.83]
4 User satisfaction: Average endpoint score - by 12 and 24 months (CSQ-8, high score= good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 by one year	1	419	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-3.07, -0.73]
4.2 by two years	1	369	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-4.14, -2.26]
5 Compliance with treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 treatment stopped in spite of need - by one year	1	507	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.42]
5.2 treatment stopped in spite of need - by two years	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.29, 1.50]
6 Death other than suicide - by 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 accident	1	506	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.59]
6.2 unexplained	1	507	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.56]
7 Suicide: Death - by 12 months	1	506	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.81]

8 Service use: Average mean number of days per month in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 by one year	1	507	Mean Difference (IV, Fixed, 95% CI)	-1.39 [-2.83, 0.05]
8.2 by two years	1	436	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.88, 0.54]
9 Social outcomes: 1. Not living independently	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 by one year	1	507	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.17]
9.2 by two years	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.36, 1.53]
10 Social outcomes: 2. Not working or in education	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 by one year	1	507	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.65, 1.17]
10.2 by two years	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.54, 0.97]

WHAT'S NEW

Last assessed as up-to-date: 22 August 2006.

15 February 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 2, 2004

30 October 2008	Amended	Converted to new review format.
23 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Max Marshall - designed the review, developed the search strategy, screened the search results, appraised the papers and extracted data, analysed and interpreted the data and wrote the final report.

Austin Lockwood - co-ordinated the review and collected data, screened the search results, organised the retrieval of papers, appraised the papers and extracted data, managed the data and entered data in RevMan, analysed and interpreted the data and wrote the final report.

John Rathone - (2006 update) screened the search results, appraised the papers and extracted data, analysed and interpreted the data and wrote the final report.

DECLARATIONS OF INTEREST

Max Marshall and Austin Lockwood received funding for the review from the UK Department of Health, which is committed to a policy of implementing Early Intervention teams across England and are in the early stages of developing a fidelity scale for early intervention teams. Max Marshall is Clinical Director of the Lancashire Early Intervention Service.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Psychotic Disorders [diagnosis; therapy]; * Schizophrenia [diagnosis; therapy]; Early Diagnosis; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans