Benzodiazepines for psychosis-induced aggression or agitation (Review)

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[Intervention Review]

Benzodiazepines for psychosis-induced aggression or agitation

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ABSTRACT

Background

Acute psychotic illness, especially when associated with agitated or violent behaviour, can require urgent pharmacological tranquillisation or sedation. In several countries, clinicians often use benzodiazepines (either alone or in combination with antipsychotics) for this outcome.

Objectives

To estimate the effects of benzodiazepines, alone or in combination with antipsychotics, when compared to placebo or antipsychotics, to control disturbed behaviour and reduce psychotic symptoms.

Search methods

We searched the Cochrane Schizophrenia Group's register (October 2002 and April 2005), inspected reference lists of included and excluded studies and contacted authors of relevant studies.

Selection criteria

We included all randomised clinical trials comparing benzodiazepines, alone or in combination with antipsychotics, with placebo or sole use of antipsychotics, for people with acute psychotic illnesses.

Data collection and analysis

We reliably selected studies, quality assessed them and extracted data. For binary outcomes we calculated standard estimates of relative risk (RR) and their 95% confidence intervals (CI), and weighted number needed to treat or harm (NNT/NNH) statistics. For continuous outcomes we estimated a weighted mean difference between groups. If heterogeneity was found, we used a random effects model.

Main results

We included eleven studies with a total of 648 participants. When comparing benzodiazepines with placebo, sedation was equally prevalent (n=102, 1 RCT, RR 1.67 CI 0.4 to 6.6), however, fewer people allocated lorazepam remained excited at 24 hours (n=102, RR 0.62 CI 0.4 to 1.0, NNT 5 CI 3 to 59). The lorazepam and placebo group experienced similar non-significant, low levels of adverse effects. In the comparison of benzodiazepines versus use of antipsychotics without use of anticholinergics/antihistamines, people allocated benzodiazepines did not clearly need additional medication compared with those given antipsychotics (n=216, 2 RCTs, RR

1.28 CI 0.5 to 3.2). Numbers sedated were also equivocal between groups (n=324, 6 RCTs, RR 0.76 CI 0.5 to 1.2) as were mental state ratings. Extrapyramidal symptoms were significantly higher in the antipsychotic treatment group (n=391, 7 RCTs, RR 0.17 CI 0.1 to 0.4, NNT 6 CI 2 to 17). Two trials (total n=83) comparing lorazepam plus haloperidol with lorazepam alone found no clear difference for the need of additional medication (n=83, 2 RCTs, RR 1.02 CI 0.8 to 1.3) or 'not improved' at one hour (n=20, 1 RCT, RR 1.47 CI 0.66 to 3.25). There was no difference in the incidence of extrapyramidal symptoms (n=83, 2 RCTs, RR 1.94 CI 0.2 to 20.3). Finally when the benzodiazepine plus antipsychotic combination was compared with antipsychotics alone (2 RCTs, n=95) there was no difference between groups in the need for additional medications (n=67, 1 RCT, RR 0.95 CI 0.8 to 1.2) or for mental state measures. Extrapyramidal symptoms were significantly lower for people receiving both benzodiazepines and antipsychotics compared with those receiving antipsychotics alone (n=95, 2 RCTs, RR 0.45 CI 0.2 to 0.9, NNH 2 CI 1 to 5). There was no significant difference in the number of participants unfit for early discharge (n=28, 1 RCT, RR 0.90 CI 0.54 to 1.5).

Authors' conclusions

There is insufficient data from these studies to support or refute the use of benzodiazepines with or without antipsychotics where emergency drugs are needed. The sole use of older antipsychotics unaccompanied by anticholinergic drugs may be problematic, but studies in this review are not large enough to identify any serious adverse effects of benzodiazepines such as respiratory depression. Larger, more informative studies are needed before definite conclusions can be drawn as to the efficacy of benzodiazapines.

PLAIN LANGUAGE SUMMARY

Benzodiazepines alone or in combination with antipsychotic drugs for acute psychosis

In this review we estimated the effects of benzodiazepines (e.g. diazepam, lorazapam, midazolam, clonazepam), for controlling acutely disturbed behaviour and psychotic symptoms when compared with placebo, antipsychotic drugs such as haloperidol, or a combination of both antipsychotics and benzodiazepines. We concluded from this review that there is little difference between benzodiazepines and antipsychotics for the management of acute psychotic behaviour, and that the few small trials we found were often poorly reported. The lower incidence of distressing acute movement disorder in people receiving benzodiazepines may encourage use of benzodiazepines in preference to the older antipsychotics (administered without additional anti-movement-disorder medication), but these adverse effects can be prevented with the use of alternative drugs such as procyclidine and promethazine. However, all the studies included in this review were underpowered and failed to identify potentially serious adverse effects of benzodiazepines such as respiratory depression. This review highlights the need for further more comprehensive studies in this area.

BACKGROUND

Acutely agitated people with serious mental illness may exhibit disruptive and dangerous behaviour. Control of this behaviour, with or without sedation, may be an initial treatment goal (Levy 1996). Ideally, in order to ensure a safe and therapeutic environment, attempts should be made to calm the patient through either verbal de-escalation or intensive nursing techniques. Frequently however, the behaviour may be too disturbed or agitated for 'verbal tranquillisation' to be effective and it might prove imperative that further action in the form of rapid tranquillisation is given.

Rapid tranquillisation is commonly used in an emergency situation, although the chosen drug regimen varies greatly. A survey of emergency prescribing in one large UK hospital showed that rapid medical tranquillisation occurred almost every day (Pilowsky 1992). Eight different drugs were used, the most common being diazepam, haloperidol and droperidol (Table 1). In the developing world, where most emergency incidents occur due to the sheer weight of numbers, practice may be more uniform. A recent survey in Rio de Janeiro, Brazil showed that a haloperidol-promethazine mixture (intramuscular) was commonly used (Huf 2000) although benzodiazepines were also administered (Table 2). Recommendations as to which drugs should be used for the emergency drug management of aggressive people often differ (Cunnane 1994, Binder 1999).

Cochrane reviews of the effects of droperidol (Cure 2001) and haloperidol (Joy 2001) are complete but the authors found no systematic reviews of the effects of benzodiazepines in the acute psychiatric emergency. Traditional literature reviews are inconclu-

sive and therefore unhelpful. In one review, the authors concluded that benzodiazepines may be most useful as adjunct therapy in the management of psychotic agitation (Wolkowitz 1991). Extein 1980, however, suggested that benzodiazepines were likely to be of most use when used in less severe states of anxiety. Stimmel 1996, concluded that benzodiazepines, either as monotherapy or used as adjuncts to antipsychotic agents, produced antipsychotic effects in 50% of people in controlled trials. The effects of benzodiazepines in the treatment of acute psychosis may not be limited to their sedative/anxiolytic affects. Benzodiazepines, used as an adjunct to antipsychotics may also decrease positive and negative symptoms of schizophrenia (Wolkowitz 1986, Csernansky 1988) and may also be of value in the treatment of people whose schizophrenic illness is resistant to traditional antipsychotic agents (Wolkowitz 1989).

Both benzodiazepines and antipsychotics can cause undesirable adverse effects and it is unclear whether the combination of benzodiazepines with antipsychotic drugs compounds or dilutes their individual adverse effects. Acute phase treatment with antipsychotic drugs may result in debilitating extrapyramidal symptoms and rarely, neuroleptic malignant syndrome can occur (Dubin 1988) and it has been suggested that benzodiazepines may decrease the incidences of these side effects (Battaglia 1997). However, benzodiazepines are associated with adverse effects such as sedation, cognitive impairment and behavioural disinhibition (Mendelson 1992). The association with behavioural disinhibition can mean that benzodiazepines may sometimes be an inappropriate choice for patients with aggression resulting from psychotic illness (Fava 1997).

OBJECTIVES

To estimate the effects of benzodiazepines, used alone or in combination with antipsychotic drugs, for acutely disturbed people with psychosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. Where a trial was described as 'double-blind' but did not mention that the study was randomised, we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes when these studies were added, we included these in the final analysis. If there was a substantive difference, we used only clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

Any people presenting to the adult services with acutely disturbed/aggressive/agitated behaviour believed to be secondary to psychotic illnesses such as schizophrenia, schizoaffective disorder, mixed affective disorders, manic phase of bipolar disorder or brief psychotic episode. For the purposes of this review, we have defined 'acute' as where authors of trials state or imply that the behavioural disturbance is of sudden onset and/or extreme in nature. Where trials included people with organic illnesses or people abusing substances, we only included these trials if over 60% of participants were exhibiting disturbed behaviour resulting from a psychotic episode.

Types of interventions

1. Benzodiazepines: any dose given alone, orally or by intramuscular or intravenous injection.
2. Benzodiazepines: any dose, in combination with any antipsychotic drug, given orally or by intramuscular or intravenous injection.
3. Any antipsychotic.
4. Placebo.

Types of outcome measures

As this was a review of the effects on acute psychosis, we only included those outcomes up to and including 48 hours after the initial dose of medication was given. Outcomes were divided into immediate (within 15 minutes), short term (>15 minutes - one hour) and medium term (>1 - 48 hours).

Primary outcomes

1. Behaviour
1.1 No clinical improvement

Secondary outcomes

1. Global impression
1.1 Tranquillisation (feeling of calmness and/or calm, non-sedated behaviour)
1.2 Aggression
1.3 Self harm, including suicide
1.4 Injury to others
1.5 Clinically important improvement in self care, or degree of improvement in self care
1.6 Compulsory administrations of treatment
1.7 Leaving the study early
1.8 Sedation (sleepiness and drowsiness)

1.9 Use of additional doses of medication
2. Behaviour
2.1 Clinically important change in behaviour
3. Mental state
3.1 No clinically important change in general mental state
3.2 Average endpoint general mental state score
4. Symptoms
4.1 Clinically important reduction of symptoms as defined by each study
4.2 Any reduction in severity of symptoms
4.3 Increase in symptoms
4.4 Degree of change in severity of symptoms
5. Side effects
5.1 Incidence of side effects, general or specific
5.2 Measured acceptance of treatment
5.3 Use of antiparkinson treatment
5.4 Sudden and unexpected death
6. Hospital and service outcome
6.1 Time in seclusion
6.2 Hospitalisation of people in the community
6.3 Duration of hospital stay
6.4 Severity of symptoms when discharged from hospital
6.5 Changes in hospital status (for example, changes from informal care to formal detention in care, changes of level of observation by ward staff and use of secluded nursing environment)
6.6 Changes in services provided by community teams
7. Satisfaction with care
7.1 Recipient of care
7.2 Informal care givers
7.3 Professional carers
8. Economic outcomes

Search methods for identification of studies

Electronic searches

We identified relevant randomised controlled trials by searching the Cochrane Schizophrenia Group's register (October 2002) using the following search strategy which was designed to identify references relevant to benzodiazepines.
[benzodiazepine* or adinazolam or alprazolam or anthramycin or bentazepam or bromazepam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or "clorazepam clorazepate" or clotiazepam or cloxazolam or cyprazepam or diazepam or doxefazepam or estazolam or etizolam or flunitrazepam or flurazepam or flutazoram or fosazepam or girisopam or halazepam or haloxazepam or ketazolam or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or midazepam or nerisopam or nitrazepam or nordazepam or oxazepam or oxazolam or pinasepam or prazepam or temazepam or tetrazepam or tofisopam or triazolam or triflubazam]

Prior to publication of the review a further update of the Cochrane Schizophrenia Group's Trials Register was searched (April 2005) using the phrase:
[(*azepam* OR *zolam* OR *diazep* or *Anthramycin* OR *clorazepat* OR *Devazepid* OR *Flumazenil* OR *Pirenzepine* OR *clobazam* OR * flutazoram* or *girisopam* or *nerisopam* or *pinasepam* or *tofisopam* or *triflubazam*)in REFERENCE Ti/Ab/In and (*azepam* OR *zolam* OR *diazep* or *Anthramycin* OR *clorazepat* OR *Devazepid* OR *Flumazenil* OR *Pirenzepine* OR *clobazam*) in STUDY Intervention].

Searching other resources

1. Hand searching
We sought additional relevant studies by hand searching reference lists of included and excluded studies.
2. Requests for additional data
We contacted authors of relevant studies to inquire about other sources of relevant information.

Data collection and analysis

1. Study selection
Material downloaded from electronic sources included details of author, institution or journal of publication. The principal reviewer (DG) inspected all reports. These were then re-inspected by AB, AM or JR in order to ensure reliable selection. We resolved any disagreement by discussion, and where there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained, we decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and added these trials to the list of those awaiting assessment.
2. Assessment of quality
We independently allocated trials to three quality categories, based on allocation concealment, as described in the Cochrane Collaboration Handbook (Alderson 2004). When disputes arose as to which category a trial was allocated, we resolved these by consensus following discussion.
3. Data management
3.1 Data extraction
Two of the four reviewers (AB, AM, DG, JR) independently extracted the data from each study. If there was disagreement regarding extracted data, we resolved any disputes by discussion and consensus or by referral to the third reviewer. Where further clarification or missing data were needed from study authors, all reasonable attempts to contact the authors were made.

3.2 Sensitivity analysis
We excluded data from studies where more than 50% of participants in any group were lost to follow up. Regarding the outcomes of 'aggression', 'self harm' and 'harm to others', as they are major

risks of non-treated acute psychotic illness, we considered 5% of the people leaving the study early to have a negative outcome. For other events, in studies with less than 50% dropout rate, we considered people leaving early to have had the negative outcome, except for the event of death. We analysed studies with high attrition rates (more than 5% within the first 2 hours or 25-50% overall) in a sensitivity analysis. If inclusion of data from this latter group did result in a substantive change in the estimate of effect, then we id not pool the data but presented them separately.

4. Data analysis

4.1 Binary data

For binary outcomes we calculated a standard estimation of the relative risk (RR) [fixed effect] and its 95% confidence interval. We also calculated the number needed to treat or harm statistic (NNT, NNH), and its 95% confidence interval. 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, the following standards are applied 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. Endpoint scores on scales often have a finite start and end point and these rules can be applied to them.

4.2.2 Summary statistic: For continuous outcomes we calculated weighted mean differences (WMD) and respective 95% CI (fixed effect). If heterogeneity was found (see section 5) we used a random effects model.

4.2.3 Valid scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and it has been shown that the use of rating scales which have not been described in a peer-reviewed journal (Marshall 2000) are associated with bias, or may not be valid, or even ad hoc. Therefore, some minimum standards were set: (a) the psychometric properties of the instrument should have been described in a peer-reviewed journal; (b) the instrument should either be a self-report, or completed by an independent rater or relative (not the therapist); and (c) the instrument should be a global assessment of an area of functioning.

4.2.4 Endpoint versus change data: where possible, we presented endpoint data and if both endpoint and change data were available for the same outcomes then we only reported the former in this review.

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-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted 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).

5. Test for heterogeneity

We used a Mantel-Haenszel chi-squared test to investigate the possibility of heterogeneity. A significance level of less than 0.10 was interpreted as evidence of heterogeneity. An I2 value was also generated. If heterogeneity was significant and/or the I2 value was greater than 50%, we re-analysed data using a random effects model.

6. Addressing publication bias

We entered all data from the 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 such a way that the area to the left of the line of no effect indicated a decrease in the number of unfavourable outcomes in the treatment group and the area to the right of the line indicated an increase in favourable outcomes. The treatment group was considered to be the benzodiazepine group when compared with placebo or antipsychotic, or the combined benzodiazepine/antipsychotic group when compared with benzodiazepine or antipsychotic alone.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

1. Excluded studies

We excluded nine studies. The interventions in Yang 2003 did not fit the study criteria. We had to exclude Arana 1986, Garza-Trevino 1989, Lenox 1992, Nestoros 1982, Veser 2002 and Wyant 1990 as no usable outcome data were available for meta-analysis. Finally we could not use TREC 2003 or TREC 2004 because the control antipsychotic group was also given promethazine.

2. Awaiting assessment

No studies await assessment.

3. Ongoing studies

We know of no ongoing studies.

4. Included studies

We included eleven studies in the review. One compared benzodiazepines with placebo (Meehan 2001), nine compared benzodiazepines with antipsychotics (Battaglia 1997, Chouinard 1993, Dorevitch 1999, Foster 1997, Lerner 1979, Meehan 2001, Salzman 1991, Solomon 1990, Subramaney 1998 - Subramaney gave haloperidol 10 mg/IM to both arms and we have assumed that any effect is negligible i.e. 'background noise'). Two studies compared combined benzodiazepines and antipsychotics with benzodiazepines (Battaglia 1997, Bienek 1998) and another two compared combined benzodiazepines and antipsychotics with antipsychotics alone (Barbee 1992, Battaglia 1997).

4.1 Setting

All studies were conducted in hospitals. Battaglia 1997 and Chouinard 1993 took place in general hospital and three were set in a general hospital that had a specialist psychiatric service (Barbee 1992, Bienek 1998, Foster 1997). Another three were conducted in psychiatric hospitals (Lerner 1979, Subramaney 1998, Solomon 1990) and the remainder (Dorevitch 1999, Meehan 2001, Salzman 1991) also appear to have been undertaken in a hospital setting (Dorevitch 1999, Salzman 1991 in a psychiatric hospital and Meehan 2001 in a general hospital) although this was not explicit.

4.2 Length of trials

We included trials that varied in their duration between two hours and seven days. As this is a review of the effects on acute psychosis, we included only those outcomes up to and including 48 hours after the initial dose of medication. We divided outcomes into immediate (within 15 minutes), short term (>15 minutes - one hour) and medium term (>1 - 48 hours). Where data were given for multiple times within each of the intervals, we used data at the first time interval for the meta-analysis. The only exception to this was the data from Lerner 1979. This trial reported CGI data at four and 24 hours (medium term) however, as the loss to follow up was 50% at four hours but complete at 24 hours, we used the 24 hour data for this analysis.

4.3 Participants

In four of the included studies, patients were already inpatients (Dorevitch 1999, Meehan 2001, Salzman 1991, Solomon 1990), in six, patients were newly admitted (Battaglia 1997, Barbee 1992, Bienek 1998, Foster 1997, Lerner 1979, Subramaney 1998) and in one, patients were a mixture of inpatients and newly admitted patients (Chouinard 1993). In seven of the studies patients were of mixed diagnoses (Chouinard 1993, Dorevitch 1999, Foster 1997, Lerner 1979, Salzman 1991, Solomon 1990 and Subramaney 1998). Participants in Barbee 1992 were diagnosed as suffering from schizophrenia, in Meehan 2001 the diagnosis was bipolar disorder and in the remaining two studies diagnoses were not clear (Battaglia 1997 "psychosis and uncontrolled behaviour", Bienek 1998 "acutely agitated behaviour").

4.4 Study size

The overall sample size in all the included studies was quite small. The total number of participants in each study ranged from 16 (Chouinard 1993) to 201 (Meehan 2001).

4.5 Interventions

Benzodiazepines versus placebo

We were able to include one study comparing benzodiazepines to placebo. This study by Meehan 2001 compared one to three intramuscular (IM) injections of lorazepam (2-5 mg) to IM placebo.

Benzodiazepines versus antipsychotics

Four studies compared lorazepam with haloperidol. Battaglia 1997, Foster 1997, Solomon 1990, Salzman 1991. All compared 2mg of lorazepam with 5mg of haloperidol. All doses were given as an intramuscular injection, although some participants were able to receive the administered dose as an oral concentrate in the study by Foster 1997. Outcomes appear to have been measured 24 hours after a single injection in the study by Solomon 1990. In the study by Foster 1997, doses were administered every 30 minutes for four hours or until the patient was sedated. Additional doses could be given in the study by Salzman 1991 where the mean number of doses of lorazepam was 1.13 and the number of doses of haloperidol was 1.10. Participants in Battaglia 1997 could be given up to six doses over eight hours. The majority of patients however received less than three doses (71% of patients receiving haloperidol and 74% of patients receiving lorazepam alone).

Two other studies also compared lorazepam with an antipsychotic (Meehan 2001, Subramaney 1998). Meehan 2001 compared 2-5mg of IM lorazepam with 10-25mg of IM olanzapine. Subramaney 1998 compared 4mg of IM lorazepam with 40mg of IM clothiapine at six hourly intervals. Subramaney 1998 also gave both groups 10mg of haloperidol IM at the same time as the intervention.

The remaining three studies that compared benzodiazepines with antipsychotics, all compared IM benzodiazepine with IM haloperidol. Chouinard 1993 compared 1-2mg of clonazepam with 5-10mg of haloperidol at 0, 0.5 and one hour. Dorevitch 1999 compared single doses of flunitrazepam (1mg) with haloperidol (5mg). The study by Lerner 1979 compared diazepam (mean dose of 35mg/3h) with high-dose haloperidol (35mg/3h) and low-dose haloperidol (20mg/3h).

Combined benzodiazepines/antipsychotics versus

benzodiazepines

Two studies compared a combination of lorazepam with haloperidol to lorazepam alone (Battaglia 1997, Bienek 1998). Both compared a combination of lorazepam (2mg IM) with haloperidol (5mg IM) to lorazepam alone (2mg IM). Participants in Bienek 1998 could receive a second dose within the first hour, and in Battaglia 1997 patients could be given up to six doses over eight hours. The majority of participants, however, received less than three doses (91% of patients receiving both drugs and 74% of patients receiving lorazepam alone).

Combined benzodiazepines/antipsychotics versus antipsychotics

Barbee 1992 compared 1mg alprazolam plus 5mg of haloperidol to 1mg of alprazolam, administered as a daily oral dose. Battaglia 1997 compared 2mg of lorazepam plus 5mg of haloperidol to 2mg of lorazepam. All drugs were administered as an IM injection with 91% of the patients (combined group) receiving both drugs and 71% of the patients receiving haloperidol received less than three doses.

4.6 Outcomes

In this review all outcome data reported for the period from immediately after administration up to and including 48 hours were collected. In the trials frequency counts were reported, such as adverse events or percentage of improvement, and we made these binary and presented the results under the following heading: 'need for additional medication', 'sedation', 'leaving the study early', 'remaining excited' (PANSS derived), 'extrapyramidal symptoms', 'requiring anticholinergic medication', behaviour -'not improved' (OAS derived), mental state 'not improved' (IMPS derived), 'adverse events' and 'early discharge from hospital'.

4.6.1 Outcomes scales

4.6.1.1 Global impression

4.6.1.1.1 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. Usable data were reported by Barbee 1992 and Foster 1997.

4.6.1.2 Behaviour

4.6.1.2.1 Overt Aggression Scale - OAS (Yudofsky 1986)

The Overt Aggression Scale is designed to assess observable aggressive or violent behaviour rather than tendencies and is divided into two parts. The first section consists of four categories: verbal aggression, physical aggression, physical aggression against self, and physical aggression against other people. Within each category, aggressive behaviour is rated according to its severity. The second part of the scale rates staff intervention at the time of the aggressive incident. Usable data from this scale was reported by Bienek 1998, Dorevitch 1999 and Subramaney 1998.

4.6.1.3 Mental state

4.6.1.3.1 Brief Psychiatric 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. Barbee 1992 and Foster 1997 reported data from this scale. Barbee 1992 and Battaglia 1997 also reported data from the BPRS-psychosis subscale with high score indicating a worse outcome.

4.6.1.3.2 Inpatient Multidimensional Psychiatric Scale -IMPS (Lorr 1963)

This psychopathology scale yields scores for ten syndromes which define the psychotic state. Higher scores indicated a worse outcome. Data were reported by Chouinard 1993.

4.6.1.3.3 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. Meehan 2001 was the only study to report usable data for this scale. Meehan 2001 also used the PANSS-EC subscale which measured excitation predefined as at least 40% reduction.

Risk of bias in included studies

1. Randomisation

All 11 studies used random allocation. We contacted authors to clarify methods but no further information regarding allocation was obtained. In three studies it was stated that a table of random numbers was used to allocate patients (Battaglia 1997, Bienek 1998, Dorevitch 1999) with no further detail. There was no description of the method of allocation in the remaining studies.

2. Blinding

Seven of the included studies were double-blinded (Barbee 1992, Battaglia 1997, Bienek 1998, Chouinard 1993, Dorevitch 1999, Foster 1997, Solomon 1990 and Subramaney 1998), two studies were single/observer blinded (Lerner 1979, Salzman 1991) and the method of blinding was not clear in Meehan 2001.

3. Leaving the study early

No one left the study early in Barbee 1992, Dorevitch 1999 and Subramaney 1998. Chouinard 1993 and Meehan 2001 reported only small numbers leaving the study early. Numbers of people leaving for all the remaining studies were unclear. We attempted to contact authors regarding this outcome but were unable to obtain further information.

4. Data reporting

Many studies presented data in graphs or as 'p' values alone. Scale data were often reported without standard deviations and other data were reported from non-validated subscales.

5. Overall quality

The quality criteria used in this review was based on allocation concealment i.e. A: adequate, B: unclear, C: inadequate or D: not used. We attempted to contact the authors of all included studies to obtain information regarding allocation concealment, but as no further information could be obtained, we rated all studies into category B: unclear. As a result of this it was not possible to undertake a sensitivity analysis based on quality criteria.

Effects of interventions

1. The search

We found 289 references from the 2002 search strategy described above. We identified an additional 19 references from the reference lists of published studies and reviews. DG, AB and AM identified 175 potentially relevant references from these 308 references and we all independently decided which of these 175 references should be inspected. We found a further 219 references in the 2005 search update of which 11 were potentially relevant (DG, JR). We selected two of these 11 for data extraction but found no additional studies in the reference lists of these eleven studies.

2. COMPARISON 1: BENZODIAZEPINES versus PLACEBO

All data for this comparison came from Meehan 2001 which randomised 102 people to placebo or the benzodiazepine lorazepam.

2.1 Global impression

The number of people needing additional medication was not significantly different for the lorazepam groups and placebo groups (n=102, RR 0.96 CI 0.7 to 1.4). Sedation was also equivocal (n= 102, RR 1.67 CI 0.4 to 6.6). Clinical Global Impression change scores showed no clear differences (n=76, WMD 0.07 CI -0.5 to 0.6). The number of people leaving the study early by 24 hours was low and no difference was evident between those allocated to lorazepam or placebo (n=102, RR 0.60 CI 0.15 to 2.38).

2.2 Mental state

The number of people remaining excited as measured by the PANSS-EC scale significantly favoured those given lorazepam (n= 102, RR 0.62 CI 0.4 to 1.0, NNT 5 CI 3 to 59). However, PANSS-EC scores were reported also as continuous data (change scores) and were not significantly different (n=101, WMD -1.91 CI -3.8 to 0.01). Also, there was no significant differences in the PANSS change scores (n=99, WMD -2.57 CI -6.2 to 1.1).

2.3 Adverse events

The lorazepam and placebo groups experienced similar non-significant, low levels of extrapyramidal symptoms (n=94, RR 0.32 CI 0.03 to 2.98). The number of people requiring anticholinergic medications was also low and not significantly different (n= 94, RR 0.33 CI 0.04 to 3.1). Results for adverse events such as dizziness, nausea and vomiting, although higher in the lorazepam group, were equivocal.

3. COMPARISON 2: BENZODIAZEPINES versus ANTIPSYCHOTICS

Nine included studies compared benzodiazepines with antipsychotics (Battaglia 1997, Chouinard 1993, Dorevitch 1999, Foster 1997, Lerner 1979, Meehan 2001, Salzman 1991, Solomon 1990, Subramaney 1998).

3.1 Global impression

For those allocated benzodiazepines, the need for additional medication was not as clearly apparent compared with those given antipsychotics (n=216, 2 RCTs, RR 1.28 CI 0.5 to 3.2). The number of people rated as under sedation was also equivocal between groups (n=324, 6 RCTs, RR 0.76 CI 0.5 to 1.2). Clinical Global Impression (severity of illness) scores for both the short term and medium term were equivocal based on two small studies as were CGI (severity of illness) change scores (n=189, 2 RCTs, WMD 0.20 CI -0.1 to 0.5). Skewed CGI data were reported by Chouinard 1993 and therefore could not be used in the meta-analysis. The number of people leaving the study early (medium term) was not significantly different between those given benzodiazepines and those given antipsychotics (n=254, 4 RCTs, RR 1.70 CI 0.1 to 27.4).

3.2. Behaviour

Dorevitch 1999 reports a binary outcome (improved - not improved) for changes in behavioural scores using the Overt Aggression Scale (OAS) at 90 minutes (n=28, RR not improved 2.60 CI 0.3 to 22.1). Subramaney 1998 also reported medium term OAS data at 24 hours. However, these data were skewed and therefore not included in the meta-analysis.

3.3 Mental state

Chouinard 1993 found the incidence of improvement, measured by the Inpatients Multidimensional Psychiatric Scale (IMPS), to be equivocal (n=16, RR 1.50 CI 0.3 to 6.7) for those given clonazepam or haloperidol. BPRS scores reported by Foster 1997 at short and medium term outcomes were also equivocal but change scores on the same scale were found to significantly favour the benzodiazepine (diazepam) group (n=20, 1 RCT, WMD -7.60 CI -13.9 to -1.3). BPRS-psychosis subscale data were equivocal (n= 66, 1 RCT, WMD -0.30 CI -4.7 to 4.1). However, medium term excitation as measured by PANSS-EC scores in a single study significantly favoured those in the control group receiving antipsychotics (n=150, RR 1.84 CI 1.1 to 3.2, NNT 7 CI 3 to 87), as did PANSS total change scores (n=146, WMD 5.64 CI 2.2 to 9.1) and PANSS-EC change scores (n=149, WMD 2.85 CI 1.1 to 4.6).

3.4 Adverse events

Extrapyramidal symptoms were significantly higher in the antipsychotic treatment group (n=391, 7 RCTs, RR 0.17 CI 0.1 to 0.4, NNT 6 CI 2 to 17). However, those requiring anticholinergic medication was not more prevalent in either group (n=150, 1 RCT, RR 0.24 CI 0.03 to 1.89). Other adverse events; ataxia, dizziness, dry mouth, nausea, speech disorder and vomiting were uncommon and did not differ significantly in either group.

4. COMPARISON 3: BENZODIAZEPINES + ANTIPSYCHOTICS versus BENZODIAZEPINES

All data for this comparison came from the studies by Bienek 1998 and Battaglia 1997 and in both cases lorazepam plus haloperidol was compared with lorazepam alone (total n=83).

4.1 Global impression

There was no clear difference for the need for additional medication between the two comparison groups (n=83, 2 RCTs, RR 1.02 CI 0.8 to 1.3) and improvements as measured by CGI scores at one hour were also equivocal (n=20, 1 RCT, RR 1.47 CI 0.66 to 3.25). Bienek 1998 (n=20) reported loss to follow up and no one left the study early in the study in the medium term.

4.2 Behaviour

Bienek 1998 provided data from the OAS scale (short term) dichotomised to 'not improved' (n=20, RR 0.11 CI 0.01 to 1.7).

4.3 Mental state

Battaglia 1997 (n=63) reported skewed medium term data from the BPRS-psychosis subscale, which therefore could not be used in the meta-analysis.

4.4 Adverse events

There was no significant difference between people given lorazepam and haloperidol and those receiving lorazepam alone in the incidence of extrapyramidal symptoms (n=83, 2 RCTs, RR 1.94 CI 0.2 to 20.3) The incidences of ataxia, dizziness, dry mouth and speech disorder were all low and Battaglia 1997 did not find any difference between groups for these adverse affects.

5. COMPARISON 4: BENZODIAZEPINES + ANTIPSYCHOTICS versus ANTIPSYCHOTICS

All data for this comparison came from the studies by Barbee 1992 (alprazolam plus haloperidol versus haloperidol, n=28) and Battaglia 1997 (lorazepam plus haloperidol versus haloperidol, n=67).

5.1 Global impression

There was no significant difference between groups for the need for additional medication (n=67, 1 RCT, RR 0.95 CI 0.8 to 1.2). Barbee 1992 (n=28) reported loss to follow up and no one in this study left early.

5.2 Mental state

Barbee 1992 reports medium term BPRS scale data, with no significant difference between the two groups (n=28, WMD 0.01 CI -7.3 to 7.3). Medium term BPRS-psychosis subscale scores from the same study were also equivocal. Battaglia 1997 (n=67) also reported medium term skewed BPRS-psychosis subscale scores that did not show a statistical difference between groups.

5.3 Adverse events

Extrapyramidal symptoms were significantly lower for people receiving both benzodiazepines and antipsychotics compared with those receiving antipsychotics alone (n=95, 2 RCTs, RR 0.45 CI 0.2 to 0.9, NNH 2 CI 1 to 5). Barbee 1992 did not find that people in one group required more anticholinergic medication than those in the other group (n=28, RR 0.56 CI 0.3 to 1.2). Adverse events such as ataxia, dizziness, dry mouth and speech disorder were infrequent. They were all reported by Battaglia 1997 and no differences were apparent between the two groups.

5.4. Hospital and service outcome

There was no significant difference in the number of participants unfit for early discharge (n=28, 1 RCT, RR 0.90 CI 0.54 to 1.5).

6. SENSITIVITY ANALYSES

We proposed three sensitivity analyses: one based on quality criteria, one based on high attrition rates and one for studies that did not state that randomised allocation was used. We were unable to carry out the first subgroup analysis because the quality criteria were identical for all the studies. We rated all studies 'B'. However the remaining sensitivity analyses were undertaken.

6.1 High versus low attrition

High attrition was defined as studies where the number of participants lost to follow-up was more than 5% in the first two hours or between 25 and 50% overall. In four of the studies the follow-up rate was unclear (Battaglia 1997, Dorevitch 1999, Foster 1997, Lerner 1979), in three of the studies there was a high attrition rate, and four studies had a low loss to follow up (Table 3).

There was no difference in the incidence of sedation in high (n=16, 1 RCT, RR 0.33 CI 0.02 to 7.1) and low (n=203, 2 RCTs, RR 0.90 CI 0.5 to 1.7) attrition studies which compared benzodiazepines with antipsychotics, nor was there any statistically significant difference in the number of participants leaving the study early or any incidence of extrapyramidal adverse effects (n=16, 1 RCT, RR in high attrition studies 0.33 CI 0.0 to 7.1 vs n=150, 1 RCT, RR in low attrition studies 5.82 CI 0.6 to 54.6). There was no incidence of extrapyramidal adverse effects (n=56, 2 RCTs, RR in high attrition studies 0.12 CI 0.0 to 0.6 and n=204, 2 RCTs, RR in low attrition studies 0.22 CI 0.0 to 1.0).

6.2 Studies with unclear randomisation

It was not clear whether Lerner 1979 and Salzman 1991 were randomised. Although Lerner 1979 did state that it was a randomised study, it also reported that there was alternation between medications so we cannot be certain that this study was randomised. Salzman 1991 did not state that allocation was randomised.

There was no difference in the incidence of sedation in randomised studies that compared benzodiazepines with antipsychotics (n=231, 4 RCTs, RR 0.71 CI 0.3 to 1.5) when compared with studies where the allocation method was not clear (n=93, 2 RCTs, RR 0.81 CI 0.5 to 1.4). There was also no difference in the incidence of extrapyramidal adverse effects (n=351, 6 RCTs, RR in randomised studies 0.21 CI 0.1 to 0.6 and those with unclear randomisation n=40, 1 RCT, RR 0.09 CI 0.01 to 0.7).

DISCUSSION

1. General remarks

1.1 Weakness

In this review there are only a relatively small number of included studies and they have small sample sizes and data were often either not reported, or if available, were presented in an unusable format. Also, because meta-analyses for several outcomes resulted in very small total numbers, it is unlikely that many of the findings are statistically significant. A further difficulty in interpreting the findings of this review is the variable and unclear doses that were used. Also, because all the studies were rated as category B (unclear allocation concealment) the findings reported in this review may be an overestimate of the true effect.

1.2 Publication bias

The outcome 'sedation' was used when benzodiazepines were compared with antipsychotics (six RCTs). We used these data for a funnel plot analysis to assess whether a systematic small trial bias existed in the studies included in this review. The funnel graph did not reveal any obvious bias toward positive studies, although there were an insufficient number of trials to clearly reveal a gap in the funnel scatter plot.

2. COMPARISON 1: BENZODIAZEPINES vs PLACEBO

It is understandable that placebo-controlled trials in this area are uncommon and it could be argued that in certain circumstances they are unethical. The evidence that benzodiazepine is superior to placebo is weak (1 RCT, n=102) with very few people in each group being sedated (5/51 vs 3/51 people, 1 RCT, RR 1.67 CI 0.4 to 6.6). Some mental state data are more encouraging with fewer people allocated to the lorazepam group being rated as excited, although this data only comes from one study with a small sample size.

3. COMPARISON 2: BENZODIAZEPINES vs ANTIPSYCHOTICS

As a global impression, people allocated benzodiazepines did not clearly need additional medication compared with those given antipsychotics (n=216, 2 RCTs) suggesting an equivalent level of effect. This is supported by the equivocal result on the number of those sedated. There were not enough data however to compare the effects of different types and doses of benzodiazepine. Mental state findings are difficult to interpret; one result favours benzodiazepines, one favours the antipsychotic and others are equivocal. However, extrapyramidal symptoms were significantly higher in the antipsychotic treatment group (n=391, 7 RCTs, NNT 6 CI 2 to 17) and this must be an important factor in choosing the correct treatment to give in the emergency situation. It should be noted however, that in clinical practice antipsychotics may often be accompanied by anticholinergic treatment that may substantially decrease the incidence of extrapyramidal symptoms.

4. COMPARISON 3: BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

In both small trials lorazepam plus haloperidol was compared with lorazepam alone (total n=83). This is an important comparison that is remarkably understudied. Ratings of global impression, mental state, behaviour and adverse effects are all equivocal between groups as would be expected in such low powered comparisons. A real and important difference could exist, but larger studies are needed before any confident conclusions can be drawn.

5. COMPARISON 4: BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Again this important comparison contains remarkably few data (total n=95) but the suggestion from these trials is that with everything else being equal, patients receiving combined benzodiazepines and antipsychotics had lower levels of extrapyramidal adverse effects than the group receiving antipsychotic alone (n=95, NNT 2 CI 1 to 5). This is an important finding, although as emphasized above, the antipsychotic alone group was not given protection of anticholinergic medication. In view of this it would mean that the benzodiazepine plus antipsychotic group in this review would be seen in a more favourable light.

6. SENSITIVITY ANALYSIS

In a sensitivity analysis we would need substantial power to show real differences with confidence. This review found few trials and all were small so we were unable to draw meaningful conclusions from the sensitivity analyses.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with agitation/aggression due to schizophrenia or schizophrenia-like illnesses

There are no strong data from these studies to support or refute the use of benzodiazepines, with or without antipsychotics, if the situation has deteriorated to such an extent that emergency drugs are needed. However, the lower incidence of distressing acute movement disorder adverse effects in people receiving benzodiazepines may be a reason to choose benzodiazepines over the older antipsychotics when the latter are to be administered without additional anti-movement-disorder medication. If a policy of sole use of a benzodiazepine or a combination of a benzodiazepine with an antipsychotic or an antipsychotic used alone is operational, the findings of this review suggests that the latter treatment option would be least effective. The studies in this review are not large enough to highlight important and potentially very serious adverse effects of the benzodiazepines such as respiratory depression.

2. For clinicians

The addition of benzodiazepines to antipsychotic medication appears to reduce antipsychotic induced extrapyramidal movement disorders and therefore clinicians should consider that the reduced incidence of this adverse effect may outweigh the small in-

creased cost of administering combined benzo-antipsychotic therapy. However, these findings are based on only two small studies. Unsurprisingly, extrapyramidal adverse effects were also significantly higher in people given antipsychotics alone, compared with those given benzodiazepines. Differences in clinical efficacy were less obvious. Outcomes such as 'sedation' and 'needing additional medication' did not show any clear differences to recommend one treatment over another. Mental state outcomes were also often equivocal, although some did favour antipsychotics over benzodiazepines. These data came from single studies. The effects of benzodiazepines combined with antipsychotics appeared comparable with those of antipsychotics alone but most of these data were derived from a study of only 28 people.

3. For managers or policy makers

Lack of good quality data leaves managers and policy makers with difficult decisions to make. There is currently insufficient clinical evidence to suggest that benzodiazepines are clearly superior to antipsychotics in reducing acute psychotic behaviour.

Implications for research

1. General

Adherence to the CONSORT statement (Moher 2001) would probably have resulted in this review being more conclusive. Clear descriptions of randomisation would have reassured users of these trials that selection bias had been minimised and well-described and tested blinding could have encouraged greater confidence in the control of performance and detection bias. The use of binary outcomes should take preference over continuous results because they are easier to interpret and the use of validated rating scales would have provided more usable data. The reporting of outcomes with their means and standard deviations again would have provided more usable data and facilitated synthesis of findings. When presenting data in a graph, the exact numbers and standard deviations should also be reported.

2. Specific

There is a need for better evidence regarding the relative effectiveness of the combined therapy compared with antipsychotics or benzodiazepines alone, particularly regarding the incidence of both short-term and long-term adverse effects. Large, well designed and clearly reported trials are possible in this area as demonstrated in TREC 2003 and TREC 2004. In addition, the atypical antipsychotics, such as intramuscular olanzapine or zotepine, should also be compared to benzodiazepines. Any outcomes of further studies in this area should include validated scales that are acceptable to clinicians working in the field, recipients of this care, researchers and those working with regulatory authorities.

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REFERENCES

References to studies included in this review

Barbee 1992 *{published data only}*

* Barbee JG, Mancuso DM, Freed CR, Todorov AA. Alprazolam as a neuroleptic adjunct in the emergency treatment of schizophrenia [published erratum appears in Am J Psychiatry 1992 Aug;149(8):1129] [see comments]. *American Journal of Psychiatry* 1992;**149**:506–10.

Battaglia 1997 *{published data only}*

* Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *American Journal of Emergency Medicine* 1997;**15**:335–40.

Bienek 1998 *{published data only}*

* Bieniek SA, Ownby RL, Penalver A, Dominguez RA. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998;**18**:57–62.

Chouinard 1993 *{published data only}*

* Chouinard G, Annable L, Turnier L, Holobow N, Szkrumelak N. A double-blind randomized clinical trial of rapid tranquilization with I.M. clonazepam and I.M. haloperidol in agitated psychotic patients with manic symptoms [see comments]. *Canadian Journal of Psychiatry* 1993;**38**:S114–S121.

Dorevitch 1999 *{published data only}*

* Dorevitch A, Katz N, Zemishlany Z, Aizenberg D, Weizman A. Intramuscular flunitrazepam versus intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. *American Journal of Psychiatry* 1999;**156**:142–4.

Foster 1997 *{published data only}*

* Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *International Clinical Psychopharmacology* 1997;**12**:175–9.

Lerner 1979 *{published data only}*

* Lerner Y, Lwow E, Levitin A, Belmaker RH. Acute high-dose parenteral haloperidol treatment of psychosis.

American Journal of Psychiatry 1979;**136**:1061–4.

Meehan 2001 *{published data only}*

* Meehan KZ. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *Journal of Clinical Psychopharmacology* 2001;**21**:389–97.

Salzman 1991 *{published data only}*

* Salzman C, Solomon D, Miyawaki E, Glassman R. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *Journal of Clinical Psychiatry* 1991;**52**(4):177–80.

Solomon 1990 *{published data only}*

* Solomon DA, Miyawaki E, Salzman C. Benzodiazepine augmentation of the treatment of disruptive psychotic behavior. [Review] [46 refs]. *Progress in Drug Research* 1990;**35**:139–49.

Subramaney 1998 *{published data only}*

* Subramaney U, Brook S, Berk M. A prospective randomised double-blind controlled study of the efficacy of lorazepam versus clothiapine in the control of acutely behaviourally disturbed patients. *South African Medical Journal* 1998;**88**:307–10.

References to studies excluded from this review

Arana 1986 *{published data only}*

* Arana GW, Ornsteen ML, Kanter F, Friedman HL, Greenblatt DJ, Shader RI. The use of benzodiazepines for psychotic disorders: a literature review and preliminary clinical findings. *Psychopharmacology Bulletin* 1986;**22**: 77–87.

Garza-Trevino 1989 *{published data only}*

* Garza-Trevino ES, Hollister LE, Overall JE, Alexander WF. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation [see comments]. *American Journal of Psychiatry* 1989;**146**: 1598–601.

Lenox 1992 *{published data only}*

* Lenox RH, Newhouse PA, Creelman WL, Whitaker TM. Adjunctive treatment of manic agitation with lorazepam versus haloperidol: a double-blind study. *Journal of Clinical Psychiatry* 1992;**53**:47–52.

Nestoros 1982 *{published data only}*

* Nestoros JN. Diazepam in high doses is effective in schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry* 1982;**6**:513–6.

TREC 2003 *{published data only}*

TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003;**327**(27 (September)):1–6.

TREC 2004 *{published data only}*

Alexander J, Tharyan P, Adams CE, John T, Mol C, Philip J. Rapid tranquilisation of violent or agitated patients in a psychiatric emergancy setting: a pragmatic randomised trial of intramuscular lorazepam versus haloperidol plus promethazine. *British Journal of Psychiatry* 2004;**185**:63–9.

Veser 2002 *{published data only}*

Veser F, Zealburg J, Veser B, Zhu Y, Gharabawi G. Oral risperidone in the management of agitated behavior in emergency settings. *Journal of the European College of Neuropsychopharmacology* 2002;**12**(Suppl 3):S313.

Wyant 1990 *{published data only}*

* Wyant M, Diamond BI, O'Neal E, Sloan A. The use of midazolam in acutely agitated psychiatric patients. Psychopharmacology Bulletin, 29th Annual Meeting of the New Clinical Drug Evaluation Unit. 1990; Vol. 26:126–9.

Yang 2003 *{published data only}*

Yang X, Wang Z, Ling Z. A randomly controlled comparison of risperidone added with intramuscular clonazepam in the treatment of excitement of schizophrenia. *Shanghai Archives of Psychiatry* 2003;**15**(2):98–9.

Additional references

Alderson 2004

Alderson P, Green S, Higgins JPT. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [: In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd]

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**:1200.

Battaglia 1997

Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *American Journal of Emergency Medicine* 1997;**15**(4):335–40.

Binder 1999

Binder RL, McNiel DE. Emergency psychiatry: contemporary practices in managing acutely violent patients in 20 psychiatric emergency rooms. *Psychiatric Services* 1999;**50**(12):1553–4.

Bland 1997

Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**:600.

Csernansky 1988

Csernansky JG, Riney SJ, Lombrozo L, Overall JE, Hollister LE. Double-blind comparison of alprazolam, diazepam, and placebo for the treatment of negative schizophrenic symptoms. *Archives of General Psychiatry* 1988;**45**(7):655–9.

Cunnane 1994

Cunnane JG. Drug management of disturbed behaviour by psychiatrists. *Psychiatric Bulletin* 1994;**18**:138–9.

Cure 2001

Cure S, Carpenter S. Droperidol for acute psychosis. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD002830]

Divine 1992
Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623–9.

Donner 2002
Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**:2971–80.

Dubin 1988
Dubin WR. Rapid tranquilization: antipsychotics or benzodiazepines?. *Journal of Clinical Psychiatry* 1988;**49** (Supplement):5–12.

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

Extein 1980
Extein I. Psychopharmacology in psychiatric emergencies. *International Journal of Psychiatry in Medicine* 1980;**10**(3): 189–204.

Fava 1997
Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatric Clinics of North America* 1997;**20**(2): 427–51.

Gulliford 1999
Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149**: 876–83.

Guy 1970
Guy W, Bonato RR, eds. Clinical Global Impressions. *In: Manual for the ECDEU Assessment Battery 2. Rev ed*. National Institute of Mental Health, 1970.

Huf 2000
Huf G, Countino E, Adams CE. A survey of rapid tranquillisation in psychiatric emergency rooms of Rio de Janeiro. manuscript in preparation 2000.

Joy 2001
Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic reviews* 2001, Issue 2. [DOI: 10.1002/ 14651858.CD003082.pub2]

Kay 1987
Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 1987;**13**:261–76.

Levy 1996
Levy RH. Sedation in acute and chronic agitation. *Pharmacotherapy* 1996;**16**(6 pt 2):152S-9S; 166S-168S.

Lorr 1963
Lorr M, Klett CJ, McNair DM, Lasky JJ. *Inpatient Multidimensional Psychiatric Scale*. Palo Alto: Consulting Psychologists Press, 1963.

Marshall 2000
Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**: 249–52.

Mendelson 1992
Mendelson WB. Clinical distinctions between long-acting and short-acting benzodiazepines. *Journal of Clinical Psychiatry* 1992;**53**(Supplement):4-7; discussion 8-9.

Moher 2001
Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;**285**:1987–91.

Overall 1962
Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Reports* 1962;**10**:799–812.

Pilowsky 1992
Pilowsky LS, Ring H, Shine PJ, Battersby M, Lader M. Rapid tranquillisation. A survey of emergency prescribing in a general psychiatric hospital. *British Journal of Psychiatry* 1992;**160**:831–5.

Stimmel 1996
Stimmel GL. Benzodiazepines in schizophrenia. *Pharmacotherapy* 1996;**16**(6 pt 2):148S-51S; 166S-8S.

TREC 2004
Alexander J, Tharyan P, Adams CE, John T, Mol C, Philip J. Rapid tranquilisation of violent or agitated patients in a psychiatric emergancy setting: a pragmatic randomised trial of intramuscular lorazepam versus haloperidol plus promethazine. *British Journal of Psychiatry* 2004;**185**:63–9.

Ukoumunne 1999
Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organistation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5): 1–75.

Wolkowitz 1986
Wolkowitz OM, Pickar D, Doran AR, Breier A, Tarell J, Paul SM. Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. *American Journal of Psychiatry* 1986;**143**(1):85–7.

Wolkowitz 1989
Wolkowitz OM, Breier A, Doran A, Lucas P, Kelsoe J, Paul SM. Alprazolam augmentation of neuroleptics in schizophrenia. *American Journal of Psychiatry* 1989;**146**(8): 1087–8.

Wolkowitz 1991
Wolkowitz OM, Pickar D. Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. *American Journal of Psychiatry* 1991;**148**(6):714–26.

Yudofsky 1986
Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the Objective Rating

of Verbal and Physical Aggression. *American Journal of Psychiatry* 1986;**143**(1):35–9.
* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barbee 1992

Methods	Allocation: randomised. Blindness: double. Duration: 72 hours. Design: antipsychotic versus combined benzodiazepine/antipsychotic
Participants	Diagnosis: schizophrenia (DSM-III R). N=28. Age: mean 33 years. Sex: 12 M; 16 F. History: gave informed consent. Setting: psychiatric emergency service, US hospital.
Interventions	1. Alprazolam + haloperidol: dose alprazolam 1mg/oral, haloperidol 5 mg/oral. N=14 2. Haloperidol + placebo: dose 5 mg/bid. N=14. Repeat dose given within first 24 hours if psychotic subscale was>11. Total dose administered on day 1 repeated days 2 and 3. Each patient received a minimum of 2 doses Mean number of doses: haloperidol 2.1, combination 3.2.
Outcomes	Leaving the study early. Mental state: BPRS, BPRS-psychosis subscale. Adverse events: EPS, anticholinergic medication. Hospital & service: Early discharge. Unable to use - Mental state: SANS, SAPS (no usable data).
Notes	ITT: not stated. Follow-up: 70%.

Risk of bias

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

Battaglia 1997

Methods	Allocation: randomised - computer generated random numbers. Blindness: double. Duration: 24 hours. Design: randomised trial of benzodiazepine versus antipsychotic versus combined benzodiazepine/antipsychotic
Participants	Diagnosis: psychosis and uncontrolled behaviour (agitated, aggressive, destructive, assault or restless behaviour). N=98. Age: mean 34 years. Sex: 73 M; 25 F. History: informed consent wherever possible. Setting: ED, US hospital.
Interventions	1. Lorazepam + haloperidol: dose lorazepam 2 mg/IM, haloperidol 5 mg/IM/max. 6 doses. N=32 2. Lorazepam: dose 2 mg/IM/max. 6 doses. N=31. 3. Haloperidol: dose 5 mg/IM/max. 6 doses. N=35. Administered during first 12 hrs of study. First three injections at least 1 hr apart and remainder 2 hrs apart. Total not to exceed 6 doses. Need for subsequent doses made by blinded evaluator. Most patients had < 3 doses (lorazepam: 74%; haloperidol: 71%; combination: 91%)
Outcomes	Global impression: Additional medication. Mental state: BPRS-psychosis subscale. Adverse events: EPS, side-effects. Unable to use - Behaviour: ABS. Mental state: BPRS-anxiety subscale (unvalidated subscores). Global impression: CGI (no usable data).
Notes	ITT: not stated. Follow-up: not clear.

Risk of bias

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

Bienek 1998

Methods	Allocation: randomised. Blindness: double. Duration: 48 hours, 7 days in total. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: acutely agitated behaviour. N=20. Age: mean 41 years.

Bienek 1998 (*Continued*)

	Sex: 13 M; 7 F. History: informed consent waived. Setting: psychiatric emergency service, US hospital.
Interventions	1. Lorazepam + haloperidol: dose lorazepam 2 mg/IM, haloperidol 5 mg/IM. N=9 2. Lorazepam: dose 2 mg/IM. N=11. Repeated once at 60 min if patients were still severely agitated
Outcomes	Leaving the study early. Global impression: Additional medication, CGI. Behaviour: OAS. Adverse events: EPS.
Notes	ITT: not applicable. Follow-up: 100%.

Risk of bias

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

Chouinard 1993

Methods	Allocation: randomised. Blindness: double. Duration: 2 hours. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: bipolar affective illness, manic phase schizoaffective disorder, schizophreniform disorder, brief reactive disorder or atypical psychosis, (DSM-III). N=16. Age: range 18-60 years. Sex: 10 M; 6 F. History: informed consent given. Setting: ED, hospital, Canada.
Interventions	1. Clonazepam: dose 1-2 mg/IM. N=8. 2. Haloperidol: dose 5-10 mg/IM. N=8. Given at 0, 0.5 and 1 hour; mean dose clonazepam (5.4 mg), haloperidol (19.4 mg) Dosage adjusted by blinded psychiatrist; procyclidine given to haloperidol group and procyclidine placebo given to clonazepam group. Both groups still received medications as usual
Outcomes	Leaving the study early. Global impression: Sedation, CGI. Mental state: IMPS. Adverse events: EPS. Unable to use -

Chouinard 1993 (*Continued*)

	Behaviour: TMBS (no usable data). Mental state: NOSIE-subscore (unvalidated subscale data).
Notes	ITT: not stated. Follow-up: 88%.

Risk of bias

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

Dorevitch 1999

Methods	Allocation: randomised, table of random numbers. Blindness: double, not clear whether dose adjustment was blinded. Duration: 2 hours. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: schizophrenia (N=19), schizoaffective disorder (N=7), bipolar (N=2) (DSM IV, axis 1 SCID) . N=28. Age: range 20-60 years. Sex: 13 M; 15 F. History: did not need consent. Setting: psychiatric hospital, Israel.
Interventions	1. Flunitrazepam: dose 1 mg/IM/single dose. N=15. 2. Haloperidol: dose 5 mg/IM/single dose. N=13. Patients were monitored for 120 minutes. Subjects on routine psychotropic treatment
Outcomes	Leaving the study early. Global impression: Sedation. Behaviour: OAS. Adverse events: EPS.
Notes	ITT: not stated. Follow-up: 100%.

Risk of bias

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

Foster 1997

Methods	Allocation: randomised. Blindness: double, unclear whether the decision to give additional doses was blinded. Duration: 4 hours. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: schizophrenia (N=13), bipolar (N=13), schizoaffective (N=4), psychotic disorder not otherwise specified (N=7). N=37. Age: range 18-61 years. Sex: 26 M; F 11. History: judged by emergency room staff to be an imminent danger to themselves and required 4-point restraint. Setting: psychiatric emergency service, US hospital.
Interventions	1. Lorazepam: dose 2 mg/oral or IM/every 30 minutes for 4h. N=17 2. Haloperidol: dose 5 mg/oral or IM/every 30 minutes for 4h. N=20 Medication was administered every 30 min for 4h until the patient was sedated or no longer posed a danger to themselves or staff
Outcomes	Global impression: Sedation, CGI. Mental state: BPRS. Adverse events: EPS.
Notes	ITT: not stated. Follow-up: not clear.

Risk of bias

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

Lerner 1979

Methods	Allocation: randomised*. Blindness: observer-blinded. Duration: 24 hours. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: paranoid schizophrenia (N=9), schizoaffective schizophrenia (N=9), schizophrenia subtypes (N=5), paranoid states (N=2), manic (N=5), no diagnosis (N=10). N=40. Age: mean 33 years. Sex: 27 M; 13 F. History: newly admitted psychotic patients. Setting: psychiatric hospital, Israel.

Lerner 1979 (*Continued*)

Interventions	1. Diazepam: dose mean 5-15 mg/IM/tds. N=20. 2. Haloperidol: dose 10-15 mg/IM/tds. N=20. All free from neuroleptics for 48 hours before the study began
Outcomes	Global impression: Sedation, CGI. Mental State: BPRS. Unable to use - Mental state: BPRS-agitation and hostility subscore (unvalidated subscale data)
Notes	ITT: not applicable. Follow-up: not clear. *States that it was randomised but also states that there was alternation between meds

Risk of bias

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

Meehan 2001

Methods	Allocation: randomised. Blindness: unclear. Duration: 24 hours. Design: benzodiazepine versus antipsychotic versus placebo.
Participants	Diagnosis: bipolar disorder (DSM-IV). N=201. Age: mean 40 years. Sex: 107 M; 94 F. History: inpatients of at least 18 years. Setting: hospitals in Romania & US.
Interventions	1. Lorazepam: dose 2-5 mg/IM. N=51. 2. Olanzapine: dose 10-25 mg/IM. N=99. 3. Placebo. N=51. Randomised 2:1:1; patients received 1-3 doses over 3-20 hours after the first injection based on clinical judgement of investigator
Outcomes	Leaving the study early. Global impression: Additional medication, sedation, CGI-S. Mental state: PANSS, PANSS-EC. Adverse events: EPS, anticholinergic medication, side-effects Unable to use - Behaviour: ABS, ACES (no usable data). Mental state: YMRS (no usable data).

Meehan 2001 (*Continued*)

Notes	ITT: yes. Follow-up: 96%. Placebo group who received a third injection were excluded at 24h analysis

Risk of bias

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

Salzman 1991

Methods	Allocation: not stated. Blindness: raters blinded to treatment. Duration: 48 hours. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: schizophrenia, bipolar, schizoaffective, psychotic depression. N=60. Age: mean 34.2 years. Sex: not stated. History: consent not required. Setting: locked ward, US hospital.
Interventions	1. Lorazepam: dose 2 mg/IM/mean no. of injections 1.13. N=30 2. Haloperidol: dose 5 mg/IM/mean no. of injections 1.10. N=30 Not clear when additional doses were given.
Outcomes	Global impression: Sedation. Adverse events: EPS. Unable to use - Global impression: CGI (no SD). Behaviour: OAS (no SD). Mental state: BPRS (no SD).
Notes	ITT: not stated. Follow-up: leaving the study early - not clear; sedation 88%; EPS 67%

Risk of bias

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

Solomon 1990

Methods	Allocation: randomised. Blindness: double. Duration: 7 days. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: schizophrenia, schizoaffective disorder or bipolar disorder. N=60. Age: not stated. Sex: not stated. History: inpatients requiring chemical restraint for control of acute psychotic agitation. Setting: on a locked ward in a US Mental Health Center.
Interventions	1. Lorazepam: dose 2 mg/IM. N=30. 2. Haloperidol: dose 5 mg/IM. N=28. Appears to have been given as single dose.
Outcomes	Adverse events: EPS. Unable to use - Behaviour: OAS (no SD). Mental state: BPRS (no SD). Global impression: sedation (no usable data).
Notes	ITT: not stated Follow-up: leaving the study early -not clear; EPS - unclear, appears to have been 100%

Risk of bias

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

Subramaney 1998

Methods	Allocation: randomised. Blindness: double. Duration: 7 days. Design: benzodiazepine versus antipsychotic.
Participants	Diagnosis: psychoactive substance abuse (N=24), schizophrenia (N=16) or bipolar disorder (N=14) (DSM-III R) no diagnosis (N=6). N=60. Age: range 18-45 years. Sex: 46 M, 14 F. History: consent obtained from patient or relative. Setting: psychiatric hospital, South Africa.

Subramaney 1998 (*Continued*)

Interventions	1. Clothiapine + *haloperidol: dose clothiapine 40 mg/IM, haloperidol 10 mg/IM. N=30 2. Lorazepam + *haloperidol: dose lorazepam 4 mg/IM, haloperidol 10 mg/IM. N=30 Dose repeated 6 hourly "if warranted".
Outcomes	Leaving the study early. Behaviour: OAS. Unable to use - Mental state: BPRS (no data within 48 hours). Adverse events: SAS (no data within 48 hours).
Notes	*haloperidol was given to both groups at a fixed dose and assumptions have been made that the effect of this is 'background noise', and therefore this study has been included under the comparison of 'antipsychotics versus benzodiazepines' ITT: not stated. Follow-up: 100%.

Risk of bias

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

Diagnostic tools:
DSM - Diagnostic Statistical Manual.
SCID - Structured clinical interview.
Rating Scales:
Behaviour -
ABS - Agitated Behavior Scale.
ACES - Agitation-Calmness Evaluation Scale.
OAS - Overt Agression Scale.
TMBS - Target Manic Behaviour Scale.
Global state -
CGI - Clinical Global Impression.
MCGRS - Modified Clinical Global Rating Scale.
Mental state -
BPRS - Brief Psychiatric Rating Scale.
IMPS - Inpatient Multidimensional Psychiatric Scale.
MBPRS - Modified Brief Psychiatric Rating Scale.
NOSIE - Nurses' Observation Scale for Inpatient Evaluation.
PANSS - Positive and Negative syndrome Scale.
YMRS - Young Mania Rating.
Side-Effects -
EPS - Extrapyramidal Side Effects.
SAS - Simpson Angus Score.
VAS - Visual Analogue Scale.
ITT - Intention to Treat Analysis.

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

Study	Reason for exclusion
Arana 1986	Allocation: unclear. Participants: people with schizophrenia. Interventions: lorazepam versus lorazepam and haloperidol. Outcomes: no usable data.
Garza-Trevino 1989	Allocation: randomised. Participants: people with mania, schizophrenia, atypical psychosis, miscellaneous diagnoses. Interventions: lorazepam versus haloperidol versus lorazepam and haloperidol. Outcomes: no usable data.
Lenox 1992	Allocation: randomised. Participants: people with bipolar illness, manic type. Interventions: lorazepam versus haloperidol. Outcomes: no usable data.
Nestoros 1982	Allocation: randomised. Participants: people with schizophrenia. Interventions: diazepam versus placebo. Outcomes: no usable data.
TREC 2003	Allocation: randomised. Participants: people who are aggressive or agitated Intervention: midazolam IM versus haloperidol IM with promethazine
TREC 2004	Allocation: randomised. Participants: people who are aggressive or agitated Interventions: lorazepam IM versus haloperidol IM and promethazine
Veser 2002	Allocation: randomised. Participants: people with acute agitation or psychosis. Interventions: risperidone and lorazepam versus haloperidol and lorazepam versus placebo and lorazepam. Outcomes: no usable data.
Wyant 1990	Allocation: randomised. Participants: people with schizophrenia. Interventions: midazolam versus haloperidol. Outcomes: no usable data.
Yang 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone and clonazepam versus haloperidol versus clozapine

DATA AND ANALYSES

Comparison 1. BENZODIAZEPINES vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: 1. Need for additional medication - medium term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.40]
2 Global impression: 2. Sedation - medium term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.42, 6.61]
3 Global impression: 3. Average change - medium term (CGI-S, high = poor)	1	76	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.46, 0.60]
4 Global impression: 4. Leaving the study early - medium term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.38]
5 Mental state: 1. Remaining excited - medium term (PANSS-excited component)	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.97]
6 Mental state: 2. Average change - medium term (PANSS, high = poor)	1	99	Mean Difference (IV, Fixed, 95% CI)	-2.57 [-6.23, 1.09]
7 Mental state: 3. Average change - medium term (PANSS-excited component, high = poor)	1	101	Mean Difference (IV, Fixed, 95% CI)	-1.91 [-3.83, 0.01]
8 Adverse events: 1. Extrapyramidal effects	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 2.96]
9 Adverse events: 2. Requiring anticholinergic medication - medium term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.10]
10 Adverse events: 3. General	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 dizziness	1	102	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.89, 54.87]
10.2 nausea	1	102	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 162.97]
10.3 vomiting	1	102	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.89]

Comparison 2. BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: 1. Need for additional medication - medium term	2	216	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.51, 3.22]
2 Global impression: 2. Sedation - medium term	6	324	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.48, 1.21]

3 Global impression: 3. Average score (CGI-S, high = poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Short term	1	16	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.58, 1.98]
3.2 Medium term	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.36, 0.12]
4 Global impression: 4. Average change - medium term (CGI-S, high = poor)	2	189	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.07, 0.47]
5 Global impression: 5. Average score - medium term (CGI-S, skewed)			Other data	No numeric data
6 Global impression: 6. Leaving the study early -medium term	4	254	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.11, 27.35]
7 Behaviour: 1. Not improved - medium term (OAS)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.6 [0.31, 22.05]
8 Behaviour: 2. Average aggression score - medium term (OAS, skewed)			Other data	No numeric data
9 Mental state: 1. Not improved - medium term (IMPS)	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.70]
10 Mental state: 2. Average score (BPRS, high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Short term	1	37	Mean Difference (IV, Fixed, 95% CI)	-3.26 [-10.65, 4.13]
10.2 Medium term	1	37	Mean Difference (IV, Fixed, 95% CI)	-4.07 [-10.76, 2.62]
11 Mental state: 3. Average change - medium term (BPRS, high = poor)	1	20	Mean Difference (IV, Fixed, 95% CI)	-7.60 [-13.87, -1.33]
12 Mental state: 4. Average change - medium term (BPRS-psychosis subscale, high score = poor)	1	66	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-4.65, 4.05]
13 Mental state: 5. Remaining excited - medium term (PANSS-excited component)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [1.06, 3.18]
14 Mental state: 6. Average change - medium term (PANSS, high = poor)	1	146	Mean Difference (IV, Fixed, 95% CI)	5.64 [2.20, 9.08]
15 Mental state: 7. Average change - medium term (PANSS-Excited component, high = poor)	1	149	Mean Difference (IV, Fixed, 95% CI)	2.85 [1.14, 4.56]
16 Adverse events: 1. Extrapyramidal effects	7	391	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.06, 0.43]
17 Adverse events: 2. Requiring anticholinergic medication - medium term	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 1.89]
18 Adverse events: 3. General	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 ataxia	1	66	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.22, 23.71]
18.2 dizziness	2	216	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.63, 3.07]
18.3 dry mouth	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.49, 7.24]
18.4 nausea	1	150	Risk Ratio (M-H, Fixed, 95% CI)	7.76 [0.89, 67.67]
18.5 speech disorder	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.11, 2.87]

18.6 vomiting	1	150	Risk Ratio (M-H, Fixed, 95% CI)	13.46 [0.71, 255.70]

Comparison 3. BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: 1. Need for additional medication - medium term	2	83	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
2 Global impression: 2. Not improved - short term (CGI)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.66, 3.25]
3 Global impression: 3. Leaving the study early - medium term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Behaviour: 1. Not improved - short term (OAS)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.74]
5 Mental state: 1. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed)			Other data	No numeric data
6 Adverse events: 1. Extrapyramidal effects	2	83	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [0.18, 20.30]
7 Adverse events: 2. General	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 ataxia	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.26, 8.11]
7.2 dizziness	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.12, 3.61]
7.3 dry mouth	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.15, 2.23]
7.4 speech disorder	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.26, 8.11]

Comparison 4. BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: 1. Need for additional medication - medium term	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.15]
2 Global impression: 2. Leaving the study early - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Mental state: 1. Average score - medium term (BPRS, high = poor)	1	28	Mean Difference (IV, Fixed, 95% CI)	0.01 [-7.26, 7.28]
4 Mental state: 2. Average score - medium term (BPRS-psychosis subscale, high = poor)	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.93 [-5.73, 1.87]
5 Mental state: 3. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed)			Other data	No numeric data

6 Adverse events: 1. Extrapyramidal effects	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.94]
7 Adverse events: 2. Requiring anticholinergic medication - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.24]
8 Adverse events: 3. General	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 ataxia	1	67	Risk Ratio (M-H, Fixed, 95% CI)	3.28 [0.36, 29.97]
8.2 dizziness	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.13, 4.09]
8.3 dry mouth	1	67	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.24, 5.04]
8.4 speech disorder	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.20, 3.39]
9 Hospital and service outcome: Unfit for early discharge	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.54, 1.50]

Comparison 5. SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: 1. Sedation - medium term	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 high	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
1.2 low	2	203	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.47, 1.73]
2 Global impression: 2. Leaving the study early - medium term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 high	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.14]
2.2 low	1	150	Risk Ratio (M-H, Fixed, 95% CI)	5.82 [0.62, 54.58]
3 Adverse events: Extrapyramidal effects	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 high	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.62]
3.2 low	2	204	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.95]

Comparison 6. SENSITIVITY ANALYSIS: 2. RANDOMISED vs UNKNOWN

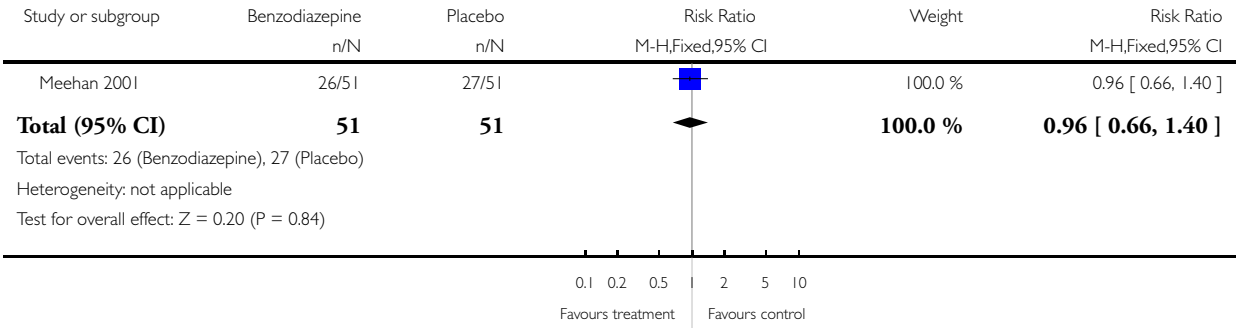
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: Sedation - medium term	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 randomised	4	231	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.49]
1.2 unknown	2	93	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.45, 1.44]
2 Adverse events: 1. Extrapyramidal effects	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 randomised	6	351	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.07, 0.63]
2.2 unknown	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.65]

Analysis 1.1. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 1 Global impression: 1. Need for additional medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 1 Global impression: 1. Need for additional medication - medium term

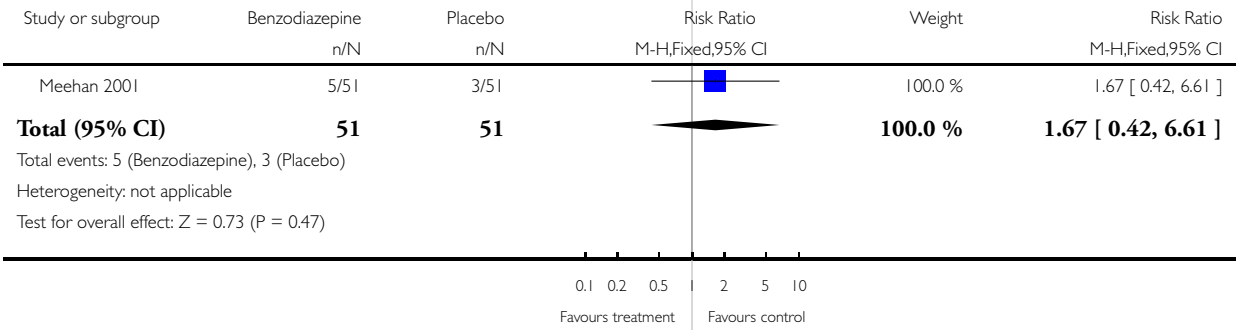


Analysis 1.2. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 2 Global impression: 2. Sedation - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 2 Global impression: 2. Sedation - medium term



Analysis 1.3. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 3 Global impression: 3. Average change - medium term (CGI-S, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 3 Global impression: 3. Average change - medium term (CGI-S, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Meehan 2001	49	-0.63 (0.81)	27	-0.7 (1.27)		100.0 %	0.07 [-0.46, 0.60]
Total (95% CI)	**49**		**27**			**100.0 %**	**0.07 [-0.46, 0.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.26 (P = 0.80)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 4 Global impression: 4. Leaving the study early - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

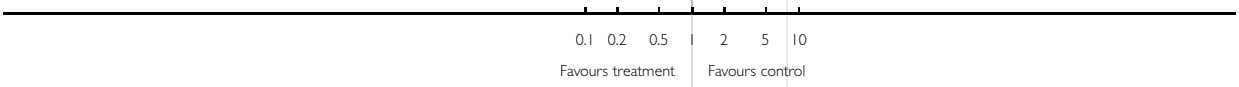
Outcome: 4 Global impression: 4. Leaving the study early - medium term

Study or subgroup	Benzodiazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Meehan 2001	3/51	5/51		100.0 %	0.60 [0.15, 2.38]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.60 [0.15, 2.38]**

Total events: 3 (Benzodiazepine), 5 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.73 (P = 0.47)



Analysis 1.5. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 5 Mental state: 1. Remaining excited - medium term (PANSS-excited component).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 5 Mental state: 1. Remaining excited - medium term (PANSS-excited component)

Study or subgroup	Benzodiazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Meehan 2001	18/51	29/51		100.0 %	0.62 [0.40, 0.97]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.62 [0.40, 0.97]**
Total events: 18 (Benzodiazepine), 29 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					

Analysis 1.6. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 6 Mental state: 2. Average change - medium term (PANSS, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 6 Mental state: 2. Average change - medium term (PANSS, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Meehan 2001	51	-11.65 (9.72)	48	-9.08 (8.85)		100.0 %	-2.57 [-6.23, 1.09]
Total (95% CI)	**51**		**48**			**100.0 %**	**-2.57 [-6.23, 1.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							
Test for subgroup differences: Not applicable							

Analysis 1.7. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 7 Mental state: 3. Average change - medium term (PANSS-excited component, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

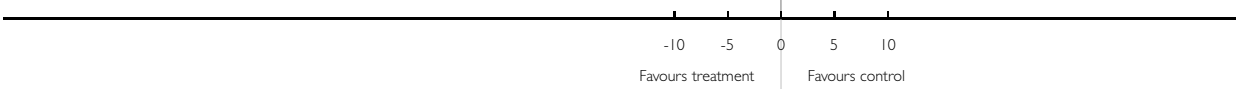
Outcome: 7 Mental state: 3. Average change - medium term (PANSS-excited component, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Meehan 2001	51	-6.75 (5.2)	50	-4.84 (4.66)		100.0 %	-1.91 [-3.83, 0.01]
Total (95% CI)	**51**		**50**			**100.0 %**	**-1.91 [-3.83, 0.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.94 (P = 0.052)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 8 Adverse events: 1. Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

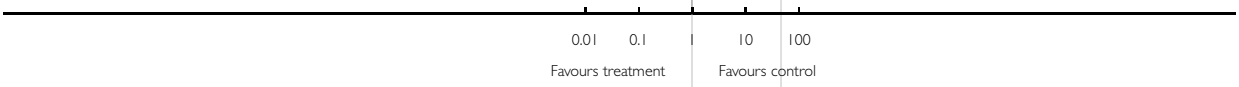
Outcome: 8 Adverse events: 1. Extrapyramidal effects

Study or subgroup	Benzodiazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Meehan 2001	1/48	3/46		100.0 %	0.32 [0.03, 2.96]
Total (95% CI)	**48**	**46**		**100.0 %**	**0.32 [0.03, 2.96]**

Total events: 1 (Benzodiazepine), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.00 (P = 0.32)

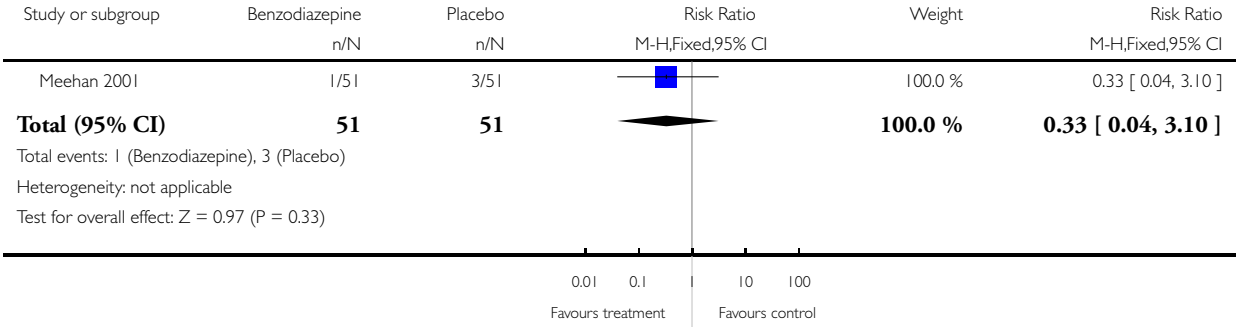


Analysis 1.9. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 9 Adverse events: 2. Requiring anticholinergic medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 9 Adverse events: 2. Requiring anticholinergic medication - medium term

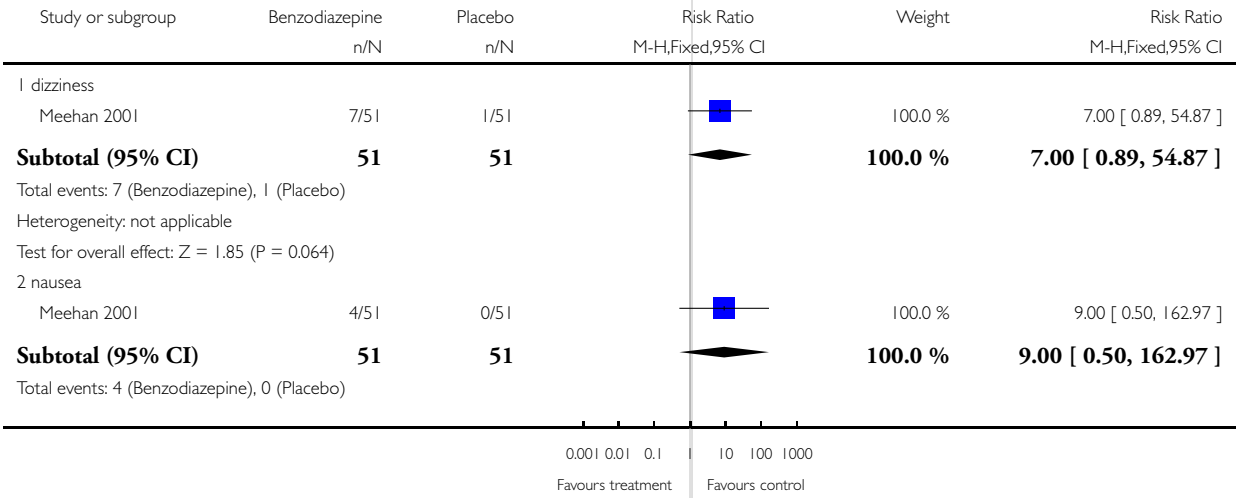


Analysis 1.10. Comparison 1 BENZODIAZEPINES vs PLACEBO, Outcome 10 Adverse events: 3. General.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 1 BENZODIAZEPINES vs PLACEBO

Outcome: 10 Adverse events: 3. General



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Study or subgroup	Benzodiazepine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					
3 vomiting					
Meehan 2001	3/51	1/51		100.0 %	3.00 [0.32, 27.89]
Subtotal (95% CI)	**51**	**51**		**100.0 %**	**3.00 [0.32, 27.89]**
Total events: 3 (Benzodiazepine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					

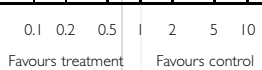
Analysis 2.1. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 1 Global impression: 1. Need for additional medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 1 Global impression: 1. Need for additional medication - medium term

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Battaglia 1997	24/31	31/35		51.9 %	0.87 [0.70, 1.09]
Meehan 2001	26/51	26/99		48.1 %	1.94 [1.27, 2.97]
Total (95% CI)	**82**	**134**		**100.0 %**	**1.28 [0.51, 3.22]**
Total events: 50 (Benzodiazepine), 57 (Antipsychotic)					
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 14.69$, df = 1 (P = 0.00013); $I^2 = 93\%$					
Test for overall effect: Z = 0.53 (P = 0.60)					



Analysis 2.2. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 2 Global impression: 2. Sedation - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 2 Global impression: 2. Sedation - medium term

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chouinard 1993	0/8	1/8		4.6 %	0.33 [0.02, 7.14]
Dorevitch 1999	3/15	3/13		9.9 %	0.87 [0.21, 3.58]
Foster 1997	1/17	2/20		5.7 %	0.59 [0.06, 5.94]
Lerner 1979	6/20	10/20		30.7 %	0.60 [0.27, 1.34]
Meehan 2001	5/51	13/99		27.2 %	0.75 [0.28, 1.98]
Salzman 1991	8/27	7/26		21.9 %	1.10 [0.47, 2.60]
Total (95% CI)	**138**	**186**		**100.0 %**	**0.76 [0.48, 1.21]**

Total events: 23 (Benzodiazepine), 36 (Antipsychotic)

Heterogeneity: Chi^2 = 1.41, df = 5 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 1.15 (P = 0.25)

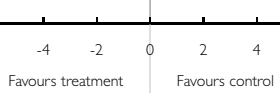
Analysis 2.3. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 3 Global impression: 3. Average score (CGI-S, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 3 Global impression: 3. Average score (CGI-S, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short term							
Chouinard 1993	8	4.7 (1.2)	8	4 (1.4)		100.0 %	0.70 [-0.58, 1.98]
Subtotal (95% CI)	**8**		**8**			**100.0 %**	**0.70 [-0.58, 1.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.07 (P = 0.28)							
2 Medium term							
Foster 1997	17	3.53 (1.23)	20	4.15 (1.04)		100.0 %	-0.62 [-1.36, 0.12]
Subtotal (95% CI)	**17**		**20**			**100.0 %**	**-0.62 [-1.36, 0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							
Test for subgroup differences: Chi^2 = 3.07, df = 1 (P = 0.08), I^2 =67%							

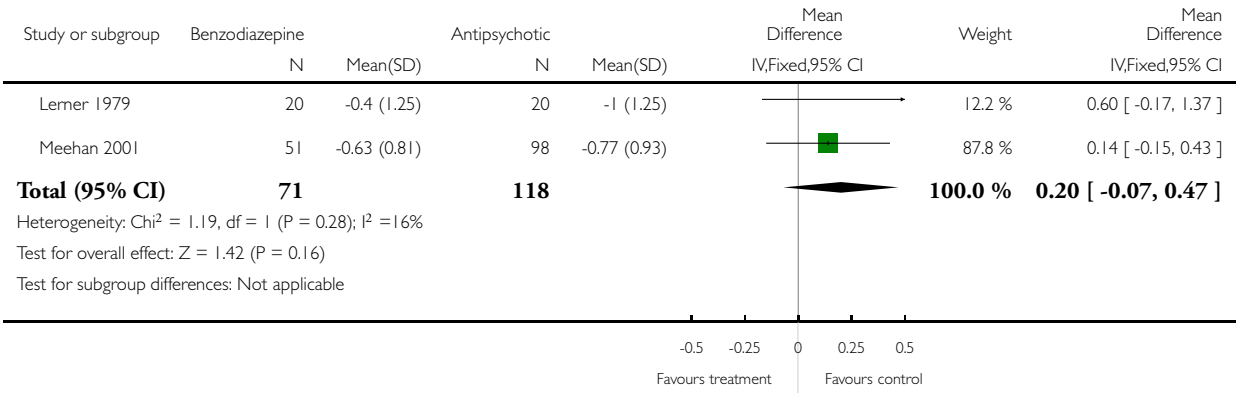


Analysis 2.4. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 4 Global impression: 4. Average change - medium term (CGI-S, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 4 Global impression: 4. Average change - medium term (CGI-S, high = poor)



Analysis 2.5. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 5 Global impression: 5. Average score - medium term (CGI-S, skewed).

Global impression: 5. Average score - medium term (CGI-S, skewed)

Study	Intervention	mean	SD	N
Chouinard 1993	Clonazepam	2.60	1.70	8
Chouinard 1993	haloperidol	2.80	0.60	8

Analysis 2.6. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 6 Global impression: 6. Leaving the study early -medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 6 Global impression: 6. Leaving the study early -medium term

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chouinard 1993	0/8	1/8		43.0 %	0.33 [0.02, 7.14]
Dorevitch 1999	0/15	0/13			Not estimable
Meehan 2001	3/51	1/99		57.0 %	5.82 [0.62, 54.58]
Subramaney 1998	0/30	0/30			Not estimable
Total (95% CI)	**104**	**150**		**100.0 %**	**1.70 [0.11, 27.35]**

Total events: 3 (Benzodiazepine), 2 (Antipsychotic)

Heterogeneity: $Tau^2 = 2.22$; $Chi^2 = 2.19$, df = 1 (P = 0.14); $I^2 = 54\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Analysis 2.7. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 7 Behaviour: 1. Not improved - medium term (OAS).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 7 Behaviour: 1. Not improved - medium term (OAS)

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dorevitch 1999	3/15	1/13		100.0 %	2.60 [0.31, 22.05]
Total (95% CI)	**15**	**13**		**100.0 %**	**2.60 [0.31, 22.05]**

Total events: 3 (Benzodiazepine), 1 (Antipsychotic)

Heterogeneity: not applicable

Test for overall effect: Z = 0.88 (P = 0.38)

Analysis 2.8. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 8 Behaviour: 2. Average aggression score - medium term (OAS, skewed).

Behaviour: 2. Average aggression score - medium term (OAS, skewed)

Study	Intervention	mean	SD	N
Subramaney 1998	Lorazepam	1.83	3.14	30
Subramaney 1998	Clothiapine	1.33	2.78	30

Analysis 2.9. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 9 Mental state: 1. Not improved - medium term (IMPS).

Review: Benzodiazepines for psychosis-induced aggression or agitation
Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS
Outcome: 9 Mental state: 1. Not improved - medium term (IMPS)

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chouinard 1993	3/8	2/8		100.0 %	1.50 [0.34, 6.70]
Total (95% CI)	**8**	**8**		**100.0 %**	**1.50 [0.34, 6.70]**
Total events: 3 (Benzodiazepine), 2 (Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					

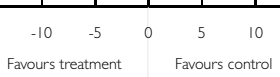
Analysis 2.10. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 10 Mental state: 2. Average score (BPRS, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 10 Mental state: 2. Average score (BPRS, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short term							
Foster 1997	17	52.12 (11.2)	20	55.38 (11.69)		100.0 %	-3.26 [-10.65, 4.13]
Subtotal (95% CI)	**17**		**20**			**100.0 %**	**-3.26 [-10.65, 4.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.86 (P = 0.39)							
2 Medium term							
Foster 1997	17	45.29 (10)	20	49.36 (10.75)		100.0 %	-4.07 [-10.76, 2.62]
Subtotal (95% CI)	**17**		**20**			**100.0 %**	**-4.07 [-10.76, 2.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.19 (P = 0.23)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%							



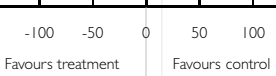
Analysis 2.11. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 11 Mental state: 3. Average change - medium term (BPRS, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 11 Mental state: 3. Average change - medium term (BPRS, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lerner 1979	11	-11.4 (6.25)	9	-3.8 (7.75)		100.0 %	-7.60 [-13.87, -1.33]
Total (95% CI)	**11**		**9**			**100.0 %**	**-7.60 [-13.87, -1.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.38 (P = 0.017)							
Test for subgroup differences: Not applicable							

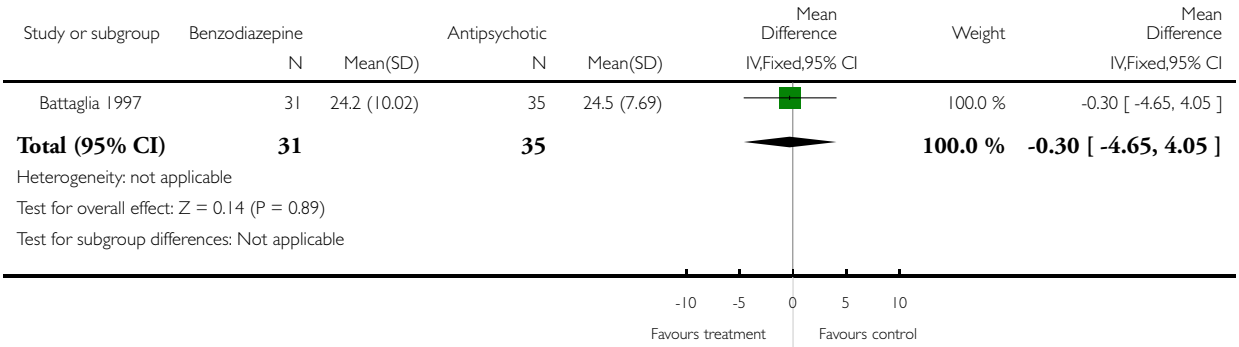


Analysis 2.12. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 12 Mental state: 4. Average change - medium term (BPRS-psychosis subscale, high score = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 12 Mental state: 4. Average change - medium term (BPRS-psychosis subscale, high score = poor)

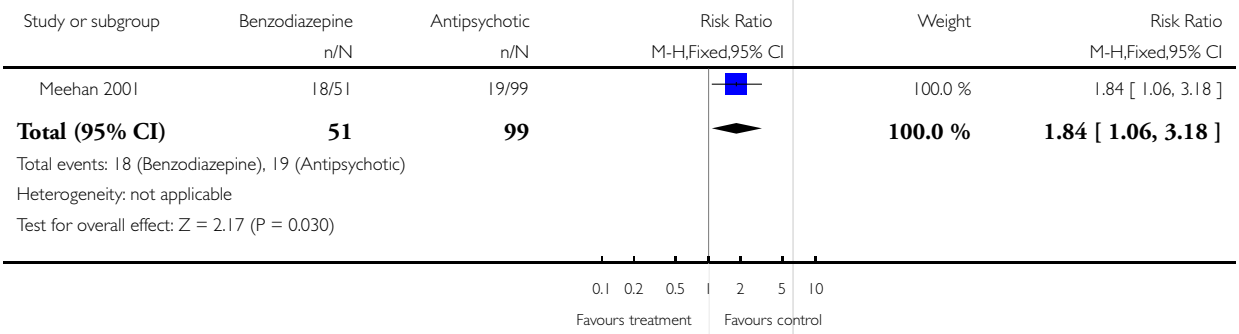


Analysis 2.13. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 13 Mental state: 5. Remaining excited - medium term (PANSS-excited component).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 13 Mental state: 5. Remaining excited - medium term (PANSS-excited component)



Analysis 2.14. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 14 Mental state: 6. Average change - medium term (PANSS, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 14 Mental state: 6. Average change - medium term (PANSS, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Meehan 2001	51	-11.65 (9.72)	95	-17.29 (10.78)		100.0 %	5.64 [2.20, 9.08]
Total (95% CI)	**51**		**95**			**100.0 %**	**5.64 [2.20, 9.08]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.22 (P = 0.0013)

Test for subgroup differences: Not applicable

Analysis 2.15. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 15 Mental state: 7. Average change - medium term (PANSS-Excited component, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 15 Mental state: 7. Average change - medium term (PANSS-Excited component, high = poor)

Study or subgroup	Benzodiazepine N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Meehan 2001	51	-6.75 (5.2)	98	-9.6 (4.74)		100.0 %	2.85 [1.14, 4.56]
Total (95% CI)	**51**		**98**			**100.0 %**	**2.85 [1.14, 4.56]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.27 (P = 0.0011)

Test for subgroup differences: Not applicable

Analysis 2.16. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 16 Adverse events: 1. Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 16 Adverse events: 1. Extrapyramidal effects

Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Battaglia 1997	1/31	7/35		23.1 %	0.16 [0.02, 1.24]
Chouinard 1993	0/8	1/8		5.3 %	0.33 [0.02, 7.14]
Dorevitch 1999	0/15	0/13			Not estimable
Foster 1997	0/17	0/20			Not estimable
Meehan 2001	1/48	8/98		18.5 %	0.26 [0.03, 1.98]
Salzman 1991	1/22	9/18		34.8 %	0.09 [0.01, 0.65]
Solomon 1990	1/30	5/28		18.2 %	0.19 [0.02, 1.50]
Total (95% CI)	**171**	**220**		**100.0 %**	**0.17 [0.06, 0.43]**

Total events: 4 (Benzodiazepine), 30 (Antipsychotic)

Heterogeneity: Chi^2 = 0.74, df = 4 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 3.69 (P = 0.00023)

Analysis 2.17. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 17 Adverse events: 2. Requiring anticholinergic medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 17 Adverse events: 2. Requiring anticholinergic medication - medium term

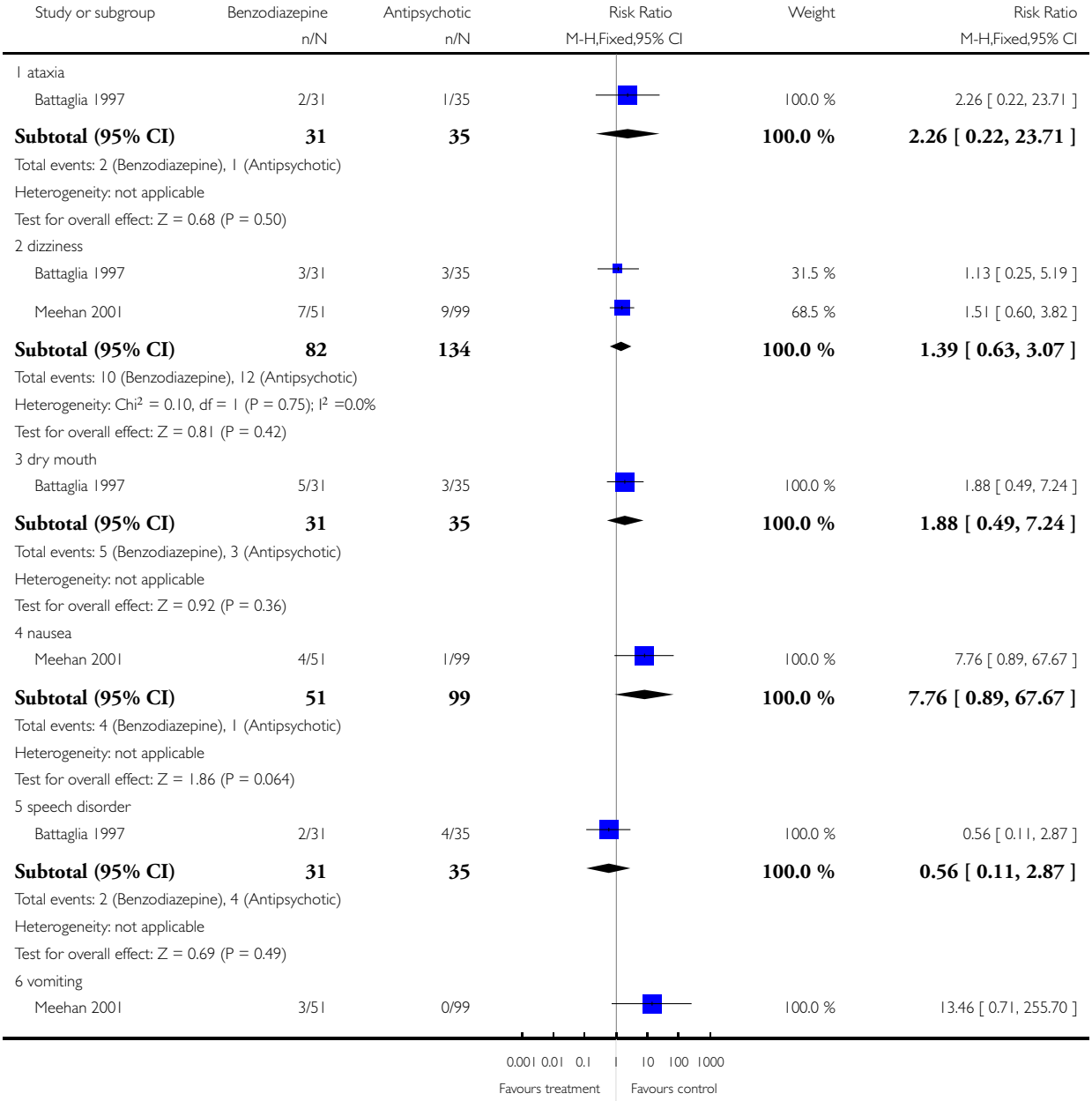
Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Meehan 2001	1/51	8/99		100.0 %	0.24 [0.03, 1.89]
Total (95% CI)	**51**	**99**		**100.0 %**	**0.24 [0.03, 1.89]**
Total events: 1 (Benzodiazepine), 8 (Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					

Analysis 2.18. Comparison 2 BENZODIAZEPINES vs ANTIPSYCHOTICS, Outcome 18 Adverse events: 3. General.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 2 BENZODIAZEPINES vs ANTIPSYCHOTICS

Outcome: 18 Adverse events: 3. General



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Study or subgroup	Benzodiazepine n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**51**	**99**		**100.0 %**	**13.46 [0.71, 255.70]**
Total events: 3 (Benzodiazepine), 0 (Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.083)					

Analysis 3.1. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 1 Global impression: 1. Need for additional medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 1 Global impression: 1. Need for additional medication - medium term

Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Battaglia 1997	27/32	24/31		91.5 %	1.09 [0.86, 1.39]
Bienek 1998	0/9	2/11		8.5 %	0.24 [0.01, 4.44]
Total (95% CI)	**41**	**42**		**100.0 %**	**1.02 [0.79, 1.32]**
Total events: 27 (Combination), 26 (Benzodiazepine)					
Heterogeneity: Chi^2 = 1.25, df = 1 (P = 0.26); I^2 =20%					
Test for overall effect: Z = 0.13 (P = 0.90)					

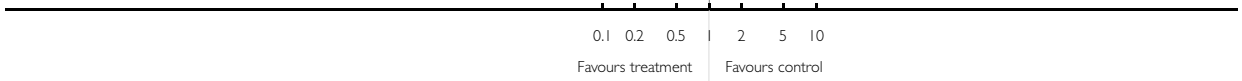
Analysis 3.2. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 2 Global impression: 2. Not improved - short term (CGI).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 2 Global impression: 2. Not improved - short term (CGI)

Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bienek 1998	6/9	5/11		100.0 %	1.47 [0.66, 3.25]
Total (95% CI)	**9**	**11**		**100.0 %**	**1.47 [0.66, 3.25]**
Total events: 6 (Combination), 5 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.35)					



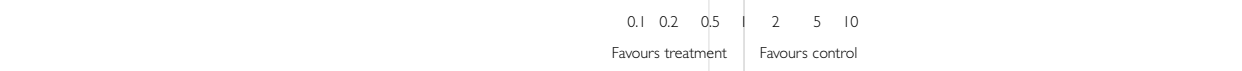
Analysis 3.3. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 3 Global impression: 3. Leaving the study early - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 3 Global impression: 3. Leaving the study early - medium term

Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bienek 1998	0/9	0/11			Not estimable
Total (95% CI)	**9**	**11**			**Not estimable**
Total events: 0 (Combination), 0 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

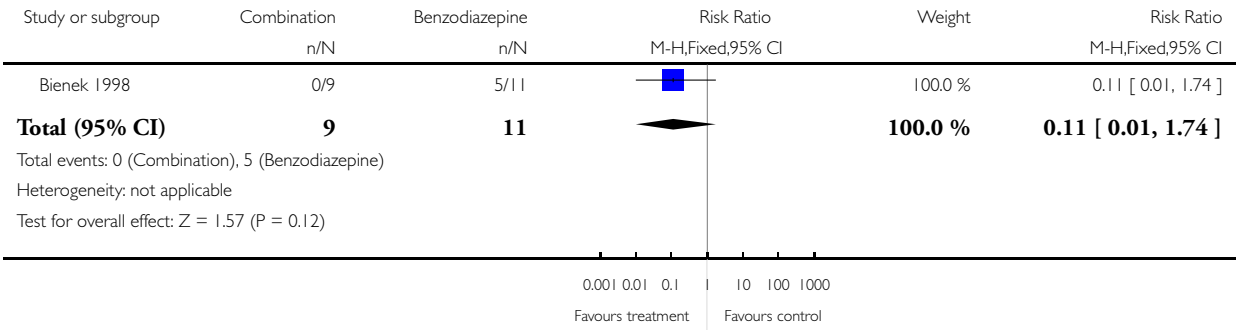


Analysis 3.4. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 4 Behaviour: 1. Not improved - short term (OAS).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 4 Behaviour: 1. Not improved - short term (OAS)



Analysis 3.5. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 5 Mental state: 1. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed).

Mental state: 1. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed)

Study	Intervention	mean	SD	N
Battaglia 1997	Lorazepam + haloperidol	17.50	10.18	32
Battaglia 1997	Lorazepam	24.20	10.02	31

Analysis 3.6. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 6 Adverse events: 1. Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 6 Adverse events: 1. Extrapyramidal effects

Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Battaglia 1997	2/32	1/31		100.0 %	1.94 [0.18, 20.30]
Bienek 1998	0/9	0/11			Not estimable
Total (95% CI)	**41**	**42**		**100.0 %**	**1.94 [0.18, 20.30]**
Total events: 2 (Combination), 1 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 3.7. Comparison 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES, Outcome 7 Adverse events: 2. General.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 3 BENZODIAZEPINES + ANTIPSYCHOTICS vs BENZODIAZEPINES

Outcome: 7 Adverse events: 2. General

Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 ataxia					
Battaglia 1997	3/32	2/31		100.0 %	1.45 [0.26, 8.11]
Subtotal (95% CI)	**32**	**31**		**100.0 %**	**1.45 [0.26, 8.11]**
Total events: 3 (Combination), 2 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
2 dizziness					
Battaglia 1997	2/32	3/31		100.0 %	0.65 [0.12, 3.61]
Subtotal (95% CI)	**32**	**31**		**100.0 %**	**0.65 [0.12, 3.61]**
Total events: 2 (Combination), 3 (Benzodiazepine)					
Heterogeneity: not applicable					

(*Continued . . .*)

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Study or subgroup	Combination n/N	Benzodiazepine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.50 (P = 0.62)					
3 dry mouth					
Battaglia 1997	3/32	5/31		100.0 %	0.58 [0.15, 2.23]
Subtotal (95% CI)	**32**	**31**		**100.0 %**	**0.58 [0.15, 2.23]**
Total events: 3 (Combination), 5 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
4 speech disorder					
Battaglia 1997	3/32	2/31		100.0 %	1.45 [0.26, 8.11]
Subtotal (95% CI)	**32**	**31**		**100.0 %**	**1.45 [0.26, 8.11]**
Total events: 3 (Combination), 2 (Benzodiazepine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					

Analysis 4.1. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 1 Global impression: 1. Need for additional medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 1 Global impression: 1. Need for additional medication - medium term

Study or subgroup	Combination n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Battaglia 1997	27/32	31/35		100.0 %	0.95 [0.79, 1.15]
Total (95% CI)	**32**	**35**		**100.0 %**	**0.95 [0.79, 1.15]**
Total events: 27 (Combination), 31 (Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					

Analysis 4.2. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 2 Global impression: 2. Leaving the study early - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 2 Global impression: 2. Leaving the study early - medium term

Study or subgroup	Combination n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Barbee 1992	0/14	0/14			Not estimable
Total (95% CI)	**14**	**14**			**Not estimable**

Total events: 0 (Combination), 0 (Antipsychotic)

Heterogeneity: not applicable

Test for overall effect: not applicable

Analysis 4.3. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 3 Mental state: 1. Average score - medium term (BPRS, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 3 Mental state: 1. Average score - medium term (BPRS, high = poor)

Study or subgroup	Combination N	Mean(SD)	Antipsychotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Barbee 1992	14	24.86 (11.91)	14	24.85 (7.14)		100.0 %	0.01 [-7.26, 7.28]
Total (95% CI)	**14**		**14**			**100.0 %**	**0.01 [-7.26, 7.28]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.00 (P = 1.0)

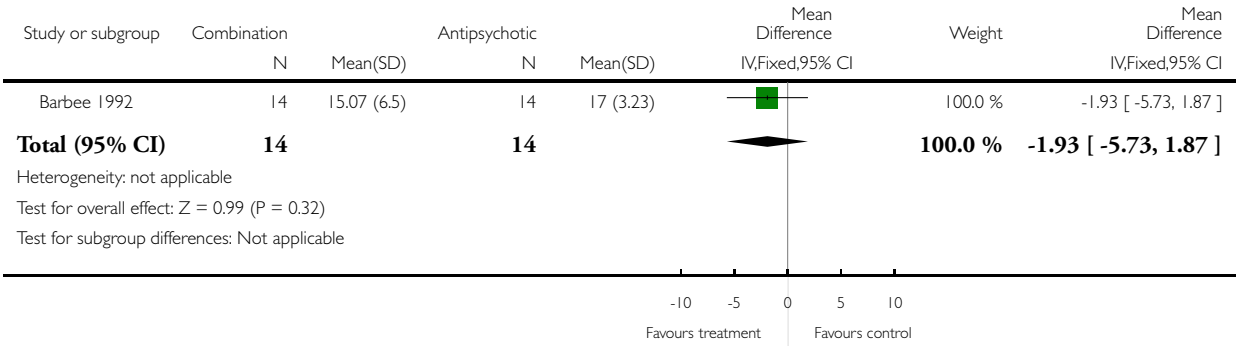
Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 4 Mental state: 2. Average score - medium term (BPRS-psychosis subscale, high = poor).

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 4 Mental state: 2. Average score - medium term (BPRS-psychosis subscale, high = poor)



Analysis 4.5. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 5 Mental state: 3. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed).

Mental state: 3. Average change - medium term (BPRS-psychosis subscale, high = poor, skewed)

Study	**Intervention**	**mean**	**SD**	**N**
Battaglia 1997	Lorazepam + haloperidol	17.50	10.18	32
Battaglia 1997	Haloperidol	24.50	7.69	35

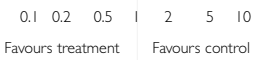
Analysis 4.6. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 6 Adverse events: 1. Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 6 Adverse events: 1. Extrapyramidal effects

Study or subgroup	Combination n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Barbee 1992	5/14	9/14		57.4 %	0.56 [0.25, 1.24]
Battaglia 1997	2/32	7/35		42.6 %	0.31 [0.07, 1.40]
Total (95% CI)	**46**	**49**		**100.0 %**	**0.45 [0.22, 0.94]**
Total events: 7 (Combination), 16 (Antipsychotic)					
Heterogeneity: Chi^2 = 0.49, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.11 (P = 0.035)					



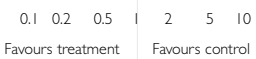
Analysis 4.7. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 7 Adverse events: 2. Requiring anticholinergic medication - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 7 Adverse events: 2. Requiring anticholinergic medication - medium term

Study or subgroup	Combination n/N	Antipsychotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Barbee 1992	5/14	9/14		100.0 %	0.56 [0.25, 1.24]
Total (95% CI)	**14**	**14**		**100.0 %**	**0.56 [0.25, 1.24]**
Total events: 5 (Combination), 9 (Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					

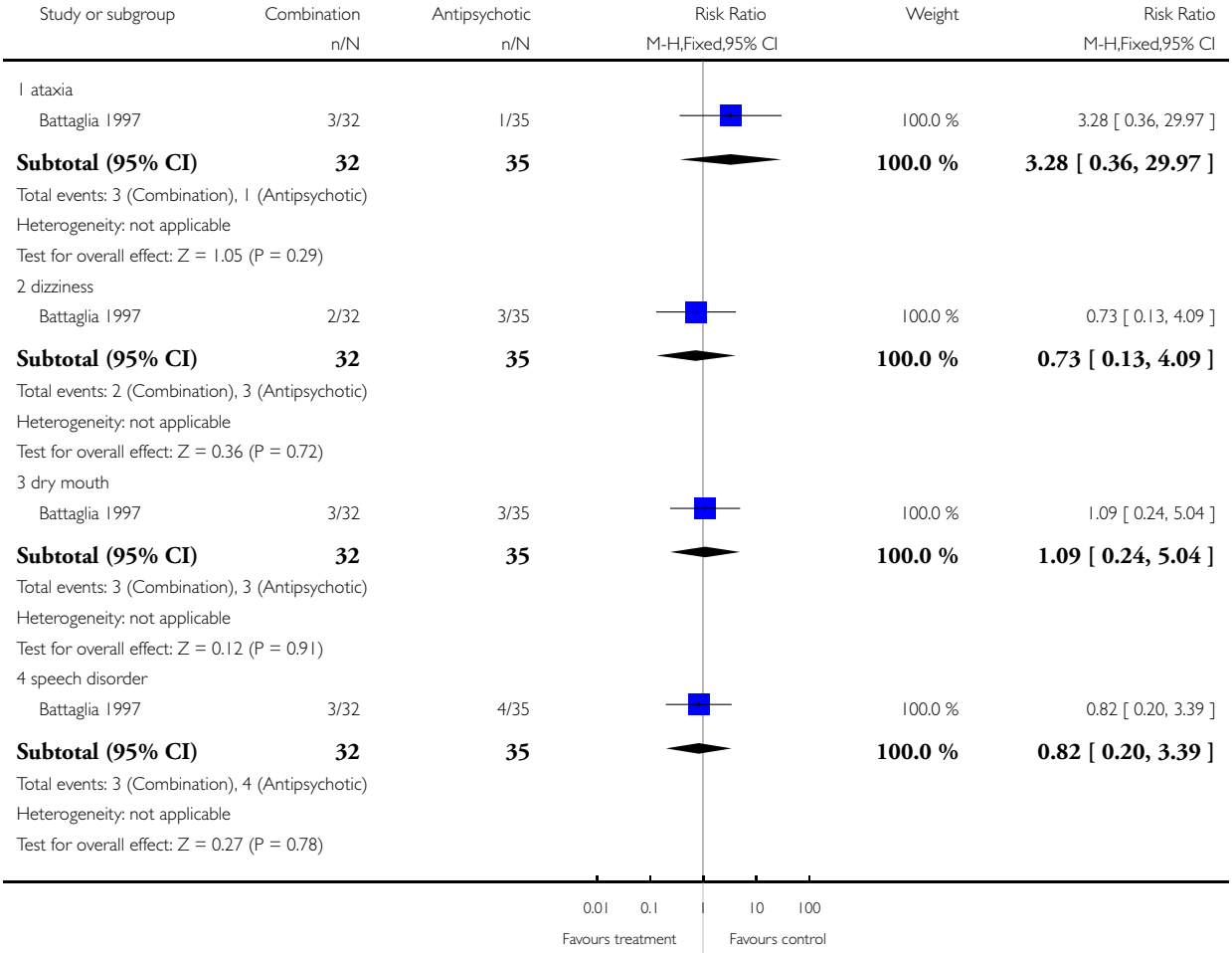


Analysis 4.8. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 8 Adverse events: 3. General.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 8 Adverse events: 3. General

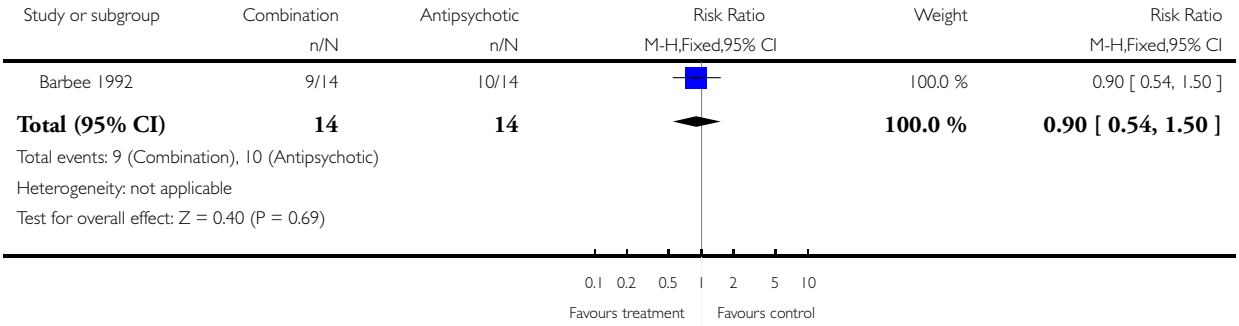


Analysis 4.9. Comparison 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS, Outcome 9 Hospital and service outcome: Unfit for early discharge.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 4 BENZODIAZEPINES + ANTIPSYCHOTICS vs ANTIPSYCHOTICS

Outcome: 9 Hospital and service outcome: Unfit for early discharge

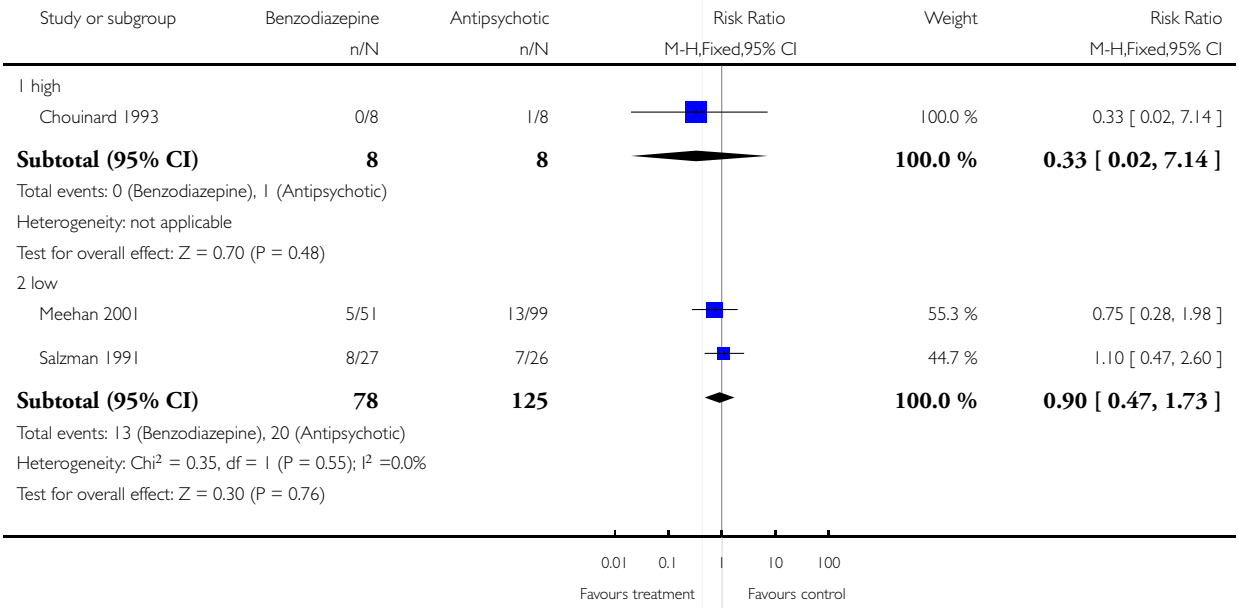


Analysis 5.1. Comparison 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION, Outcome 1 Global impression: 1. Sedation - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION

Outcome: 1 Global impression: 1. Sedation - medium term

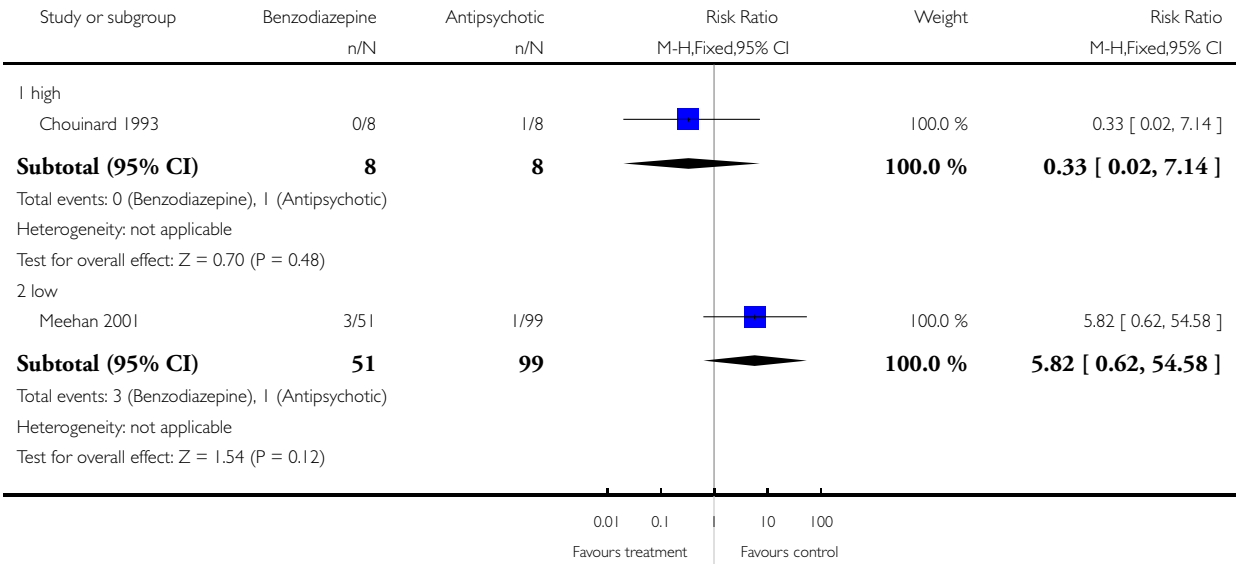


Analysis 5.2. Comparison 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION, Outcome 2 Global impression: 2. Leaving the study early - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION

Outcome: 2 Global impression: 2. Leaving the study early - medium term

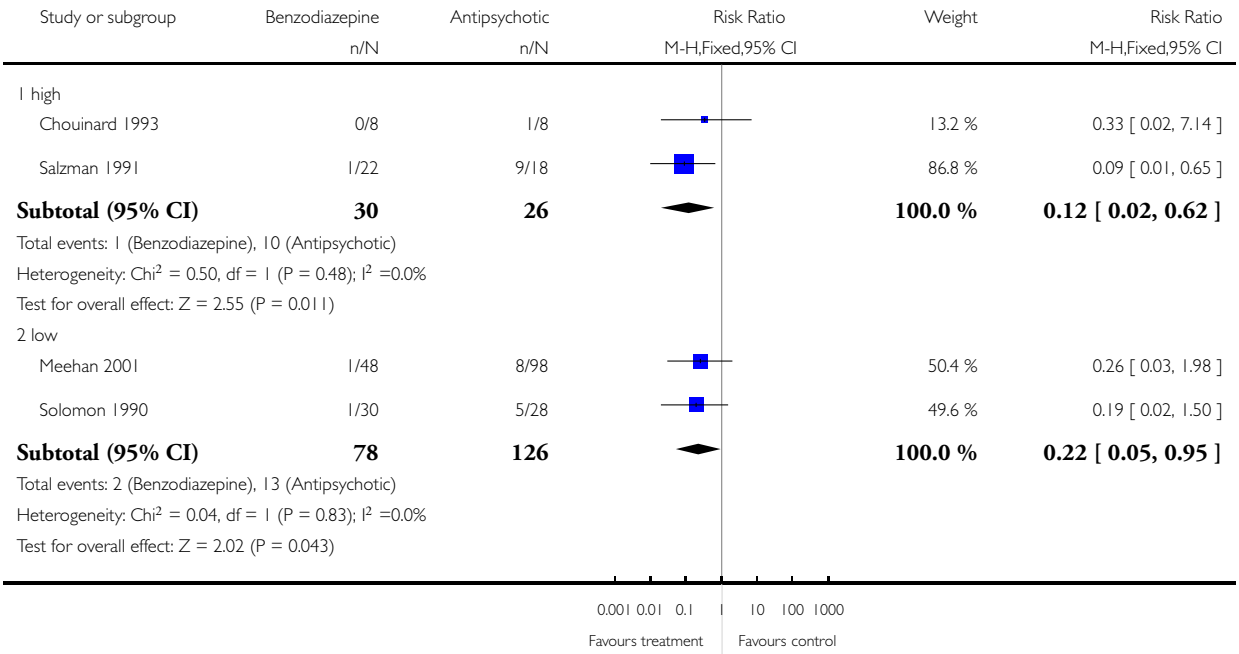


Analysis 5.3. Comparison 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION, Outcome 3 Adverse events: Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 5 SENSITIVITY ANALYSIS: 1. HIGH vs LOW ATTRITION

Outcome: 3 Adverse events: Extrapyramidal effects

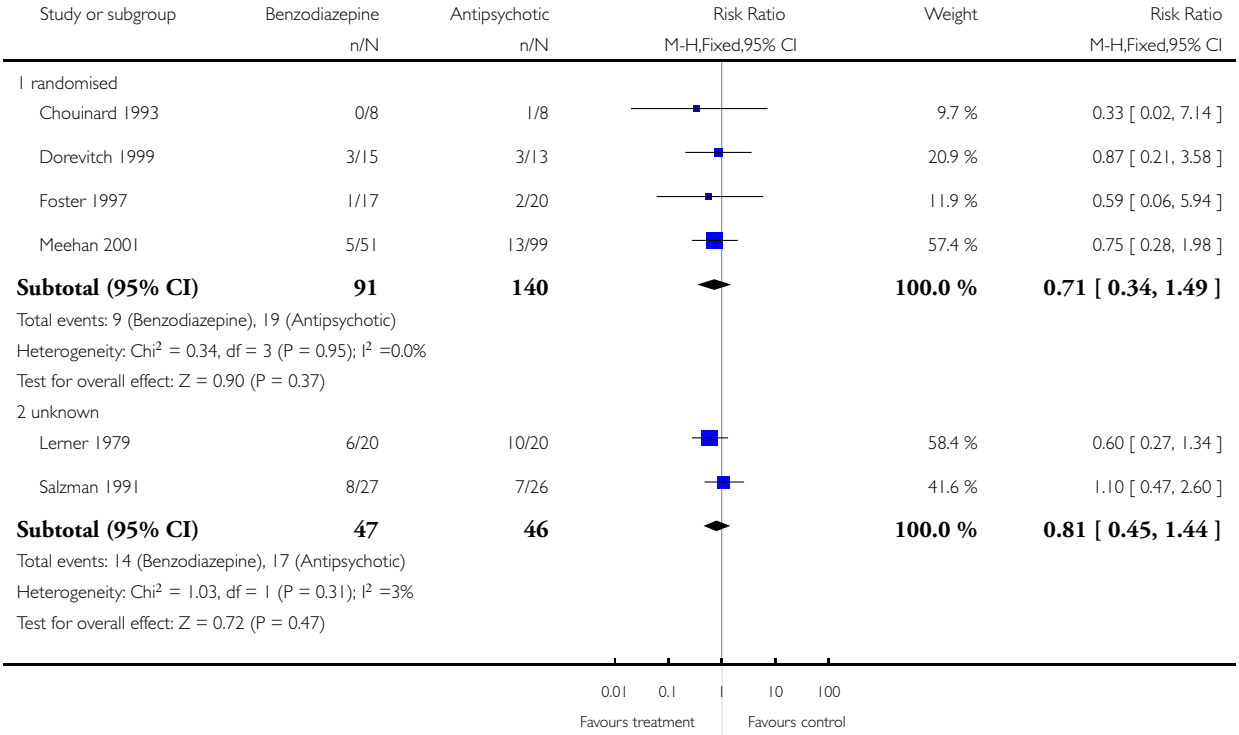


Analysis 6.1. Comparison 6 SENSITIVITY ANALYSIS: 2. RANDOMISED vs UNKNOWN, Outcome 1 Global impression: Sedation - medium term.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 6 SENSITIVITY ANALYSIS: 2. RANDOMISED vs UNKNOWN

Outcome: 1 Global impression: Sedation - medium term

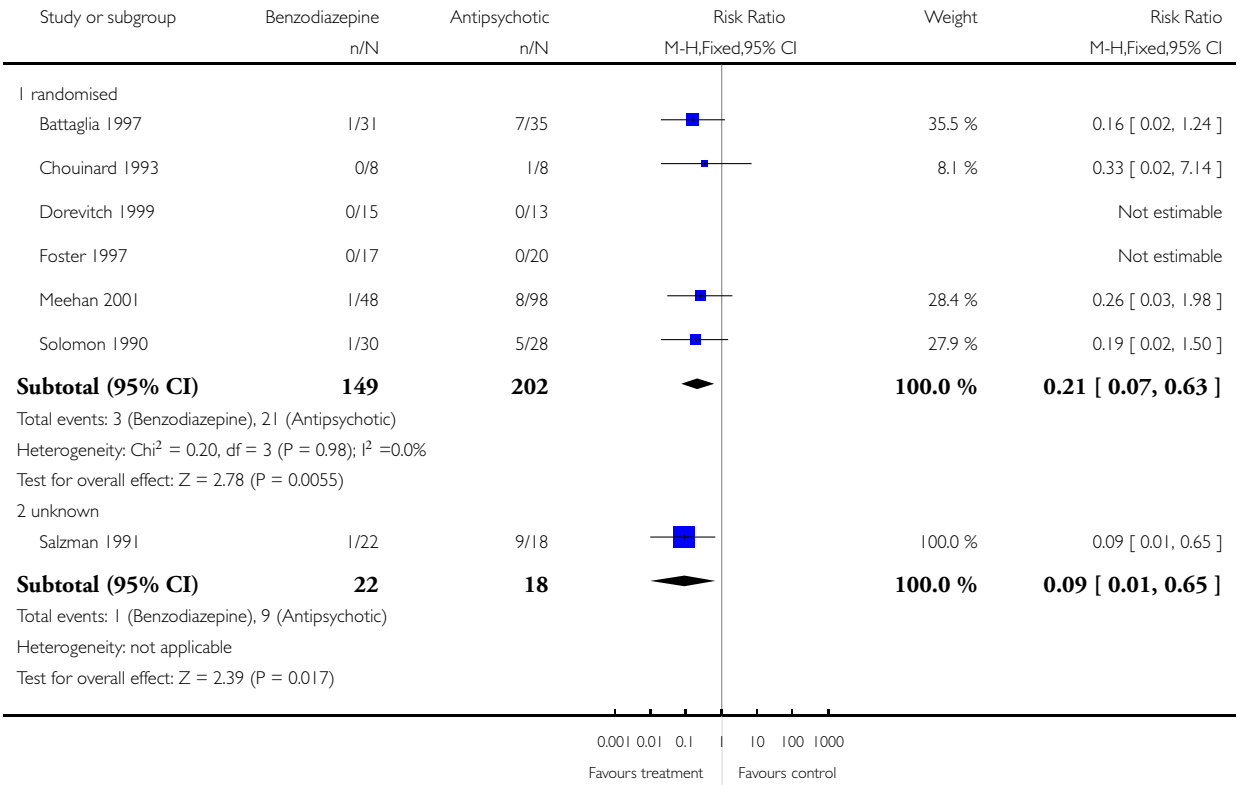


Analysis 6.2. Comparison 6 SENSITIVITY ANALYSIS: 2. RANDOMISED vs UNKNOWN, Outcome 2 Adverse events: 1. Extrapyramidal effects.

Review: Benzodiazepines for psychosis-induced aggression or agitation

Comparison: 6 SENSITIVITY ANALYSIS: 2. RANDOMISED vs UNKNOWN

Outcome: 2 Adverse events: 1. Extrapyramidal effects



ADDITIONAL TABLES

Table 1. Drugs for rapid tranquillisation in London survey

Drug of choice	Mean dose
diazepam*	27 (10-80)
haloperidol	22 (10-60)
chlorpromazine	162 (50-400)
droperidol	14 (10-20)

Table 1. Drugs for rapid tranquillisation in London survey (*Continued*)

paraldehyde	U/K
amytal	U/K
lorazepam	U/K
nitrazepam**	U/K
*most frequent	
** least frequent	

Table 2. Preferred medication for rapid tranquillisation in Rio de Janeiro

Drug of choice	Mean dose	Frequency of use
haloperidol + promethazine	5 (2.5-10) + 50 (25-100)	61%
haloperidol + promethazine + diazepam	5 (2.5-10) + 50 (25-100) +10	15%
diazepam	10	9%
haloperidol + promethazine + chlorpromazine	5 + 50 + 25	7%
chlorpromazine + diazepam + promethazine	25 + 10 + 50	1%
chlorpromazine + promethazine	25 + 50	1%
chlorpromazine	25	1%
diazepam + promethazine	10 + 50	1%
haloperidol + diazepam	5 + 10	1%
promethazine	50	1%

Table 3. High and low attrition studies

Attrition	Study	% loss	Duration	Notes
High	Barbee 1992	31	72 hours	
	Chouinard 1993	12	2 hours	

Table 3. High and low attrition studies (*Continued*)

	Salzman 1991	33	48 hours	- for EPS outcome; 12% loss for 'sedation'
Low	Bienek 1998	0	7 days	
	Meehan 2001	4	24 hours	
	Solomon 1990	0	7 days	
	Subramaney 1998	0	7 days	

WHAT'S NEW

Last assessed as up-to-date: 4 August 2005.

Date	Event	Description
14 April 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2005

Date	Event	Description
5 August 2009	Amended	Contact details updated.
22 October 2008	Amended	Converted to new review format.
5 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Donna Gillies - protocol development, data extraction, analysis, writing-up.

Alison Beck - protocol development, data extraction, analysis, writing-up.

Annie McCloud - protocol development, data extraction, analysis, writing-up.

John Rathbone - data extraction, analysis, writing-up.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- The Children's Hospital at Westmead, Sydney, Australia.
- Central Wandsworth Community Mental Health Team, London, UK.
- St George's Mental Health NHS Trust, London, UK.

External sources

- NHS National R&D Programme on Forensic Mental Health, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antipsychotic Agents [*therapeutic use]; Benzodiazepines [*therapeutic use]; Drug Therapy, Combination; Emergency Treatment; Lorazepam [therapeutic use]; Psychotic Disorders [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans