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Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis

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1 INTRODUCTION

Acute agitation is a common and important clinical management problem in major psychotic and mood disorders such as schizophrenia**, schizoaffective disorder** and bipolar affective disorder, particularly in the manic phase of the latter (Nordstrom K, 2009, Sachs GS, 2006). Agitation is a **poorly defined term generally used to describe excessive verbal or motor activity with a** range of symptoms that may vary in intensity from mild to severe (Citrome L, 2004a, Nordstrom K, 2009, Schleifer JJ, 2011)**. Allen (Allen MH, 2000) defines it as "a temporary disruption of the typical physician–patient collaboration, which interferes with assessment and treatment, during a period when immediate treatment is needed." As a lack of consensus in definition, agitation is often used interchangeably with the terms anxiety, hyperactivity, disruptive behaviour and non-purposeful behaviour (Schleifer JJ, 2011). Its hallmark features include motor restlessness, irritability, inappropriate or purposeless psychomotor activity and heightened responsivity to stimuli (Lindenmayer JP, 2000). It** is distressing both emotionally and physically and severely agitated patients are at risk of causing harm to themselves and others. The intensity of agitation can rapidly escalate from mild to severe (Nordstrom K, 2009). Agitation, even when severe, does not necessarily entail aggression however, aggression is often preceded by agitation.

The effective management of agitation is a key therapeutic target in the acute setting and for the longer-term care of patients with major psychiatric disorders. It impedes the assessment and evaluation of an acutely psychotic patient and the clinician will need to deal initially with the agitation before moving on to other aspects of treatment. Managing agitation effectively greatly improves patient outcomes, alleviates family burden and reduces societal costs.

It is estimated that more than 90% of people with schizophrenia or bipolar disorder will experience agitation with an average of 12 episodes of acute agitation annually (National Institute for Health and Clinical Excellence, 2011). Lower levels of agitation are treated with psychological interventions aimed at reducing tension and anxiety. Behavioural approaches have also proven to be valuable and effective in reducing agitation. In the UK, the use of de-escalation techniques have been formally recommended by the National Institute for Care and Clinical Excellence (NICE) to prevent situations that may lead to violence and aggression(National Institute for Health and Clinical Excellence, 2005). However, cases of severe agitation may require urgent pharmacological treatment to reduce potential risk to self and others when appropriate psychological and behavioural approaches have failed to de-escalate acutely disturbed behaviour.

The pharmacological treatment of patients with agitation in individuals with psychiatric disorders is an area that is poorly researched and evidenced and there is currently wide variation in clinical practice (Brown S, 2011). Clinical guidelines by NICE for the treatment of schizophrenia (National Institute for Health and Care Excellence, 2014b) and bipolar disorder (National Institute for Health and Care Excellence, 2014a) do not make specific recommendations for the pharmacological management of acute agitation. In clinical practice antipsychotics, either typical (e.g. haloperidol) or atypical (e.g. risperidone and olanzapine) are used to treat acute agitation and are administered with or without supplemental benzodiazepines (e.g. lorazepam). These treatments may be given orally or intramuscularly.

Our systematic review aimed to identify effective short-term pharmacological interventions that could be used for the management of agitation in patients with schizophrenia or bipolar disorder.

2 METHOD

2.1 Overview

We conducted a systematic review of pharmacological interventions to treat agitation in people with psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder) and bipolar disorder. The main purposes of the review were to signpost those interventions that warrant **further investigation and to highlight the gaps** in the evidence base. The review was conducted in accordance with the PRISMA (Moher D et al., 2009) guidelines and the Centre for Reviews and Dissemination (CRD) published guidance on conducting systematic reviews in healthcare (Centre for Reviews and Dissemination, 2009).

2.2 Search strategy

The major electronic databases including Medline, EMBASE, PsycInfo and the Cochrane Library, were searched for relevant published literature. **Searches were conducted for randomised controlled trials (RCTs) involving comparisons between current treatments for agitation and placebo. Search terms included a combination of index terms (e.g. agitation, aggression, violence, tranquilisation, psychotic disorders, schizophrenia, mood disorders, bipolar disorder and drug therapy or emergency treatment) and free text words (e.g. psychosis, bipolar, schizophrenia, antipsychotics and benzodiazepines) combined with specific drug terms including benzodiazepines (e.g. lorazepam, alprazolam, midazolam, clonazepam) and antipsychotics (e.g. haloperidol, risperidone, olanzapine, asenapine, ziprasidone). The database searches were conducted up to March 2015 and limited to English language. Reference lists of**

retrieved articles were also searched to identify further studies (details of the search strategies used are available upon request).

2.3 Inclusion and exclusion

We (YD and JG) included **RCTs that** involved adults with agitation associated with psychotic or bipolar disorder according to ICD10 (1994b) (F20, F23, F25 and F31) or DSM IV(1994a) who were seen in specialist mental health services including in-patient and community mental health services. The interventions included a range of pharmacological treatments: oral, inhaled or intramuscular preparations (e.g. benzodiazepines (such as lorazepam) and antipsychotics (such as haloperidol, risperidone, olanzapine, ziprasidone and loxapine). The comparators were the aforementioned treatments compared with each other, placebo or no intervention. The outcomes of interest were agitation levels as measured by accepted standard scales (e.g. Positive and Negative Syndrome Scale Excited Component [PANSS-EC]), and adverse events (AEs), but these were not considered as inclusion criteria.

We excluded RCTs that involved patients with psychotic presentations that were primarily due to medical conditions (including dementia) or substance misuse, and RCTs that measured agitation at 24-hour intervals only. We also excluded dose-ranging trials in which there was no comparator intervention.

2.4 Data extraction and quality assessment

Data were extracted relating to trial design, intervention(s) used including dose and preparation type, participant characteristics and outcome measures taken. Missing data were requested from trial authors.

2.5 Data analysis

The trial characteristics, trial quality criteria and trial outcomes are summarised in *Tables 1 and 2*.

2.6 Statistical analysis

2.6.1 Paired meta-analysis

A fixed effects model was used to combine the data at 60 minutes and 120 minutes for PANSS-EC score using RevMan (The Nordic Cochrane Centre, 2014) The mean difference and 95% confidence intervals are presented for each comparison. There were insufficient studies combined in order to construct a funnel plot to assess publication bias, conduct subgroup analyses or sensitivity analyses. Heterogeneity was assessed by visually assessing the forest plots, the I^2 statistic (Higgins et al., 2003) and Chi-squared (p<0.1).

2.6.2 Network meta-analysis

The analyses were conducted using WinBugs version 1.4. The control and intervention effect parameters were given flat (uninformative) Normal (0, 1000) priors and the standard deviation flat Uniform distributions with an appropriately large range given the scale of measurement. Fixed and random effects models were investigated for the network meta-analysis. The deviance information criterion statistic and the total residual deviance were observed to ensure that the model's overall fit was adequate. In all cases a burn in of at least 30,000 simulations were discarded. All results presented are based on a further sample of 50,000 simulations.

As both fixed effects and random effects models were investigated, it was necessary to consider the **Deviance Information Criterion** (DIC) and total residual deviance values for each model, in order to decide which would be the most appropriate to fit the data. The value of the total residual deviance should be as close to the number of data points as possible, while smaller DIC values indicate better model fit.

3 RESULTS

The literature searches yielded 1798 hits; 105 were selected for full text review and application of inclusion/exclusion criteria. A total of 17 RCTs were selected for inclusion in the review.

3.1 Characteristics of included trials and participants

The key trial and participant characteristics are described in *Table 1*. The 17 RCTs (Allen et al., 2011, Andrezina et al., 2006, Breier et al., 2002, Currier et al., 2004, Fang et al., 2012, Hsu et al., 2010, Hwang TJ et al., 2012, Katagiri H. et al., 2013, Kinon et al., 2004, Kwentus et al., 2012, Lesem et al., 2011, Lim et al., 2010, Meehan et al., 2001, Tran-Johnson et al., 2007, Wright et al., 2001, Zhang et al., 2013, Zimbroff et al., 2007) recruited a combined total of 3841 patients. The majority of the trials included only patients with schizophrenia, schizophreniform disorder or schizoaffective disorder, whilst three trials (Kwentus et al., 2012, Meehan et al., 2001, Zimbroff et al., 2007) included only patients with bipolar disorder. Three trials included patients with schizophrenia or bipolar disorder (Currier et al., 2004, Hsu et al., 2010, Lim et al., 2010). The numbers of patients recruited to each trial ranged from 42 (Hsu et al., 2010) to 448(Andrezina et al., 2006).

The trials were published between 2001 and 2013 and the mean ages of the participants across the trials ranged from 32 years to 47 years. Three trials included a substantially higher percentage of males compared to females.(Allen et al., 2011, Kinon et al., 2004, Lesem et al., 2011)

A range of interventions and comparators were employed. The most frequently investigated treatment was haloperidol monotherapy (Andrezina et al., 2006, Breier et al., 2002, Fang et al., 2012, Kinon et al., 2004, Lim et al., 2010, Tran-Johnson et al., 2007, Wright et al., 2001, Zhang et al., 2013).

Olanzapine was used in six trials (Breier et al., 2002, Hsu et al., 2010, Katagiri H. et al., 2013, Kinon et al., 2004, Meehan et al., 2001, Wright et al., 2001), aripiprazole featured in three trials (Andrezina et al., 2006, Tran-Johnson et al., 2007, Zimbroff et al., 2007), loxapine in three trials (Allen et al., 2011, Kwentus et al., 2012, Lesem et al., 2011), risperidone monotherapy was utilised in two trials (Hsu et al., 2010, Lim et al., 2010) and lorazepam monotherapy in two trials.(Meehan et al., 2001, Zimbroff et al., 2007). Three trials employed a combined treatment approach: one assessed the use of risperidone with lorazepam (Currier et al., 2004), one risperidone with clonazepam (Fang et al., 2012) and two trials used haloperidol with lorazepam(Currier et al., 2004, Hwang TJ et al., 2012). The trials assessing inhaled loxapine (Allen et al., 2011, Kwentus et al., 2012, Lesem et al., 2011) all included two dose sizes of loxapine (5mg and 10mg), a range of dose sizes of olanzapine were included in another trial (Breier et al., 2002) whilst a range of doses of aripiprazole were included in a third trial (Tran-Johnson et al., 2007).

In the majority of the included trials, the protocol prescribed that up to three doses of medication could be given across a 24-hour period with at least 2 hours between any subsequent doses. The exceptions to this were the Fang (Fang et al., 2012) and Hsu (Hsu et al., 2010) trials in which a single daily dose of trial drug was given.

The majority of the trials were conducted over a 24-hour period; the exceptions were Fang (5 days), Kinon (3 weeks) and Zhang (72 hours). The latter three trials were included in the review as agitation was measured at regular timepoints during the first 24 hours.

The dose sizes and method of administration of the interventions were consistent across the inhaled loxapine trials (Allen et al., 2011, Kwentus et al., 2012, Lesem et al., 2011), however, the dose sizes and method of administration across the remainder of the trials varied. Aripiprazole was administered in an intramuscular (IM) formulation with doses ranging between 1mg and 15mg. Haloperidol was administered as an IM formulation at single doses ranging between 5mg and 7.5mg and in an oral formulation of 10mg. Three different formulations of olanzapine were employed, IM (doses ranging between 2.5mg and 10mg) ODT (10mg) and oral (10mg). Risperidone was given orally at 2mg or (2-6 ml) either alone, or with lorazepam or clonazepam. In the single trial using ziprasidone, treatment was administered as IM at 10 to 20mg. Where lorazepam was employed as a comparator, it was given IM at 2mg.

The primary outcome of the majority of trials was change in the excited component of the Positive and Negative Syndrome Scale (PANSS-EC) from baseline either as measured at 2 hours or 24 hours. The PANSS-EC scale measures five symptoms associated with agitation: poor impulse control, tension, hostility, uncooperativeness and excitement. Each symptom is rated on a scale of 1 (absent) to 7 (extreme), and scores are summed. Therefore, total scores can range from 5 (all symptoms

absent) to 35 (all symptoms extreme). The mean baseline agitation scores across all trials as measured by PANSS-EC ranged from 12.69 (Meehan et al., 2001) to 26 (Hsu et al., 2010). All trials with PANSS-EC as a primary outcome had specified that included patients should have a score of at least 14; however, participants in the Meehan (Meehan et al., 2001) trial had a mean agitation score of 12.69. The time intervals of the measurement of PANSS-EC varied across trials.

Three trials did not use the PANSS-EC scale as a measure of agitation. One trial (Currier et al., 2004) reported a primary outcome as 5 items from PANSS (excitement, hostility, uncooperativeness, hallucinatory behaviour, poor impulse control) and another (Kinon et al., 2004) as the reduction in PANSS agitation 10-item subscale. One trial reported the primary outcome as change from baseline on the Brief Psychiatric Rating Scale (BPRS) at 72 hours (Zhang et al., 2013). The trial measuring agitation using a 10 item agitation subscale of the PANSS reported mean baseline scores of 37.74 (Kinon et al., 2004). The trial measuring agitation on the BPRS scale reported a mean baseline score of 56.6.

All trials reported a range of secondary outcomes. These included (but were not limited to) the Clinical Global Impressions Scale (CGI), Agitation-Calmness Evaluation Scale, Brief Psychiatric Rating Scale, Overt Aggression Scale, Behavioural Activity Rating Scale and PANSS overall scale.

All trials with the exception of Hsu (Hsu et al., 2010) were funded by pharmaceutical companies.

3.2 Quality assessment

Quality assessment of the included trials was conducted in accordance with the CRD published guidance (Centre for Reviews and Dissemination, 2009). The assessment criteria include six main quality domains: randomisation, comparability of participants, eligibility criteria, blinding procedures, participant withdrawals and outcome reporting bias. Each item is scored as either yes, no, not stated, not applicable or unclear.

Only four of the included trials (Andrezina et al., 2006, Kwentus et al., 2012, Lesem et al., 2011, Lim et al., 2010) provided sufficient information for the randomisation procedures and allocation concealment to be assessed. With the exception of the Hwang (Hwang TJ et al., 2012) trial (abstract only available) all trials reported details of numbers of participants, their baseline comparability and the eligibility criteria for inclusion in the trial. For the most part, participant characteristics were comparable between trial arms. The majority of trials reported the use or potential use of co-medication, such as rescue treatments (generally lorazepam) or treatments for extra-pyramidal symptoms. In the trials that included blinding, it was not always apparent who was blinded. One trial reported assessing the blinding procedures (Lesem et al., 2011). In 11 trials, the participants were reported to be blinded to their treatment assignment (Allen et al., 2011, Andrezina et al., 2006, Breier

et al., 2002, Katagiri H. et al., 2013, Kinon et al., 2004, Kwentus et al., 2012, Lesem et al., 2011, Meehan et al., 2001, Tran-Johnson et al., 2007, Wright et al., 2001, Zimbroff et al., 2007) All trials appeared to include at least 80% of participants in the final analyses. In all cases where appropriate, the last observation carried forward method was used to compensate for patient losses. No trial appeared to report fewer outcomes than were measured.

3.3 Clinical outcomes

In this review we focus on the outcomes of PANSS-EC and AEs of treatment. The PANSS-EC outcome was measured at different time points across the trials. The author conclusions for individual trials are reported in *Table 2*.

The AEs were reported differently across the included trials. We report (*Table 2*) the number and percentage of any treatment-related AEs and numbers of patients who withdrew from the trial due to AEs. **The AEs included headache, dizziness, sleep problems, hypotension, sedation, extra-pyramidal symptoms**.

3.4 Pairwise meta-analysis

3.4.1 Olanzapine versus haloperidol

Four trials (Breier et al., 2002, Hsu et al., 2010, Kinon et al., 2004, Wright et al., 2001) investigated this comparison, (n= 465). However, only three trials (Breier et al., 2002, Hsu et al., 2010, Wright et al., 2001) (n=365) reported data for change in PANSS-EC scores at 60 and 120 min. Kinon (Kinon et al., 2004) did not report this outcome. At 60 minutes, the mean difference was -3.64 (95% CI: -6.90, -0.38) indicating a statistically significant difference in change in PANSS-EC score at 60 minutes favouring olanzapine, although this was only based on one small trial (n=22). There was no significant difference at 120 minutes (MD -0.65 [95% CI:-1.76, 0.46]). Only Kinon (Kinon et al., 2004) and Hsu (Hsu et al., 2010) reported AEs. The risk ratio was not significant (0.91 [95% CI: 0.73, 1.14]) indicating no difference between the treatments.

3.4.2 Loxapine inhaled 5mg versus loxapine inhaled 10mg

Three trials (Allen et al., 2011, Kwentus et al., 2012, Lesem et al., 2011) investigated this comparison, (n=524) and all reported data for change in PANSS-EC scores at 60 and 120 min and AEs. The mean difference in change in PANSS-EC scores at 60 minutes was not statistically significant although the results appear to favour loxapine 10mg (MD 0.79 [95% CI: -0.01, 1.59]). At 120 minutes, the difference is statistically significant (MD 0.87 [95% CI: 0.04, 1.69]). The change in PANSS-EC score is 0.87 more on 10mg compared to 5mg. For AEs, the risk ratio was not significant (0.99 [95% CI: 0.78, 1.25]), indicating no difference between the treatments.

3.4.3 Haloperidol versus risperidone

Two trials (Hsu et al., 2010, Lim et al., 2010) investigated this comparison (n=145) but only one trial (Hsu et al., 2010) (n=21) reported data for change in PANSS-EC scores, 60 and 120 min . Both studies reported data for AEs. The mean difference in the change in PANSS-EC scores at both 60 and 120 minutes was not statistically significant, MD 2.25 (95% CI:-0.61, 5.11) and 0.63 (95% CI: -2.17, 3.43). For AEs, the risk ratio was not significant (0.59 (95% CI: 0.31, 1.11)), indicating no difference between the treatments.

3.4.4 Olanzapine versus lorazepam

One trial (Meehan et al., 2001) investigated this comparison, (n=150) and reported data for change in PANSS-EC scores at 120 min and AEs. The mean difference in the change in PANSS-EC scores at 120 minutes was statistically significant, MD -2.85 (95% CI: -4.56, -1.14). The change in PANSS-EC scores is 2.85 more on olanzapine compared to lorazepam. For AEs, the risk ratio was significant (0.67 [95% CI: 0.46, 0.9]), indicating a 33% reduction in risk of AEs for olanzapine compared to lorazepam.

3.4.5 Aripiprazole versus lorazepam

One trial (Zimbroff et al., 2007) investigated this comparison (n=148) but did not report any data for change in PANSS-EC scores at 60 and 120 min. Zimbroff (Zimbroff et al., 2007) reported overall AEs not AEs by treatment group.

3.4.6 Haloperidol versus risperidone plus clonazepam

One trial (Fang et al., 2012) investigated this comparison, (n=162 but only data for change in PANSS-EC scores, 120 min and AEs are reported. The mean difference in the change in PANSS-EC scores at 120 minutes was not statistically significant, MD -0.50 (95% CI: -2.90, 1.90). For AEs, the risk ratio was significant (1.72 [95% CI: 1.29, 2.29]), indicating a 72% increase in risk for haloperidol compared to risperidone plus clonazepam.

3.4.7 Haloperidol versus aripiprazole

Two trials (Tran-Johnson et al., 2007) investigated this comparison (n=465) but only Andrezina (Andrezina et al., 2006) reported data for change in PANSS-EC scores at 60 and 120 min. Both trials report AEs, but Andrezina (Andrezina et al., 2006) appears to only report serious AEs. The mean differences in the change in PANSS-EC scores at 60 and 120 minutes were not statistically significant, MD -0.90 (95% CI: -2.42, 0.62) and MD -0.48 (95% CI: -2.11, 1.15), respectively. For AEs and serious AEs, the risk ratios were not significant (0.91 [95% CI: 0.61, 1.35]) and 1.06 (95% CI: 0.27, 4.16)), indicating no difference between the treatments.

3.4.8 Risperidone and lorazepam versus haloperidol and lorazepam

One trial (Currier et al., 2004) investigated this comparison (n=162) but no data for change in PANSS-EC scores at 60 and 120 min or AEs were reported.

3.4.9 Olanzapine versus haloperidol and lorazepam

One trial (Hwang TJ et al., 2012) investigated this comparison (n=67) but only reported data for change in PANSS-EC scores at 120 min. The mean difference in the change in PANSS-EC scores at 120 minutes was not statistically significant, MD -0.20 (95% CI: -3.10, 2.70). No data were reported for AEs.

3.4.10 Interventions versus placebo

Nine of the included trials (Allen et al., 2011, Andrezina et al., 2006, Breier et al., 2002, Katagiri H. et al., 2013, Kwentus et al., 2012, Lesem et al., 2011, Meehan et al., 2001, Tran-Johnson et al., 2007, Wright et al., 2001) compared interventions to a placebo arm.

3.5 Network meta-analysis

Assessing model fit

As a lower DIC value was observed for fixed effects **than random effects for data at both 60 minutes (DIC=96.705 and DIC=97.517 for fixed effects and random effects, respectively) and 120 minutes (DIC=194.647 and DIC=196.004 for fixed effects and random effects, respectively), it was decided that the fixed effects models were the most suitable.**

Inconsistency

DIC and total residual deviance values**, show that the fixed effects model fits the data very well (DIC 96.705, total residual deviance 11.02 for the data measured at 60 mins, and DIC 194.647, total residual deviance 20.06 for the data measured at 120 mins), and therefore there is no evidence that inconsistency between direct and indirect estimates of treatment effects may exist.**

Results

None of the results from the network meta-analysis are statistically significant ***(Table 3)***. However, the confidence intervals are very wide due to the small sample sizes so it may be that there are differences in treatment effects but there is not enough statistical power to detect them. At 60 minutes olanzapine has the highest probability of being best **(29.08%), followed by risperidone (17.72%), and loxapine 10 mg (17.45%). At 120 minutes risperidone plus clonazepam has the highest probability of being best (27.68%), followed by haloperidol plus lorazepam (22.88%), and aripiprazole (16.42%).**

4 DISCUSSION

Main findings

We included 17 RCTs (3841 participants) that assessed pharmacological interventions for people with agitation associated with schizophrenia or bipolar disorder. The majority of the trials used the PANSS-EC as a measure of agitation. We focussed on the outcome measured at 60 minutes and 120 minutes as those time intervals were most frequently reported. We also consider that these time intervals are of key interest to clinicians.

Of the trials that compared active treatment with placebo, the active treatment was found to be superior in all but the comparison of haloperidol versus placebo at 120 minutes. **Appropriate use of de-escalation techniques may increase the placebo effect and partly explain the non-significant differences found in a number of trials comparing active pharmacological intervention versus placebo.** However, in our view, the most useful information for clinicians is whether one treatment is more effective than another. The pair-wise comparisons suggest that after 60 minutes, olanzapine is superior to haloperidol; no other treatment (where comparisons were available) was more effective than any other. At 120 minutes, loxapine 10mg was found to be more effective than loxapine 5mg and olanzapine more effective than lorazepam.

The results of our NMA did not demonstrate any treatment was more effective than any other. However, the results of the NMA indicate that at 60 minutes, treatment with olanzapine has the greatest possibility to be the most effective treatment and at 120 minutes, treatment with risperidone plus clonazepam has the greatest possibility to be the most effective treatment.

In terms of AEs, our review noted a reduction in risk in favour of olanzapine when compared with lorazepam and a substantial increase in risk for haloperidol when compared with clonazepam.

Strengths and limitations

To our knowledge, this is the first systematic review in this clinically important area and in this patient group. Our review compares the efficacy of all pharmacological treatments used in patients with agitation associated with schizophrenia or bipolar disorder. We did not include patients with agitation seen in emergency departments of hospitals and who required rapid tranquilisation for aggression or agitation, or patients with agitation associated with other conditions. Existing Cochrane Reviews (Ahmed et al., 2010, Gillies et al., 2013, Powney et al., 2012) have considered specific pharmacological interventions (benzodiazepines, haloperidol, chlorpromazine) for the treatment of aggression or agitation associated with psychosis in patients requiring rapid tranquilisation.

The results from our review must be interpreted with considerable caution. The aim of the review was to identify the most effective pharmacological treatments available for use in appropriate patients with

schizophrenia or bipolar disorder who experience agitation. It is difficult to reach any conclusion based on the trials available for inclusion in our review.

A number of factors presented challenges to the data extraction and synthesis processes of our review. A range of treatments and comparisons were reported across the 17 trials, including combinations of treatment. In addition, different treatment doses were employed across the trials and different methods of treatment administration were used, oral, intra-muscular, ODT and inhaled. The majority of trials assessed the reduction of agitation measured by changes in PANSS-EC scores, however PANSS-EC measurements were taken at a variety of time intervals across the trials.

The methodological quality of all of the included trials is questionable, for example, only four trials reported any information regarding the randomisation procedures used. It is notable that the RCTs rated as being of the highest quality were those involving the use of loxapine. We have concerns about the lack of any blinding procedures in the majority of trials and the small numbers of patient numbers recruited to the trials, ranging from 42 to 448. It is uncertain whether these limited sample sizes would be sufficiently powered to detect treatment differences. All trials with PANSS-EC as a primary outcome specified that included patients should have a score of at least 14, mean baseline agitation scores across all (Bhandari M et al., 2004, Rochon PA et al., 1994) trials ranged from 12.69 (Meehan et al., 2001) to 26 (Hsu et al., 2010). We do not know if the patients in the trials are representative of patients in clinical practice who would be considered for pharmacological treatment. It has been documented elsewhere that severely agitated patients are excluded from clinical trials due to their inability to provide informed consent (Centorrino et al., 2007). We also note that the PANSS-EC scale is used only as a measure in clinical trials and is not used in clinical practice. Our review relies on the use of PANSS-EC, a surrogate measure of an ill-defined and poorly understood mental health event. The outward signs of agitation may vary between disorders and cultures (Montoya et al., 2011).

A further significant reason for caution is that all but one of the trials included in our review was conducted with pharmaceutical company support, a factor known to cause bias in reported studies (Bhandari M et al., 2004, Flacco et al., Rochon PA et al., 1994).

Of great importance to patients and clinicians is the issue of AEs of treatment. We encountered difficulties with extracting data from the trial publications. These difficulties were due to the inconsistent reporting of AEs across the included trials. Not all trials reported on AEs of treatment. We consider the lack of clarity in the reporting of AEs a matter of concern as patient safety, particularly in the area of patient mental health is a key consideration**. We acknowledge that safety information is available in the relevant Summary of Product Characteristics for each drug.**

Clinical implications

Due to limitations of available research, we are unable to quantify the clinical value of any of the treatments included in our review. No firm conclusions can be drawn regarding the efficacy and safety of any of the interventions reviewed and there are clear research needs in this area. We found no consistent pattern of superiority of one treatment over another. **Consideration should therefore be given to a sufficiently large, non-commercially supported, good quality trial to allow direct comparisons of key treatments.** The trial should be sufficiently powered to detect treatment differences in a well-defined patient group. In addition, the reporting of AEs must be clear and be of value to clinicians and patients. A particularly valuable component of any new trial would be a quality of life outcome and a qualitative review. The latter would give important insights into patients' perceptions of and satisfaction with their treatment.

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Table 1 Trial characteristics

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
Allen 2011	N=129 Loxapine Inhaled 10mg (n=41) Loxapine Inhaled 5mg (n=45) Placebo Inhaled (n=43)	105 (81)	Parallel double blind placebo controlled trial 18 centres in USA	Alexza Pharmaceuticals (4 authors with financial interest in Alexza Pharmaceuticals and 2 authors employed by Novartis)	Change from baseline on PANSS-EC measured 2 hours post-intervention	• ≥ 18 and ≤65 years • DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder • clinical agitation defined as PANSS-EC ≥14 with at least 1 item ≥4	24 hours
Andrezina 2006	N=448 Aripiprazole IM 9.75mg up to 3/day(max 29.25mg during IM treatment); (n=175) Haloperidol IM 6.5mg up to 3/day(max 1.95mg during IM treatment); (n=183) Placebo (n=87)	110 (63) 109 (59) 55 (63)	Parallel double blind placebo controlled trial USA (68 centres)	Bristol-Myers Squibb and Otsuka Pharmaceutical (1 author employed by Bristol-Myers Squibb , 2 authors employed by Otsuka Pharmaceutical)	Change from baseline on PANSS-EC measured 2 hours post-intervention	• ≥ 18 years • DSM-IV criteria for schizophrenia or schizoaffective disorder evidence of clinical agitation during screening period defined as PANSS-EC ≥15 and ≤32 with at least 2 items ≥4	24 hours

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
Breier 2002	N=270 Olanzapine IM 2.5mg up to 3/day; (n=48) Olanzapine IM 5.0mg up to 3/day; as above (n=45) Olanzapine IM 7.5mg up to 3/day; as above (n=46) Olanzapine IM 10.0mg up to 3/day as above (n=46) Haloperidol IM 7.5mg up to 3/dayas above (n=40) Placebo IM (n=45)	 31 (64.6) 27 (60.0) 26 (56.5) 26 (56.5) 22 (55.0) 23 (51.1)	Parallel double blind placebo controlled trial Europe and South Africa (14 centres), setting not reported	Eli Lilly and Co (10 of 12 authors employed by Eli Lilly and Co.)	Change from baseline on PANSS-EC measured 30, 60 and 90 minutes and 2, 4, 6, 12, and 24 hours post-intervention	• ≥ 18 years • DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder • evidence of clinical agitation during screening period defined as PANSS-EC ≥14 with at least 1 item ≥4	24 hours
Currier 2004	N=162 Risperidone (2mg) +lorazepam (2mg) (oral) N= 83 Haloperidol IM (5mg) + lorazepam IM (2mg) N=79	 56 (67) 49 (62)	Rater-blinded RCT USA (24 sites) emergency department/hospitalised patients	Janssen Pharmaceutical (4 of the authors were employed by Janssen Pharmaceutical)	Change from baseline on 5 items from PANSS (excitement, hostility, uncooperativeness, hallucinatory behaviour, poor impulse control) measured 30 minutes, 1, 2, 3, 6 and 24 hours post-intervention	• 18 to 65 years • DSM-IV criteria for acute exacerbation of schizophrenia, schizoaffective disorder, mania with psychotic features, acute paranoid reaction, delusional disorder • score ≥ 14 on the PANSS and ≥3 on CGI-S	24 hours
Fang 2012	N=205 Risperidone oral 2-6 ml plus Clonazepam 0-8 mg per day (n=104) Haloperidol IM 10-20mg per day (n=101)	48 (46.2) 32.3 (9.4) 31.7 (9.2)	Parallel, open-label China (6 centres)	Xian-Janssen Pharmaceutical Ltd	Primary: Change from baseline on PANSS-EC measured at 2, 4, and 24 hours post-intervention during first, third and fifth day	• 18 to 45 years • DSM-IV criteria for acute exacerbation of schizophrenia or schizoaffective disorder, • score ≥ 14 on the PANSS EC and ≥60 on PANSS	5 days

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
Hsu 2010	N=42 Olanzapine IM 10mg (n=11) Olanzapine ODT 10mg (n=10) Risperidone oral 3mg (n=10) Haloperidol IM 7.5mg (n=11)l	20 (49) 6 (55) 6 (60) 3 (33) 5 (45)	Parallel, rater-blinded Taiwan (single centre) Inpatients	None	Change from baseline on PANSS-EC over 24 hours	• 18 to 65 years • DSM-IV criteria for schizophrenia or schizoaffective disorder, bipolar 1 disorder, delusional disorder, other psychotic disorders • score ≥ 14 on the PANSS EC with ≥4 on at least one item	24 hours
Hwang 2013	N=67 Olanzapine IM 10mg (n=37) Haloperidol IM 5 mg and Lorazepam IM 2mg (n=30)	Not reported	Single-blind, parallel, multicenter China, hospital	None reported	Change from baseline PANSS-EC score over 2 hours	Recently hospitalised acutely agitated patients with schizophrenia or schizoaffective disorder	24 hours
Katagiri 2013	N=90 Olanzapine IM 10mg (n=45) Placebo IM (n=44)	 21 (47) 23 (51)	Double-blind, parallel-group, multicenter Japan, outpatients (requiring hospitalization) and inpatients	Eli Lilly	Change from baseline on PANSS-EC over 2 hours	• 20 to 65 years • DSM-IV-TR criteria for schizophrenia • ACES score of 1 or 2	24 hours
Kinon 2004	N=100 Olanzapine oral (n=52) Haloperidol (n=48)	 71% 71%	Parallel, double-blind, multicentre USA, inpatients	Eli Lilly	Change in PANSS Agitation score at 1, 4, 8, 16 and 24hrs after treatment initiation and then daily for the first week and weekly until 3 week study completion	• 18 to 50 years • schizophrenia, schizophreniform disorder or schizoaffective disorder • PANSS Agitation subscale score ≥20 and CGI-S score ≥4	3 weeks
Kwentus 2012	N=314 Loxapine inhaled 5mg (n=104)	 47 (45) 53 (51)	Double blind placebo controlled, parallel USA (17 centres),	Alexza Pharmaceuticals (4 authors were consultants to	Change from baseline in the PANSS-EC score 2 hours after dose 1	• 18 to 65 years • DSM-IV criteria for bipolar • I disorder, with either manic or mixed episodes	24 hrs

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
	Loxapine inhaled 10mg (n=105) Placebo inhaled (n=105)	56 (53)	hospital	Alexza and 3 others were employees of Alexza. The employees all held Alexza stock and stock options)		• PANSS-EC Agitation subscale score ≥14 and ≥4 on at least 5 items	

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
Lesem 2011	N=344 Loxapine inhaled 5mg (n=116) Loxapine inhaled 10mg (n=113) Placebo (n=115)	 87(75) 86(76) 80(70)	Double blind placebo controlled, parallel USA (24 centres), hospital	Alexza Pharmaceuticals (5 authors were consultants to or employees of Alexza Pharmaceuticals)	Change from baseline in the PANSS-EC score 2 hours after first dose	• 18 to 65 years • DSM-IV criteria for schizophrenia • PANSS-EC score ≥14 with a score of ≥4 on at least 5 items	24 hrs
Lim 2010	N=124 Risperidone ODT 2mg (n=62) Haloperidol IM 5mg (n=62)	 34 (55) 32 (52)	Open label, rater blinded parallel group Korea (single centre), hospital	Janssen Korea Pharmaceutical	Change from baseline in the PANSS-EC, CGI-S	• 18 to 65 years • DSM-IV criteria for schizophrenia, schizoaffective disorder, bipolar 1, delusional disorder, psychotic disorder NOS • PANSS-EC score ≥14 with a score of ≥4 on at least 5 items and CGI-S score ≥3	24 hours
Meehan 2001	N=201 Olanzapine IM doses 1and 2=10mg, dose 3= 5 mg (n=99) Lorazepam doses 1and 2=2mg, dose 3= 1 mg (n=51) Placebo doses 1 and 2 = placebo, dose 3 = olanzapine 10mg (n=51)	 57 (58) 21 (41) 29 (57)	Double blind, placebo controlled, parallel USA and Romania, setting not reported	Eli Lilly (9 authors employed by Eli Lilly)	Change from baseline in the PANSS-EC at 2hrs and 24hrs CGI-S	• ≥18 years • DSM-IV criteria for bipolar disorder, manic or mixed, assessed as having agitation severe enough to be treated with injections • PANSS-EC score ≥14 with a score of ≥4 on at least 1 item	24hrs
Tran Johnson 2007	N=357 Aripiprazole IM 1 mg (n=57) Aripiprazole IM 5.25mg (n=63)	 37 (65) 35 (56)	Double blind, placebo controlled, parallel Worldwide (30 centres in USA, 20 centres	Bristol-Myers Squibb Otsuka Pharmaceuticals (1 author a consultant for	Change from baseline in PANSS-EC at 2hrs	• ≥18 years • appropriate for IM therapy for agitation • DSM-IV criteria for schizophrenia,	24hrs

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
	Aripiprazole IM 9.75 mg (n=57) Aripiprazole IM 15 mg (n=58) Haloperidol IM 5.25 mg (n=60) Placebo doses 1 and 2= placebo, dose 3= aripiprazole IM 15mg (n=62)	36 (63) 35 (60) 39 (65) 32 (52)	elsewhere)	Bristol-Myers Squibb, 2 authors employed by Bristol- Myers Squibb, 2 authors employed by Otsuka Pharmaceuticals, one is stock shareholder in Bristol Myers Squibb as well as being a former employee)		schizoaffective disorder, schizophreniform disorder, agitation severe enough to be treated with injections • PANSS-EC score ≥15 with a score of ≥4 on at least 2 items	

Trial name	Interventions Drug & dose, n	Male %	Study design location and setting	Commercial support	Outcomes	Inclusion criteria	Trial duration
Wright 2001	N=311 Olanzapine IM 10mg (n=131) Haloperidol IM 7.5mg (n=126) Placebo (n=54)	Not reported	Double blind, placebo controlled, parallel non-inferiority Australia, Austria, Belgium, Canada, Czech Republic, France, Greece, Hungary, Israel, South Africa, Spain, UK, USA Hospital	Eli Lilly	Change from baseline on PANSS-EC at 2 hours	• ≥18 years • DSM-IV criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder • agitation severe enough to be treated with injections • PANSS-EC score ≥14 with a score of ≥4 on at least 1 item	24hrs
Zhang 2013	N= 376 Ziprasidone IM (n=189) Haloperidol IM (n-187)	90 (47.6) 89 (47.6)	Rater-blind, active-controlled, parallel-group, multicenter China Hospital	Pfizer	Change from baseline on BPRS at 72 hours Secondary: Change from baseline to 2, 4, 24, 48, and 72 hours in BPRS agitation subscale	• 18 to 65 years • ICD-10 criteria for schizophrenia, only those with acute phase of schizophrenia, who could receive IM medication for ≥3 days • BPRS (1-7) score ≥40 and BPRS agitation subscale score ≥10, (≥3 score on at least 3 items)	72 hours
Zimbroff 2007	N=301 Aripiprazole IM 9.75mg (n=78) Aripiprazole IM 15mg (n=78) Lorazepam IM 2mg (n=70) Placebo IM (n=75)	157 (52)	Double blind, placebo controlled, parallel non-inferiority Hospital	Bristol-Myers Squibb and Otsuka Pharmaceutical (1 author had acted as consultant to Bristol- Myers Squibb, 4 were employees of Bristol-Myers Squibb and 2 were employees of Otsuka Pharmaceutical)	Change from baseline on PANSS-EC at 2 hours	• ≥18 years • DSM-IV criteria for bipolar 1 disorder, manic or mixed, PANSS-EC score 15 to 32 with a score of ≥4 on at least 2 items	24hrs

ACES=agitation calmness evaluation scale; BPRS=brief psychiatric rating scale; CGI-S=clinical global impressions (scale)-severity; DSM IV=diagnostic and statistical manual of mental disorders; ICD-10=international classification of diseases; IM=intramuscular; ODT=orally disintegrating tablet; PANSS-EC=positive and negative syndrome scale-excited component

Table 2 Trial outcomes

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Allen 2011	Loxapine inhaled 10mg	17.32 (2.02) Range 14-21	-6.51 (5.10)	-7.46 (4.89)	-8.39 (5.05)	-8.56 (4.90)	Not reported	16/41 (39) **Sedation (22%) Dysgeusia (17%) Throat irritation (7%)**	Compared with placebo, statistically significant differences in efficacy were found for the 10mg dose in score change from baseline on the PANSS-EC 20 min after administration, continuing through 2 hours.
	Loxapine inhaled 5mg	17.56 (1.94) Range 14-22	-5.71 (5.14)	-6.69 (5.26)	-6.56 (5.05)	-6.71 (5.14)		**14/45 (31) Sedation (13% Dizziness (11%) Headache/Dysgeusia (4%)**	
	Placebo inhaled	17.72 (2.23) Range 14-24	-4.21 (4.10)	-5.02 (4.48)	-5.26 (4.41)	-4.98 (4.13)		14/43 (33) **Sedation (14%) Dysgeusia (9%) Dizziness (9%)**	
								No patient from any groups withdrew from the study due AEs	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Andrezina 2006	Aripiprazole IM n=175	18.72	-2.50 (SE 0.45)	-5.20 (SE 0.55)	-6.26 (SE 0.57)	-7.27 (SE 0.59)	-8.28 (SE 0.50)	52/175 **Headache (7.4%)** **Dizziness (6.3%)** **Nausea/insomnia (=5.7%)**	Mean improvement in PANSS-EC at 2 hours was significantly greater for IM aripiprazole vs placebo. IM aripiprazole was non-inferior to IM haloperidol on PANSS-EC.
	Haloperidol IM n=185	18.79	-2.90 (SE 0.45)	-6.32 (SE 0.55)	-7.43 (SE 0.57)	-7.75 (SE 0.59)	-8.12 (SE 0.50)	64/183 **Insomnia (12%)** **Headache (8.2%)** **EPD (5.5%)** **Agitation (4.4%)**	
	Placebo n=88	18.74	-2.68 (SE 0.53)	-4.21 (SE 0.65)	-4.45 (SE 0.67)	-4.78 (SE 0.69)	-7.70 (SE 0.59)	22/87 **Insomnia (9.2%)** **Headache (6.9%)** **Agitation (5.8%)** 3 patients discontinued in total due to AEs	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Breier 2002	Olanzapine IM 2.5mg n=48	18.3 (2.4)	Graph	Graph	Graph	-5.5 (4.6)	-4.9 (4.3)	**Hypotension 2/48 (4.2%)**	All IM olanzapine doses and 7.5mg of IM haloperidol were superior to IM placebo in reducing agitation (this effect was sustained with IM olanzapine for up to 24h), but IM olanzapine at 2.5mg was less effective than any of the other olanzapine doses or IM haloperidol, indicating a dose-response relationship across the IM olanzapine dose groups.
	Olanzapine IM 5.0mg n=45	19.7 (3.4)				-8.1 (5.3)	-5.5 (4.9)	**Hypotension 2/45 (4.4%)** **Akathesia 2/42 (4.8%)**	
	Olanzapine IM 7.5mg n=46	18.9 (2.6)				-8.7 (5.0)	-5.5 (4.1)	**Hypotension: 1/46 (2.2%)**	
	Olanzapine IM 10.0mg n=46	19.3 (2.6)				-9.4 (4.9)	5.9 (5.2)	**Hypotension: 2/46 (4.3%)** **TE Parkinsonism: 1/35 (2.9%)**	
	Haloperidol IM 7.5mg n=40	19.3 (3.1)				-7.5 (5.9)	-4.5 (4.0)	**Acute dystonia: 2/40 (5.0%)** **TE Parkinsonism: 6/36 (16.7%)** **Akathesia: 3/38 (7.9%)**	
	IM Placebo n=45	18.8 (2.8)				-2.9 (4.7)	-3.1 (3.3)	**0 (0%)** Total AEs not reported. No between-group differences observed. Withdrawals not reported	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Currier 2004	Risperidone +lorazepam (oral) N= 83 Haloperidol + lorazepam IM N=79	19 (3.0) 19.1 (3.0)	Graph	Graph	NR	Graph	NR	1 (1) 1 (1) There were no significant between-group differences in the incidence of any AE. 1 patient from each group discontinued medication due to AE.	A single dose of risperidone plus lorazepam was significantly as effective as IM haloperidol plus lorazepam at each time point for the rapid control of psychotic agitation.

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Fang 2012	Risperidone oral 2-6 ml plus Clonazepam 0-8 mg per day	21.4 (4.6)	NR	NR	NR	-7.5 (8.5)	4.0 (5.6)	39/104 (37.5) **Akathisia 29 (27.9%) EPS 26 (25%) Tachycardia (3.8%) Insomnia 4 (3.8%)**	Significant improvements were seen at 2, 4, 24h in both treatment groups, between-treatment differences in mean change scores on the PANSS-EC.
	Haloperidol IM 10-20mg per day	22.5 (4.7)				-8.0 (9.0)	-4.3 (5.9)	65/101 (64.4) **Akathisia 46 (45.5%) EPS 56 (55.4%) Tachycardia 6 (5.9%) Insomnia 6 (5.9%)** *No withdrawals*	
Hsu 2010	Olanzapine IM N=11	25.55 (3.8)	14.45(4.80)	10.91(4.23)	8.73(3.69)	8.36(4.43)	7.18(2.52)	9/11	Olanzapine IM or olanzapine ODT had significantly greater improvement in PANSS-EC scores than haloperidol IM at points 15, 30, 45, 60, 75 and 90min after initiation of treatment (no significant differences between olanzapine IM and risperidone, olanzapine ODT and risperidone, risperidone and haloperidol IM, or olanzapine IM and olanzapine ODT at these time points).
	Olanzapine ODT N=10	24.7 (5.01)	13.90(5.80)	10.60(4.43)	10.70(4.92)	11.10(6.82)	10.10(5.72)	6/10	
	Risperidone oral N=10	25.0 (2.58)	16.20(4.26	12.30(3.16)	10.10(3.51)	9.10(2.84)	10.60(9.49)	3/10	
	Haloperidol IM N=11	28.18 (2.82)	20.36(5.2) ?	14.55(3.53)	12.00(5.12)	9.73(3.69)	10.18(5.60)	4/11 Withdrawals not stated	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Hwang 2012	Olanzapine IM 10mg (n=37) Haloperidol IM 5 mg and Lorazepam IM 2mg (n=30)	21.0 (4.6) 20.9 (3.6)	NR	NR	NR	-10.0 (6.5) -9.8 (5.6)	-9.1(5.5) -8.1(3.1)	No severe AEs were noted and EPS were observed in 2 patients in the haloperidol group	The PANSS-EC scores decreased significantly at 2 hours within both groups, but there was no significant difference between the two groups (p = 0.890). There were no significant differences in PANSS-EC or ACES scores between the two groups at 15, 30, 60 minutes and 24 hours.
Katagiri 2013	Olanzapine IM N=45 Placebo IM N=44	23.5 (6.1) 23.3 (4.9)	NR	NR	NR	-9.2 (4.5) -2.8 (5.6)	-5.6 -2.8	13 (28.9) 6 (13.3) no deaths or AEs leading to discontinuation	At the 2 hour timepoint, the IM olanzapine group showed a significant decrease in all PANSS-EC individual item scores compared with the IM placebo group (p <.001).

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Kinon 2004	Olanzapine oral N=52 Haloperidol Oral N=48	38.30 (6.80) 37.17 (6.32)	NR	Graph	NR	NR	Graph	35/52 (67.5) **Somnolence (17.3%)** **Anxiety (11.5%)** **Headache (11.5%)** 41/48 **(**85.4) **Somnolence (25%)** **Headache (25%)** **Nervousness (16%)** 8/48 (16.7%) haloperidol discontinued 1/52 (1.9%) olanzapine discontinued	Significant within group improvement was shown in PANSS scores for both groups as early as 1h after initiating treatment. At the end of the study, the olanzapine group experienced significantly greater improvement than the haloperidol group in mean PANSS agitation scores.

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Kwentus 2012	Loxapine inhaled 5mg	17.4 (2.23)	-7.54 (4.74)	-8.78 (4.74)	-8.29 (4.66)	-8.1 (4.90)	Not reported	36/104 (34.6) **Dysgeusia (17.3)** **Sedation (6.7%)** **Dizziness (5.8%)**	Both doses of inhaled loxapine significantly reduced agitation compared with placebo.
	Loxapine inhaled 10mg	17.27 (2.25)	-7.99 (4.67)	-8.80 (4.49)	-8.85 (4.74)	-9.0 (4.67)		30/105 (28.6) **Dysgeusia (17.1)** **Sedation (5.7%)** **Dizziness (4.8%)**	
	Placebo inhaled	17.74 (2.80)	-3.88 (4.37)	-4.96 (4.58)	-4.99 (4.33)	-4.9 (4.77)		24/105 (22.9) **Headache (8.6%)** **Dizziness (7.6%)** **Dysgeusia (5.7%)** 2 from 10mg group withdrew due to AE	
Lesem 2011	Loxapine inhaled 5mg	17.83(2.34)	-6.78 (4.74)	-7.67 (4.74)	-8.23 (4.88)	-8.1 (5.17)	Not reported	40/116 (30.5%) **Sedation (12.9%)** **Dygeusia (8.6%)** **Dizziness (5.2%)**	Loxapine 5mg and 10mg significantly reduced agitation compared with placebo.
	Loxapine inhaled 10mg	17.59 (2.34)	-7.61 (4.72)	-9.16 (4.41)	-9.12 (4.26)	-8.6 (4.37)		43/113 (38.1%) **Sedation (10%)** **Dygeusia (10%)** **Dizziness (10%)**	
	Placebo inhaled	17.36(1.80)	-4.15 (4.06)	-5.23 (4.78)	-5.33 (4.66)	-5.5 (4.37)		44/115 (38.3%) **Headache (13.9%)** **Sedation (9.6%)** **Dizziness (9.6%)** **1 withdrawal (10mg)**	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Lim 2010	Risperidone ODT 2mg	21.2 (3.0)	Graph only	Not measured	Not measured	Graph only	NR	17/62(27.4) **Somnolence (14.3%)** **Insomnia (9.3%)** **EPS (8%)** **1/62 discontinued**	The PANSS-EC and CGI-S scores were significantly decreased over time in both treatment groups without any significant group difference and time by group interaction effect
	Haloperidol IM 5mg	21.5 (3.3)						**EPS (12.9%)** **Somnolence (11%)** **Headache (7%)** **8/62 (29.0)** **2/62 discontinued treatment**	
Meehan 2001	Olanzapine IM	12.96 (3.18)	Not reported	Not reported	Not reported	-9.60 (4.74)	-5.78 (4.72)	34/99 (34.3%) **Somnolence (13.1%)** **Dizziness (9.1%)** **Dry mouth (3%)**	At 2 hours after the first injection, patients with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam.
	Lorazepam	12.39 (2.97)				-6.75 (5.20)	-5.65 (5.20)	26/51 (51%) **Dizziness (13.7%)** **Somnolence (9.8%)**	
	Placebo	12.72 (3.10)				-4.84 (4.66)	-3.94 (4.32)	13/51 (25.5%) **Somnolence (5.9%)** **Dizziness (2%)** No deaths. Withdrawals not reported	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Tran Johnson 2007	Aripiprazole IM 1mg	19.16	Graph only	Graph only	Graph only	Graph only	Graph only	28/56 (50) **Tachycardia (7.2%)** **Headache (7.1%)** **Dizziness (7.1%)** **Somnolence (5.4)**	Significantly greater reductions in PANSS-EC scores were observed at 2h with all doses of IM aripiprazole (except the 1mg dose) and IM haloperidol 7.5mg compared with placebo. The PANSS-EC - defined response rate with IM aripiprazole 15mg was significantly greater than the placebo at 60min. the response rate at 120min with IM haloperidol was significant at 120min, but not at 60min.
	Aripiprazole IM 5.25 mg	19.46						30/62 (48.4) **Headache (17.7%)** **Nausea (9.7%)** **Somnolence (8.1%)**	
	Aripiprazole IM 9.75 mg	19.44						25/56 (44.6) **Headache (10.7%)** **Nausea (10.7%)** **Tachycardia (7.1%)** **Somnolence (5.4%)** **Akathisia (5.4%)**	
	Aripiprazole IM 15 mg	19.34						27/58 (46.6) **Headache (13.8%)** **Dizziness (12.1%)** **Somnolence (10.3)**	
	Haloperidol IM 7.5mg	18.89						28/57 (49.1) **Somnolence(12.3 %)** **Akathisia (10.5%)** **Dizziness (7.0%)**	
	Placebo IM	19.21						18/61 (29.5) Dizziness (6.6%) Somnolence (4.9%) Nausea (3.3%) No discontinuations	

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Wright 2001	Olanzapine IM 10mg Haloperidol IM 75mg Placebo IM	18.4 (3.4) 18.2 (3.2) 18.4 (3.5)	Graph only	Graph only	Graph only	-7.7 (6.1) -7.6 (5.0) -3.6 (5.2)	-6.5 (5.3) -6.7 (4.6) -3.1 (5.1)	**EPS 1 (0.8%)** **Acute dystonia 9 (7%)** **EPS 7 (5.6%)** Witdrawals not reported	Both IM olanzapine and IM haloperidol reduced agitation significantly more than IM placebo.
Zhang 2013	Ziprasidone IM (n=189) Haloperidol IM (n-187)	BPRS 56.7 (8.1) 56.5 (8.1)	Not measured	Not measured	Not measured	Not measured	Not measured	54/189 (28.6) **Dizziness 7 (3.7%)** **Somnolence 7 (3.7%)** **EPS 4 (2.1%)** 2 discontinued 116/187 (62.0) **EPS 69 (36.9%)** **Dizziness 7 (3.7%)** **Somnolence 7 (3.7%)** 5discontinued No deaths occurred	For controlling agitation in schizophrenia in this Chinese study, ziprasidone had a favourable tolerability profile and comparable efficacy and safety compared to haloperidol.

Trial	Interventions	PANSS-EC SCORES (SD) Baseline	Change in PANSS-EC SCORES (SD) 30 min	Change in PANSS-EC SCORES (SD) 60 min	Change in PANSS-EC SCORES (SD) 90 min	Change in PANSS-EC SCORES (SD) 120 min	Change in PANSS-EC (SD) 24 hours	Any adverse events (number, total,%) (3 most frequent are listed where known)	Conclusion
Zimbroff 2007	Aripiprazole IM 9.75mg (75) Aripiprazole IM 15mg (75) Lorazepam IM 2mg (68) Placebo (73)	Not reported	Graph only	Graph only	Graph only	Graph only	NR	133/291 (46) 41/75 (55) **Headache (14.7%)** **Insomnia (10.7%)** **Nausea(10.7%)** **Somnolence (8.0%)** 56/75 (75) **Nausea (18.7%)** **Headache (17.3%)** **Dizziness 12%)** 24/69 (35) **Sedation (11.6%)** **Dizziness (10.1%)** **Somnolence (7.3%)** 29/72 (40) **Headache (12.5%)** **Insomnia (8.3%)** **Dizziness (5.6%)** 2 discontinuations: 1 x 15mg aripiprazole 1 x placebo	IM aripiprazole 9.75 and 15 mg are effective and well tolerated for acute agitation in bipolar disorder, although the low incidence of over-sedation suggests a risk–benefit profile for IM aripiprazole 9.75mg.

ACES=agitation calmness evaluation scale; AE=adverse event; CGI-S=clinical global impressions (scale)-severity; EPS=extra-pyramidal symptoms; IM=intramuscular; ODT=orally disintegrating tablet; PANSS-EC=positive and negative syndrome scale-excited component
Graph only =data presented graphically, but specific information not available.

Table 3 Change in PANSS-EC SCORES at 60 and 120 minutes

Treatment comparison		Change in PANSS-EC score (95% CI)	
		60 mins	120 mins
Haloperidol vs	Olanzapine	3.653 (-8.111, 15.43)	1.192 (-6.673, 8.992)
Risperidone vs	Olanzapine	1.373 (-9.983, 12.62)	0.7162 (-8.707, 10.39)
	Haloperidol	-2.28 (-12.95, 8.223)	-0.4753 (-9.588, 8.535)
Placebo vs	Olanzapine	5.712 (-16.86, 27.59)	5.393 (-1.408, 12.16)
	Haloperidol	2.059 (-17.32, 21.17)	4.202 (-3.804, 12.21)
	Risperidone	4.338 (-17.57, 25.88)	4.677 (-5.921, 15.27)
Loxapine 5mg vs	Olanzapine	3.096 (-20.98, 26.49)	2.949 (-7.755, 13.31)
	Haloperidol	-0.5569 (-21.49, 20.27)	1.758 (-9.544, 13.19)
	Risperidone	1.723 (-21.81, 24.69)	2.233 (-11.28, 15.4)
	Placebo	-2.616 (-10.67, 5.568)	-2.444 (-10.65, 5.497)
Loxapine 10mg vs	Olanzapine	2.327 (-22.03, 25.43)	1.867(-8.422, 12.12)
	Haloperidol	-1.326 (-22.45, 19.25)	0.6754 (-10.24, 11.64)
	Risperidone	0.954 (-22.95, 23.68)	1.151 (-11.96, 14.09)
	Placebo	-3.384 (-11.17, 4.3)	-3.526 (-11.43, 4.237)
	Loxapine 5mg	-0.7688 (-8.791, 7.425)	-1.083 (-9.42, 7.223)
Aripiprazole vs	Olanzapine	4.453 (-19.54, 28.32)	2.615 (-16.19, 21.71)
	Haloperidol	0.8 (-20.18, 22.19)	1.424 (-16.89, 20.73)
	Risperidone	3.08 (-20.31, 26.85)	1.899 (-18.01, 22.48)
	Placebo	-1.259 (-20.73, 17.88)	-2.778 (-21.3, 16.35)
	Loxapine 5mg	1.357 (-19.43, 22.76)	-0.3342 (-20.33, 19.68)
	Loxapine 10mg	2.126 (-18.73, 23.39)	0.7483 (-18.84, 20.96)
Rispiradone + Clonazepam vs	Olanzapine	NR	1.038 (-23.6, 26)
	Haloperidol	NR	-0.1534 (-23.82, 23.87)
	Risperidone	NR	0.3219 (-25.08, 26.1)
	Placebo	NR	-4.355 (-29.28, 20.65)
	Loxapine 5mg	NR	-1.911 (-28.48, 24.21)
	Loxapine 10mg	NR	-0.8288 (-26.88, 25.38)
	Aripiprazole	NR	-1.577 (-33.39, 28.92)
Lorazepam vs	Olanzapine	NR	3.085 (-10.24, 16.16)
	Haloperidol	NR	1.894 (-12.54, 16.28)
	Risperidone	NR	2.369 (-13.8, 18.28)
	Placebo	NR	-2.308 (-15.21, 10.81)
	Loxapine 5mg	NR	0.1359 (15.4, 15.16)
	Loxapine 10mg	NR	1.218 (-14.06, 16.23)
	Aripiprazole	NR	0.4701 (-22.34, 23,27)
	Rispiradone + Clonazepam	NR	2.047 (-25.28, 29.89)
Haloperidol + Lorazepam vs	Olanzapine	NR	0.1978 (-16.89, 17.7)
	Haloperidol	NR	-0.9937 (-20.14, 18.29)
	Risperidone	NR	-0.5184 (-20.23, 19.41)
	Placebo	NR	-5.196 (-23.33, 13.04)
	Loxapine 5mg	NR	-2.752 (-22.51, 17.22)
	Loxapine 10mg	NR	-1.669 (-21.61, 18.56)
	Aripiprazole	NR	-2.417 (-28.23, 22.29)
	Rispiradone + Clonazepam	NR	-0.8403 (-31.28, 29.24)
	Lorazepam	NR	-2.888 (-24.22, 18.89)