Pharmacological treatment of acute agitation associated with psychotic or bipolar disorder: a systematic review

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1 TITLE OF PROJECT
Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review

2 REVIEW TEAM
Dr Yenal Dundar¹,²
Dr Janette Greenhalgh³
Dr Rumona Dickson²
Professor Richard Whittington³
Professor Christoph Lauber⁴

¹ Acute Care Team, Hesketh Centre, Mersey Care NHS Trust
² Liverpool Reviews and Implementation Group (LRiG), University of Liverpool
³ Health and Community Care Research Unit, University of Liverpool
⁴ Department of Psychiatry, University of Liverpool

Correspondence to:
Dr Yenal Dundar
Specialist Registrar in General Psychiatry
Research Fellow, LRiG
University of Liverpool,
Whelan Building,
The Quadrangle,
Brownlow Hill
Liverpool
L69 3GB

Tel: +44 (0) 151 794 5067
Fax: +44 (0)151 794 5821
Email: yenal@liverpool.ac.uk

For details of expertise within the TAR team, see Section 6.
3 PLAIN ENGLISH SUMMARY
Agitation is a loose term used to describe a range of symptoms that may vary in intensity from mild to severe. Patients with agitation are unable to relax and show signs of restlessness such as pacing, pressured speech or shouting. Agitation is distressing both emotionally and physically and severely agitated patients are at risk of causing harm to themselves and others. Milder forms of agitation may be managed with methods aimed at engaging with the patient, reducing anxiety and tension through verbal and non-verbal communication; however, cases of more severe agitation may need treatment with medications (such as antipsychotics and benzodiazepines). Agitation is a common feature of psychotic illness such as schizophrenia and bipolar disorder. The purpose of the proposed project is to conduct a systematic review of the evidence of the clinical effectiveness of pharmacological treatments for acute agitation associated with psychotic illness or bipolar disorder. The review will be carried out in accordance with published guidelines for conducting and reporting systematic reviews. The aims of this review are to summarise the evidence from randomised controlled trials, explore the implications of the findings for clinical practice and to identify gaps in the research evidence in order to highlight the areas in need of further investigation.

4 BACKGROUND AND RATIONALE

4.1 Aims and objectives
The aim of the proposed project is to systematically review the relevant evidence for the clinical effectiveness of pharmacological interventions used for the management of acute agitation when associated with psychotic illness or bipolar disorder.

The objectives of the review are:

• to systematically review and summarise the relevant evidence
• to explore the implications of these findings for practice and service provision
• to identify gaps and weaknesses in the available research evidence base in order to inform future decisions on research priorities.

4.2 Background
Acute agitation is a nonspecific term applied to a variety of syndromes and behaviours1 and is used to describe a cluster of symptoms that may range from mild to severe.2 It may be defined as, “a state of restlessness that is experienced by the patient as inability to relax and is seen by an observer as restless activity, excess motor or verbal activity”3 or “state of motor restlessness and accompanying mental tension.”4 Similarly, Cohen3 has described agitation as “motor restlessness that accompanies anxiety.”
It is generally accepted that agitation includes both physical and emotional distress to the individual involved and to the family and care-givers and needs to be dealt with by health care professionals. The management of agitation therefore is an important part of treatment for many people who are acutely ill.\(^5\)

Agitation is a common and important clinical management problem in major psychotic and mood disorders such as schizophrenia and bipolar affective disorder (particularly in the manic phase of the latter).\(^2,6\) The behavioural manifestations of agitation include pacing, hand-wringing, fist-clenching, pressured speech, pulling of clothes, inability to sit still, shouting and threats to others.\(^4,5\) The intensity of the agitation can rapidly escalate from mild to severe.\(^2\) Whilst agitation, even when severe, does not necessarily entail aggression, aggression is often preceded by agitation. The underlying factors that lead from agitation to violent behaviour in certain individuals are not known, although patients with particular psychotic symptoms such as persecutory ideation appear to be at higher risk of behaving violently (both minor and serious).\(^2\) Situational factors, such as attempts to restrict movement or otherwise frustrate the patient, may also increase levels of agitation. In addition, there is the potential for confusion and misunderstanding of the motivations of staff who may be attempting to calm the patient. As an arousal syndrome, during episodes of agitation, vital signs such as blood pressure, respiratory rate, heart and metabolic rate are frequently elevated and abnormal.\(^5\)

The effective management of agitation is a key therapeutic target both in the acute setting, and for longer-term care of patients with major psychiatric disorders. Agitation causes distress to the patient and their behaviour may increase the risk of harm to themselves, relatives and care-givers. It also 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.

A review\(^7\) conducted in the United States of treatment guidelines and therapies (that were published between 2000 and 2006) on the treatment of agitation in various psychiatric disorders indicates that initial management of acute agitation generally involves verbal de-escalation. It concludes that seclusion or restraints are treatments of last resort due to safety issues.

We are not aware of any good quality systematic reviews of pharmacological treatments associated with psychotic or bipolar disorders. According to Brown,\(^8\) the treatment of patients with agitation is an area that is poorly researched and evidenced and there is currently wide variation in clinical practice.
4.3 Interventions and comparators

Treatment of acute agitation requires both environmental and pharmacological interventions. Intervening at early stages of agitation may prevent potential escalation from agitation to aggression and violence and decrease the need for seclusion and restraint, therefore reducing the potential risks involved both to the patient and to staff. Initial manifestations of agitation can be managed through nursing and interventions aimed at engaging with the patient, minimising confusion and reducing anxiety and tension through verbal and non-verbal communication. However, in cases of more severe agitation where such first-line interventions are not effective and the risk of violence or self-harm is significant, pharmacological treatment may be required. Such treatment may be adjunctive to that used to treat any underlying psychotic disorders. In the UK, existing clinical guidelines on the treatment of schizophrenia and bipolar disorder do not make specific recommendations for the pharmacological management of acute agitation. Where psychotic agitation occurs in the context of potential aggression, clinical guidelines issued by NICE for the management of violence recommend the use of antipsychotics, sometimes in combination with lorazepam. These guidelines note the role of agitation as a precursor, however do not cover the management of ‘non-aggressive’ agitation where hostility is low and violence is not seen as likely outcome. Current clinical practice in the UK includes the use of antipsychotics, either typical (e.g. haloperidol) or atypical (e.g. risperidone and olanzapine), administered with or without supplemental benzodiazepines (e.g. lorazepam). These treatments may be given orally or intramuscularly. In addition, the availability of oral liquid and rapidly dissolving tablet preparations of some atypical agents has provided beneficial alternatives in some cases. All pharmacological interventions have well-documented side effects.

A novel treatment for agitation in the form of an inhaler which delivers a single dose of loxapine has recently been investigated. This new treatment is innovative and members of the health team need to be aware of its effectiveness and possible side effects and or issues related to administration. Although the new treatment was suggested as a possible topic to be looked at by NICE it has not been put into their work programme. Reasons for this are not known but it is clear that assessing such a treatment within the NICE appraisal system would be difficult. The appraisal process includes calculation of utility values and overall incremental cost effectiveness ratios. Short term treatments such as those being looked at in this review do not lend themselves to these measures and so do not fit in with the current appraisal processes. This does not mean that they are not important to both patients and care providers. It is therefore important the clinical evidence be examined to inform clinical practice.

4.4 Key concepts

Psychotic disorders are a group of mental health disorders characterised by delusions, hallucinations and other problems of thought and emotion. Diagnosis is based on criteria in either the World Health
Schizophrenia is a major mental illness characterised by symptoms that alter perception, thoughts, affect and behaviour. The clinical presentation includes a range of positive symptoms such as hallucinations, delusions, difficulty thinking and feeling controlled; or negative symptoms including loss of interest, energy and emotions. It affects men and women equally, and it is estimated that over a lifetime, approximately 1% of the general population will develop schizophrenia. Symptoms can occur at any age, most often between the ages of 15 to 35.

Bipolar disorder is a mental illness which often has a long course and is characterised by episodes of significantly altered mood, which may include episodes of depressed mood, episodes of elated mood (mania or hypomania), or mixed (manic or depressive) episodes. Bipolar I disorder includes at least one manic and mixed episode, and bipolar II disorder includes at least one major depressive episode and at least one hypomanic episode. It affects men and women equally and usually starts during or after the teenage years, less commonly after the age of 40. In its more severe forms, it is often associated with significant impairment of personal and social functioning. The prevalence of bipolar disorder is estimated to be 1% of the general population. The most widely used diagnostic criteria for bipolar disorder are from the ICD-10 and DSM-IV-TR.

It is estimated that more than 90% of people with either schizophrenia or bipolar disorder will experience agitation in their lifetime.

### 4.5 Importance of the proposed research

As noted earlier, agitation is a common problem in many patients with psychotic and bipolar disorders. It has an adverse impact on many aspects of the recovery process, including direct patient care, caregiver burden and resources. Managing agitation effectively would greatly improve patient outcomes, alleviate family burden and reduce societal costs. The treatment of patients with agitation is an area that is poorly researched and evidenced and there is currently wide variation in clinical practice. Evidence-based treatment strategies of agitation are important to the individual involved, their carers and to the members of the health team in the NHS dealing with these individuals. The proposed research aims to identify effective short-term pharmacological interventions used for the management of agitation in patients with psychotic or bipolar disorder by systematically reviewing relevant evidence. It is intended that the main outcome of the systematic review will be to signpost...
those interventions that warrant further investigation, investment or implementation and to highlight where there are gaps in the evidence base.

5 METHODS FOR SYNTHESISING CLINICAL EVIDENCE

This research proposal is an evidence synthesis. Data will be extracted from existing papers and will not require contact with NHS patients or staff. The review will be conducted in accordance with the Centre for Reviews and Dissemination (CRD) published guidance on conducting systematic reviews in healthcare.16 The report will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.17

5.1 Search strategy

The major electronic databases including Medline, EMBASE, PsycInfo, SCOPUS, Web of Knowledge, CINAHL and the Cochrane Library, will be searched for relevant published literature. A sample search strategy to be used for MEDLINE is described in Appendix 1. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including the National Research Register and Current Controlled Clinical trials. Bibliographies of previous systematic reviews and retrieved articles will also be examined. A database of published and unpublished literature will be assembled from systematic searches of electronic sources, hand searching and consultation with experts in the field. The database will be held in the EndNote X5 software package.

5.1.1 Study selection

The citations identified by the search strategy will be assessed for inclusion in two stages. Firstly, two reviewers will independently screen all relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Secondly, full text copies of these potentially relevant studies will be obtained and assessed independently by two reviewers using the criteria outlined in Table 1. Any disagreements between reviewers will be resolved by discussion at each stage, and if necessary, a third reviewer will be consulted.
5.1.2 Inclusion criteria

The inclusion criteria specified in Table 1 will be applied to all studies after screening.

Table 1 Inclusion criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with agitation associated with psychotic or bipolar disorder according to ICD10 (F20, F23, F25 and F31) or DSM IV۱</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Pharmacological interventions including oral, inhaled or intramuscular preparations (e.g. benzodiazepines (such as lorazepam) and antipsychotics (such as haloperidol, risperidone, olanzapine and loxapine)</td>
</tr>
<tr>
<td>Comparators</td>
<td>The above compared with each other, placebo or no intervention</td>
</tr>
<tr>
<td>Setting</td>
<td>Specialist mental health services including in-patient and community mental health services</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Any one of the following outcome measures:</td>
</tr>
<tr>
<td></td>
<td>• Agitation level as measured by accepted standard scales (e.g. Visual Analogue Scale for Agitation, Behavioral Activity Rating Scale, Overt Agitation Severity Scale, Agitated Behaviour Scale, Positive and Negative Syndrome Scale Excited Component (PANSS-EC), Cohen Mansfield Inventory)</td>
</tr>
<tr>
<td></td>
<td>• Adverse affects of treatment</td>
</tr>
<tr>
<td></td>
<td>• Health-related quality of life</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomised controlled trial</td>
</tr>
</tbody>
</table>

۱Should studies also have involved people with other diagnoses, such as substance abuse these will be included as long as the proportion of the other groups in the study does not exceed that of the patients with schizophrenia or bipolar disorder.

5.1.3 Exclusion criteria

We will exclude trials that:

- provide only unplanned, interim findings
- provide data on only a subgroup of enrolled patients
- are continuing to recruit participants
- include patients with psychotic presentations primarily due to medical conditions (including dementia) or substance misuse.

5.1.4 Data extraction strategy

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted using a standardised data extraction form. If required and if time permits, attempts will be made to contact authors for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all relevant other publications listed.

5.1.5 Quality assessment strategy

The methodological quality of the included studies will be assessed according to appropriate criteria based on the study design (e.g. CRD guidance for undertaking reviews in healthcare and synthesising
The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted.

5.1.6 Methods of analysis/synthesis
The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. All summary statistics will be extracted for each outcome and where possible, data will be pooled using a standard meta-analysis. Heterogeneity between studies will be assessed using the $I^2$ test. Both fixed and random effects will be presented as forest plots. Where pooling is not possible, narrative tables and summaries will be presented.
6 EXPERTISE AND COMPETING INTERESTS OF TEAM

The team is comprised of individuals with extensive clinical specialist and systematic review methodology experience. The research team will be housed within the Liverpool Reviews and Implementation Group (LRiG), one of nine UK technology assessment review groups providing clinical and cost-effectiveness evidence for the UK HTA programme and NICE.

<table>
<thead>
<tr>
<th>Name</th>
<th>Role and Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Yenal Dundar</td>
<td>Team lead / systematic reviewer/ Psychiatric and information specialist</td>
</tr>
<tr>
<td>Dr. Janette Greenhalgh</td>
<td>Systematic reviewer/project co-ordination</td>
</tr>
<tr>
<td>Dr. Rumona Dickson</td>
<td>Project management</td>
</tr>
<tr>
<td>Professor Richard Whittington</td>
<td>Mental health researcher with expertise on violence</td>
</tr>
<tr>
<td>Professor Christoph Lauber</td>
<td>Consultant Psychiatrist</td>
</tr>
<tr>
<td>Research Associate</td>
<td>TBC</td>
</tr>
</tbody>
</table>

Drs Dundar and Greenhalgh have substantial expertise in systematic reviewing, literature searching and assessing clinical outcomes and are well practised in applying this expertise to health technology evaluations. Dr Dundar is also a practising psychiatrist in an acute care setting. Professor Whittington is a former mental health nurse in acute settings and has conducted extensive research on violence and self-harm in mental health settings. Professor Lauber is a consultant psychiatrist and Chair of Psychiatry at the University of Liverpool. He has extensive research experience with people with psychotic and bipolar disorders and is currently running three NIHR-funded projects. Dr Dickson is the director of the Liverpool Reviews and Implementation Group and has a number of years of experience of project management. A research associate will be recruited to complete the team. The research associate will be jointly supervised by Dr Dundar and Dr Greenhalgh.

In addition, a team of clinical experts will be established to address clinical questions and to provide feedback on drafts of the final report. We have also contacted the Director of Service Users and Carers at Mersey Care NHS Trust in order to obtain service user perspective. The findings from the review will be presented to service users and carers and their comments and opinions will be incorporated into the final report.

No member of the research team has any competing interests to declare. Any competing interests related to the external reviewers will be declared in the final report.
7 PROJECT MILESTONES

The milestones given below are notional and are dependent on an agreed project start date.

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date (estimated)</th>
</tr>
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<tbody>
<tr>
<td>Literature searches</td>
<td>June 2012</td>
</tr>
<tr>
<td>Article screening</td>
<td>June 2012</td>
</tr>
<tr>
<td>Data extraction</td>
<td>July 2012</td>
</tr>
<tr>
<td>Quality assessment</td>
<td>July 2012</td>
</tr>
<tr>
<td>Data analyses</td>
<td>August to September 2012</td>
</tr>
<tr>
<td>Final draft of report for peer review</td>
<td>October 2012</td>
</tr>
<tr>
<td>Submission of final report</td>
<td>November 2012</td>
</tr>
</tbody>
</table>

8 JUSTIFICATION OF SUPPORT REQUIRED

The costs are allocated across the research team. Costs for the time of the principal investigator (YD) will be borne through his current NHS research activity and there are no direct costs allocated in the budget for this time. Salary costs for two researchers are included; the salary of one senior researcher (JG) is budgeted for one day per week for the duration of the project and the full time salary of a junior research assistant is also budgeted, these are included as directly allocated costs. Locally, one expert in mental health (RW) will commit 3 days per month to the review and one consultant psychiatrist (CL) will commit 1 day per month to provide clinical expertise on issues arising from the review. Their time and costs are allocated in the budget. We have included the costs of a project manager (RD) who will commit a total of 6 days to the review. The team will have access to statistical advice through LRiG and we have included the costs of a statistical consultant for 3 days to provide expertise related to the data analysis. Running costs including those related to advisory meetings, consumables, computer fees and publication fees are also included.

We anticipate that there will be great interest in this project and have also budgeted to present the results at appropriate national and international conferences.

For a detailed budget breakdown, please refer to our application form.

9 DISSEMINATION

The review produced as a part of this project will be submitted to the HTA for publication in the monograph series. We will also prepare at least one paper for publication in an appropriate specialist journal. At least two conferences at which to present the findings of the review will be identified. If the review is suitable, it will be submitted to the Cochrane Collaboration to explore the possibilities of publication.
10 REFERENCES

## 11 APPENDICES

Appendix 1 Draft search strategy

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to January Week 1 2012**

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Psychomotor Agitation/</td>
<td>3984</td>
</tr>
<tr>
<td>2</td>
<td>(aggress$ or violen$ or agitat$ or tranq$).ti,ab.</td>
<td>152096</td>
</tr>
<tr>
<td>3</td>
<td>exp Psychotic Disorders/ or exp Schizophrenia/ or exp Bipolar Disorder/ or exp mood disorders/ or exp &quot;schizophrenia and disorders with psychotic features&quot;/</td>
<td>192550</td>
</tr>
<tr>
<td>4</td>
<td>(psychosi$ or psychoti$ or schizopheni$ or bipolar$).ti,ab.</td>
<td>69149</td>
</tr>
<tr>
<td>5</td>
<td>1 or 2</td>
<td>154246</td>
</tr>
<tr>
<td>6</td>
<td>3 or 4</td>
<td>223894</td>
</tr>
<tr>
<td>7</td>
<td>5 and 6</td>
<td>7151</td>
</tr>
<tr>
<td>8</td>
<td>*Benzodiazepines/ or *Drug Therapy/ or *Emergency Treatment/ or exp Antipsychotic Agents/</td>
<td>1303479</td>
</tr>
<tr>
<td>9</td>
<td>(benzodiazepine$ or alprazolam$ or bromazepam*$ or brotizolam$ or chlordiazepoxid$ or clobazam$ or clotiazepam$ or diazepam$ or dikaliumlorazepat$ or flunitrazepam$ or flurazepam$ or loprazolam$ or lorazepam$ or lormetazepam$ or medazepam$ or metaelzepam$ or midazolam$ or nitrazepam$ or nordazepam$ or oxazepam$ or prazeepam$ or temazepam$ or triazolam$).tw.</td>
<td>51443</td>
</tr>
<tr>
<td>10</td>
<td>(neurolept$ or antipsychotic$ or Amisulpride$ or Chormethiazole$ or Clomethiazole$ or Distraneurin$ or Chlorpromazin$ or Aminazine$ or Chlorazine$ or Chlordelazine$ or Contomin$ or Fenacti$ or Largactil$ or Propaphenin$ or Thorazine$ or Flupenthixol decanoate$ or Emergi$ or Fluanxol$ or Flupentixol$ or alphaFlupenthixol$ or cisFlupenthixol$ or Fluphenazine decanoate$ or Flufenazin$ or Fluphenazine Hydrochloride$ or Lyogen$ or Prolixin$ or Haloperidol$ or Haldol$ or Levomepromazin$ or Methotrimeprazin$ or Levopromazine$ or Tisercin$ or Tizercine$ or Tizertins$ or Asendin$ or Desmethylloxapine$ or Amoxapine$ or Olanzapine$ or Perphenazine$ or Chlorpiprazine$ or Perfenazine$ or Trilafonor$ or Pimozide$ or Prothipendyl$ or Quetiapine$ or Fumarate$ or Risperidone$ or Risperidal$ or Sulpiride$ or Dogmati$ or Eglonyl$ or Sulperide$ or Thoridazine$ or Melleri$ or Mellaril$ or Melleryl$ or Sonapax$ or</td>
<td>75408</td>
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</tbody>
</table>
Thioridazine Hydrochloride$ or Tiaprid$ or Tiapridal$ or Trifluoperazine Hydrochloride$ or Trifluoroperazine$ or Triftazin$ or Stelazine$ or Trifluperazine$ or Tripfluoperazine Hydrochloride$ or Cisordinol$ or Zuclopenthixol$ or Clopenthixol$ or Clozapine$ or Melperone hydrochloride$ or Ziprasidone$ or Zotemine$).tw.

11 or/8-10 1368232
12 7 and 11 2307
13 (randomized controlled trial or controlled trial).pt. 317284
14 exp Randomized Controlled Trials as Topic/ or exp Randomized Controlled Trial/ 388357
15 (placebo or trial).ti,ab. 377001
16 exp Prospective Studies/ 306306
17 random$.ti,ab. 572458
18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. 112992
19 or/13-18 1099617
20 12 and 19 640
21 limit 20 to (english language and humans) 590