NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT (NZHTA)
THE CLEARING HOUSE FOR HEALTH OUTCOMES AND
HEALTH TECHNOLOGY ASSESSMENT

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The effectiveness and safety of drug treatment for urgent sedation in psychiatric emergencies.

A critical appraisal of the literature

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NZHTA REPORT
January 2001 Volume 4 Number 1

This report should be referenced as follows:

Broadstock M. The effectiveness and safety of drug treatment for urgent sedation in psychiatric emergencies. *A critical appraisal of the literature*. *NZHTA Report* 2001; **4(1)**

2001 New Zealand Health Technology Assessment Clearing House (NZHTA)
ISBN 1-877235-15-6
ISSN 1174-5142

ACKNOWLEDGEMENTS

This systematic review was conducted by staff of NZHTA.

The review was undertaken by Ms Marita Broadstock (Research Fellow), who conducted the critical appraisals, prepared the report and coordinated the project.

Other contributors include Mrs Susan Bidwell (Information Specialist) who developed and undertook the search strategy, coordinated retrieval of documents and managed the Endnote bibliographic library. Dr Ray Kirk (Director) provided peer review of a report draft. Ms Cecilia Tolan (Administrator) provided administrative support and document formatting. Clerical assistance was provided by other NZHTA staff including Miss Becky Mogridge, Ms Tracy Smitheram and Mrs Joan Downey. Sub-editing was performed by Mrs Carolyn Davies.

We are grateful for editorial review to Dr David Menkes, psychiatrist, Department of Psychological Medicine, University of Otago, Dunedin, who acted as expert consultant throughout the review and provided peer review of a late draft of the report.

Thanks also go to Mr Andrew Booth, Director of Information Services at the School of Health & Related Research at the University of Sheffield, for his expert peer review of the preliminary search strategy.

This report was commissioned by Deputy Director of Mental Health, Dr Anthony Duncan, of New Zealand's Ministry of Health. We thank Dr Duncan for providing background material for the review, including government reports, and assisting in developing the scope of the review.

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This review was commissioned by Dr Anthony Duncan, on behalf of the New Zealand Ministry of Health. NZHTA is a Research Unit of the University of Otago and funded under contract by the New Zealand Ministry of Health.

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EXECUTIVE SUMMARY

Objective

To systematically identify and appraise international evidence for the effectiveness and safety of drug treatment for urgent sedation of individuals in psychiatric emergencies. By urgent sedation, we mean the use of drug treatments to achieve rapid, short-term behavioural control of extreme agitation, aggression and potentially violent behaviour that places the patient or those around them at risk of physical harm.

This objective is aimed to inform the choice of medication for urgent sedation in psychiatric emergencies in the context of the New Zealand Ministry of Health's Guidelines for Medical Practitioners who are using Sections 110 and 110A of the Mental Health (Compulsory Assessment and Treatment) Act 1992 (2000).

Data sources

The literature was searched using the following bibliographic databases: Medline, Embase, Healthstar, Current Contents, Science Citation Index, Social Science Citation Index, International Pharmaceutical abstracts, PsychInfo, and Cinahl. Other electronic and library catalogue sources searched included: Cochrane Library, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation database, Health Technology Assessment database, Best Evidence, US National Library of Medicine, and the British Library. Several Internet websites were also searched to access Health Departments internationally, professional associations of psychiatry and emergency medicine, and mental health organisations. In New Zealand, databases were accessed from the National Bibliographic Database, Ministry of Health website and library, university and medical library catalogues and the NZHTA in-house collection. Relevant publications referenced in material obtained in the course of research on the topic were also identified. Relevant papers that had cited included papers published from 1990 onwards were also identified using Science Citation Index.

Searches were limited to English language material from 1980 to 31 October, 2000 inclusive.

Study selection

Studies were included if they reported on urgent sedation – the use of drug treatments to achieve rapid-onset, short-term management of behavioural dyscontrol in individuals in psychiatric emergencies. Pharmacological classes eligible for inclusion were benzodiazepines or other hypnosedatives, antipsychotics and valproic acid derivatives (valproate, divalproex) or a combination of these administered intramuscularly or orally. Behavioural dyscontrol included extreme agitation, aggression, and/or behaviour that places individuals at risk of physical harm to themselves or others. Inclusion of quantitative outcomes or standardised scales relating to effectiveness and/or safety was required. Only full reports of randomised controlled trials involving samples of at least 20 participants were eligible for review. Systematic reviews and meta-analyses were also eligible for appraisal, principally as background information.

Excluded studies included abstracts and correspondence; those reporting primarily on participants with dementia, mental retardation, brain injury, epilepsy, or physical illness; those concerning sedation for surgical/invasive procedures, "rapid neurolpetisation", treatment of alcohol withdrawal, sleep disorders, panic disorders, migraine, or depression; or those evaluating drugs including general anaesthetics, opioids, anti-cholinergic agents, and zuclopenthixol acetate. Trials reporting on the use of drugs administered beyond three days, or where effectiveness outcomes were not reported within 24 hours of first dosing, were also excluded.

Of more than 800 articles identified by the search strategy, 39 articles were retrieved as full text from which a final group of 12 primary data papers and two systematic reviews were identified as eligible for inclusion in the review.

Data extraction and synthesis

A systematic method of literature searching, selection and appraisal was employed in the preparation of this report. Effectiveness could be measured by degree of reduction over time in behavioural dyscontrol, or the rapidity of onset, or duration, of a specified therapeutic end-point. Safety outcomes included adverse events and specifically extrapyramidal side effects (EPS).

Key results and conclusions

The following conclusions are based on the current evidence available from this report's critical appraisal of literature published on the effectiveness and safety of drug treatments for urgent sedation of individuals in psychiatric emergencies.

- There are few well-conducted, comparative trials in this field, and only a small range of drugs and settings are represented in the studies appraised in this review. This limits the ability to make specific conclusions to cover the many situations in which urgent sedation may be warranted.
- From the appraisal of 12 research papers reporting on randomised controlled trials in psychiatric and emergency room settings, pharmacological approaches to urgent sedation appear to be both effective and reasonably safe.
- There were no studies eligible for appraisal set in the wider community, and no studies were appraised which considered valproic acid derivatives or atypical antipsychotics.
- There is currently limited availability of drugs for urgent sedation in New Zealand, particularly those available intra-muscularly.
- Comparisons between particular drug regimens suggest no conclusive benefit in terms of *effectiveness* of one antipsychotic over another, antipsychotics over benzodiazepines, or combination drugs (of antipsychotics, benzodiazepines and hypnosedatives) over single drug regimens.
- Side effects were extremely rare in the hours shortly following initial drug administration and urgent sedation appears to be reasonably safe. Given small sample sizes and the shortness of follow-up there was limited scope for conclusive research into the longer-term safety of the drugs considered for urgent sedation in real-world settings.
- These conclusions are broadly consistent with a systematic review of the management of imminent violence by adult users of mental health services conducted by Wing and colleagues (1998), based on research published between 1980 and 1997.
- High quality, randomised controlled trials are required investigating the utility of available drugs for urgent sedation (including atypical antipsychotics), employing larger samples, situated in community settings, and systematically manipulating dosage and frequency of drug administration.

MeSH headings

emergency services, psychiatric; antipsychotic agents; benzodiazepines; randomised controlled trials, valproic acid.

Additional key words

urgent sedation; rapid sedation; rapid tranquillisation; chemical restraint; pharmacological restraint; psychiatric emergencies; acute agitation; acute psychosis.

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Chapter 1: Background

1.1 URGENT SEDATION

Urgent sedation in a psychiatric emergency is a procedure for administering a drug treatment to rapidly control extremely agitated, aggressive, disruptive behaviour of an individual at risk of causing physical harm to themselves or others. The sedative effect of medication in this context is aimed to primarily attenuate specific symptoms of behavioural dyscontrol rather than as a treatment for any underlying cause or psychiatric condition. Sedative medication may be given in short intervals of time (e.g. every 30-60 minutes) with a response anticipated within 1-4 hours (Dubin, 1988; Dubin et al., 1985), and often less in the case of intramuscular administration. Urgent sedation should only be used under medical supervision and when other, non-pharmacological methods such as talking-down, distraction, seclusion and the use of sanctions have failed (Atakan and Davies, 1997).

Various synonyms for urgent sedation exist in the research literature. The most common term in current use is "rapid tranquillisation". "Rapid sedation" and "emergency sedation" are also used. A controversial term is "chemical restraint"[1] which implies drug treatment for reasons of restraint, which may be inappropriate clinically as well as for medico-legal reasons (Hillard, 1998).

It is important to distinguish between urgent sedation and procedures favoured 10-20 years ago, which aim at rapidly treating psychoses. These include "rapid neuroleptisation" and "psychotolysis", analagous to "rapid digitalisation" which consists of giving high loading doses of antipsychotic medication to accelerate the remission of psychotic symptoms (Hillard, 1998). These procedures have been discredited in the emergency setting where high or frequently repeated doses appear to exacerbate an emergency situation through side effects including dysphoria, akathisia or acute dystonia (Great Britain Royal College of Psychiatrists, 1997). These approaches have thus been excluded from this review.

1.2 URGENT SEDATION IN NEW ZEALAND

This systematic literature review was commissioned by New Zealand's Ministry of Health to inform aspects of Guidelines for Medical Practitioners who are using Sections 110 and 110A of the Mental Health (Compulsory Assessment and Treatment) Act 1992 (2000).

Under these sections of the Act, medical practitioners may conclude, after a medical examination, that a person may be mentally disordered[2] and requires an assessment examination by a nominated medical practitioner (usually a psychiatrist). This assessment process can be difficult when the person undergoing the assessment is so disturbed that their behaviour places them or others at risk of serious physical harm. Therefore the Act provides medical practitioners with the power, in circumstances of urgency or risk, to urgently sedate a person they believe may be mentally disordered before formal assessment takes place.

It is recognised that urgent sedation may cloud a person's mental state and make subsequent assessment difficult, as well as carrying a level of risk for the patient. Therefore urgent sedation is a power that is likely to be used only rarely, and only once other de-escalation techniques have been attempted but have failed to control the behaviour. Under the Act, a duly approved officer (DAO) assists the medical practitioner in suggesting possible management alternatives to emergency use of sedation.

[1] For further discussion see correspondence by Fichtner, (2000).

[2] By mental disorder we mean an abnormal state of mind (whether of a continuous or intermittent nature), characterised by delusions, or by disorders of mood or perception or volition or cognition, of such a degree that it poses a serious danger to the health or safety of that person or of others; or seriously diminishes the capacity of that person to take care of himself or herself (Ministry of Health , 2000).

There are two situations where urgent sedation may be applicable in New Zealand:

- In rural areas, where a very disturbed person is seen by a general practitioner (GP), sometimes with police involvement, and requires sedation to permit safe transport for subsequent psychiatric assessment.
- More rarely, in urban areas, where the person is so disturbed that they are likely to cause serious harm to themselves or others before the assessment takes place, or during the assessment.

1.3 CHOICE OF DRUGS FOR URGENT SEDATION

Drug characteristics for urgent sedation

Given the context outlined above, ideally medications for urgent sedation should be rapid in action and elimination to provide quick control of potentially dangerous behaviour whilst also permitting psychiatric assessment within a period of hours. Therefore a level of sedation sought is generally one that is sufficient to minimise the risk of physical harm to the patient or those around them whilst also allowing comprehension and response to spoken messages throughout sedation (Wing et al., 1998). Over-sedation, ranging from obtundation to frank loss of consciousness, is therefore to be avoided in this setting.

Antipsychotics

Antipsychotic medications (previously called neuroleptics) have been the traditional agents for urgent sedation in psychiatry. Classified antipsychotics may be usefully subdivided into high-potency and low-potency agents. Older, low-potency antipsychotics (e.g. chlorpromazine and thioridazine) are effective in urgent sedation but require considerably higher doses as compared with high-potency agents. Low-potency antipsychotics also have relatively greater risks of over-sedation, and anti-cholinergic and cardiovascular effects, such as orthostatic hypotension. Despite these problems, 34% of a sample of British psychiatrists chose chlorpromazine as their first line drug for urgent sedation (Simpson and Anderson, 1996).

More recently, higher potency neuroleptics have been used (Dubin, 1988), such as haloperidol, droperidol, thiothixene and fluphenazine. In the United States (USA), haloperidol is used most frequently in the emergency department for urgent sedation (Blanchard and Curtis, 1999). Antipsychotics have been the preferred method for urgent sedation for patients with verified schizophrenia (Dubin, 1988).

High potency drugs have a greater effect at lower doses than low-potency medications but tend to have more extrapyramidal side effects (EPS) (Blanchard and Curtis, 1999). Extrapyramidal side effects are primarily acute and chronic neurological adverse events involving voluntary and involuntary musculature, the most common of which include parkinsonism (bradykinesia, rigidity, tremor), dystonias, and akathisia (Hughes, 1999). Young males may be at increased susceptibility to EPS, especially dystonias possibly due to an increased muscle mass (Kamin et al., 2000). EPS rarely manifest themselves as serious conditions such as laryngeal dystonias, which may cause difficulty in breathing, and oculogyric crises, which may result in a fixed gaze. Treatment of EPS includes dose reduction or discontinuation of the antipsychotic drug or offering drug treatments, commonly anti-cholinergic (e.g. benztropine) and antihistaminergic medications (often administered prophylactically if patients are not hospitalised). Whilst diagnosis and treatment of EPS is relatively straightforward for dystonias, it can be more difficult for parkinsonism and akathisia. Akathisia can masquerade as agitation and be mistaken for symptoms related to the primary psychosis, making it under-diagnosed and difficult to treat (Kamin et al., 2000). There is also a risk of neuroleptic malignant syndrome from higher doses of high-potency antipsychotics (Foster et al., 1997). This is an acute life-threatening condition characterised by severe muscular rigidity, fever, an altered level of consciousness, and an autonomic instability. Whilst it has significant mortality, detection and treatment have greatly improved outcomes (Kamin et al., 2000).

Atypical antipsychotics (e.g. clozapine, risperidone, olanzapine) may have specific anti-aggressive effects independent of sedation and antipsychotic action, with reduced EPS (Miller et al., 1998).

Whilst clozapine has the lowest risk of EPS, it is associated with other risks and requires slow titration and baseline white blood cell counts. Atypical antipsychotics are currently only available for oral administration, and have yet to be fully evaluated for urgent sedation (Dr David Menkes, *personal communication*, January 2001). They have generally been recommended in the intermediate to long-term management of chronic violence/aggression in psychosis (Buckley, 1999; Hughes, 1999), although conclusive demonstration of anti-aggressive effects has been hindered by methodological problems of the research base (Volavka and Citrome, 1999). Further development of atypical antipsychotics are likely to find a place in urgent sedation in the future (Hillard, 1998; Kamin et al., 2000).

Benzodiazepines

Given the risks associated with antipsychotics, benzodiazepines were introduced as a potential alternative or adjunctive treatment without the risk of extrapyramidal side effects. Diazepam (which is rarely used intramuscularly due to slow and erratic absorption) has been used though repeated doses can lead to prolonged sedation. However, drugs with shorter half-lives have avoided this risk; lorazepam, for example, has a half-life of 10-20 hours (Citrome and Volavka, 1999) and can be reliably and rapidly absorbed without the risk of over-sedation and without the toxicity of antipsychotics (Salzman, 1988). Moreover, when administered as therapeutic doses for brief periods there is no risk of tolerance, dependence or withdrawal (Citrome and Volavka, 1999). However, it is important to monitor vital signs closely because of risk of respiratory depression when given in very high doses or in addition to other hypnosedatives (including recent consumption of alcohol or illicit drugs), and the rare possibility of disinhibition or "paradoxical" hostility (Hillard, 1998). Respiratory depression can be readily reversed with the pharmacological antagonist, flumazenil (Kerr and Taylor, 1997).

Dubin (1988), in his literature review, has concluded that benzodiazepines are effective for patients with affective disorders such as mania. Benzodiazepines are also said to be useful when there is a suspicion of drug or alcohol withdrawal, as antipsychotics may decrease the seizure threshold in this situation and be sub-optimal for urgent sedation (Citrome and Volavka, 1999).

Combination regimens

The administration of two or more medications at about the same time has been described as the "cocktail" approach (Hughes, 1999)[3]. Combination regimens of antipsychotics and benzodiazepines have gained favour for behaviour control, and can permit lower doses being used than in single drug regimens. Salzman (1988) suggests that the intramuscular administration of low doses of a non-sedating antipsychotic like haloperidol avoids hypotension and EPS whilst short-acting benzodiazepines such as lorazepam avoids extreme and prolonged sedation. Benzodiazepines also have an anti-convulsant effect, which may offset the lowering of seizure threshold engendered by antipsychotics (Kerr and Taylor, 1997). The most common medication strategy in psychiatric emergency settings in the USA is reportedly the use of haloperidol and lorazepam in combination (Currier and Allen, 2000).

For patients amenable to oral drug administration, an oral dose of atypical antipsychotic risperidone combined with haloperidol has been recommended by Hillard (1998) for patients with a past history of psychosis, the elderly, brain damaged, or intoxicated with hypnosedatives, or for those with an adverse reaction to benzodiazepines.

Other drugs

Anti-convulsants are sometimes used in the treatment of acute mania although generally they take several days to develop a therapeutic response, making them generally inappropriate for urgent sedation. Valproate may have an effect in a shorter time period following rapid oral loading though does not tend to have an immediate effect (Kerr and Taylor, 1997).

[3] A relatively newer medication technique is the "chaser" approach where once the patient is sedated through use of a benzodiazepine, the patient is encouraged to choose an antipsychotic medication. This is aimed to optimise a patient's acceptance and long-term, compliance with the medication they select (Hughes, 1999).

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Route of transmission

The intramuscular (IM) route of transmission has usually been preferred for urgent sedation because of rapid absorption of the drug and greater bioavailability (Dubin, 1988). It can also ensure compliance in an uncooperative patient. Intravenous access can be difficult to obtain in potentially violent patients requiring urgent sedation. Whilst IM medication has been shown to have a more rapid response compared with oral concentrates for urgent sedation, Dubin (1985) has argued that the time difference may not be significant clinically to warrant it as a first intervention. He also found that many acutely psychotic patients cooperate with an oral regimen.

Drugs available in New Zealand

In New Zealand, parenteral high potency antipsychotic drugs such as haloperidol and droperidol have been used from the early 1980's. Given the risk of extrapyramidal side effects, Ministry of Health Guidelines (2000) suggest that first doses of antipsychotics be accompanied by anti-cholinergic cover (benztropine or procyclidine).

In view of the side effect profile of antipsychotics, parenteral benzodiazepines such as clonazepam have become increasingly favoured in New Zealand, mirroring overseas trends, either as sole agents or in combination with antipsychotic drugs. There are currently no benzodiazepines officially approved for use for urgent sedation in New Zealand. However, according to the Guidelines, the Ministry of Health considers that there is sufficient evidence for medical practitioners to prescribe and administer benzodiazepines to a particular patient under their care for urgent sedation under Section 25 of the Medicines Act 1981.

The benzodiazepine most commonly used for this purpose in New Zealand has been clonazepam, which according to the Guidelines has a rapid onset of predictable sedation when given intramuscularly[4]. Clonazepam carries a small risk of causing respiratory depression. For this reason, medical practitioners using clonazepam for urgent sedation are advised to carry flumazenil, a reversal drug, to treat respiratory depression intravenously if required.

The Ministry of Health Guidelines (2000) suggest that medical practitioners use only minimum effective doses of medication for sedation, with small doses repeated if an adequate effect is not obtained. Whilst drugs for urgent sedation often need to be given intramuscularly (IM) it is recommended that the person always be given the option of taking the medication orally (PO).

Three suggested pharmacological approaches in the Guidelines are:

Antipsychotic only

- Haloperidol, a high-potency antipsychotic, administered 5 – 10 mg PO or 2.5 – 5 mg IM every 30 minutes to a maximum of 30 mg orally or 20 mg IM.

Benzodiazepine only

- Diazepam, administered 5 – 10 mg PO or clonazepam, administered 2 mg IM, repeated at 30 minute intervals until control is achieved.

Antipsychotic – benzodiazepine combination

- Haloperidol, administered 2.5 – 5 mg PO or IM AND clonazepam, administered 2 mg PO or IM, every 30 minutes to a maximum of three doses.

General principles for sedation in the current Guidelines include:

- Should consider use of the antipsychotic haloperidol if the person has a clear history of schizophrenia and/or past good response to antipsychotics.
- Should consider use of a benzodiazepine if the patient has a history of mania and appears manic.

[4] Notably, clonazepam (Rivotril) is only recorded in the New Ethicals Catalogue (November, 2000) as available orally or intravenously in New Zealand.

- Should consider use of a benzodiazepine if there is a suspicion of drug or alcohol withdrawal (antipsychotics can lower the seizure threshold).
- Should consider use of a combination benzodiazepine-antipsychotic for rapid and effective sedation in most cases.

Medical considerations

Arguably the greatest risk in urgent sedation is missing a life-threatening cause of behavioural dyscontrol. Drug treatments for urgent sedation are usually employed after a patient has received a medical examination and no contraindications for the use of medication have been found (Hughes, 1999). Consistent with this approach, the New Zealand Ministry of Health Guidelines (2000) state that the medical practitioner should determine whether the person has any medically treatable causes of agitation such as hypoglycaemia, hypoxia, drug and alcohol intoxication and withdrawal, pain or delirium. Such causes of agitation should be managed as conditions in their own right.

On many occasions in psychiatric emergencies, a complete history of psychiatric and medical conditions, abuse of alcohol and illicit drugs, and use of prescribed drugs is not always available or volunteered. Therefore continuous monitoring and observation of the patient is essential (Arya, 1999). The Guidelines advise that during urgent sedation, the person's blood pressure, pulse, respiration and temperature should be monitored at 15 minute intervals until the assessment examination takes place (2000).

1.4 OBJECTIVE

To systematically identify and appraise international evidence for the effectiveness and safety of drug treatments for urgent sedation of individuals in psychiatric emergencies.

1.5 REVIEW SCOPE

Studies were included for review if they reported randomised controlled trials comparing the use of benzodiazepines or other hypnosedatives, antipsychotics and valproic acid derivatives (valproate, divalproex) or a combination of these administered intramuscularly or orally for urgent sedation. By urgent sedation, we mean the use of drug treatments to achieve rapid, short-term behavioural control of extreme agitation, aggression and potentially violent behaviour that places the patient or those around him/her at risk of physical harm.

The search was limited to full reports published in English and published between 1980 and October 2000. Full details of inclusion and exclusion criteria are provided in the next chapter.

1.6 STRUCTURE OF REPORT

This report includes four chapters, divided into sections. Chapter 2 presents the review methodology including search strategy, inclusion and exclusion criteria, and outcomes considered. Chapter 3 presents the results of the review including primary and secondary research considered. This chapter also provides detailed evidence tables, which present each appraised study's methods, results, limitations, and authors' conclusions. The final chapter summarises results, briefly discusses methodological limitations in the area, and presents key conclusions. A glossary and list of abbreviations used in the report are provided prior to the Appendices.

Chapter 2: Methodology

2.1 STUDY SELECTION

Study inclusion criteria

Publication type

Studies published between 1980 and October 31, 2000 inclusive in the English language, including primary research (published as full original reports) and secondary research (systematic reviews and meta-analyses).

Context

Studies reporting on urgent sedation; that is the use of drug treatments to achieve *rapid-onset*, *short-term* management of *behavioural dyscontrol* in individuals in psychiatric emergencies. To operationalise these terms, the following requirements were applied:

Rapid onset – measurement of outcome within a period of 24 hours of the initial dose of the drug/s being evaluated.

Short-term – administration of the drug/s being evaluated (by one administration route) for no longer than 72 hours after the initial dose.

Behavioural dyscontrol – exhibiting:

- extreme agitation
- aggressive, destructive, disruptive, assaultive, violent or hostile behaviour, and/or
- behaviour which places the individual receiving the medication or those around them at risk of physical harm.

Drug treatments

Studies reporting statistically tested comparisons between the use of benzodiazepines or other hypnosedatives, antipsychotics and valproic acid derivatives (valproate, divalproex) or a combination of these.

Route of transmission

Studies investigating drugs administered intramuscularly or orally.

Outcomes

Studies using quantitative outcomes or standardised scales relating to effectiveness and/or safety (see Section 2.5 below).

Study design

Randomised controlled trials[5] (RCT) where participants are randomly allocated into groups to receive or not receive an experimental intervention, and the groups are compared prospectively. The control arm may be a comparison drug treatment (if eligible) or the same drug using a different dosage.

[5] An initial search of literature published from 1995 onwards which was not restricted to randomised controlled trials revealed five eligible studies, all of which were RCTs. Searching prior to 1995 was therefore undertaken to identify any additional papers of comparable design quality.

Sample size

Studies with samples of at least 20 participants.

Study exclusion criteria

Research papers were excluded if they:

- were not published in English
- were "correspondence", book chapters, conference proceedings, abstracts
- reported studies with samples of fewer than 20 participants
- reported animal studies
- did not clearly describe their methods and results, or had significant discrepancies;

concerned primarily participants:

- with dementia, or people who were likely to be suffering from dementia (trials primarily focusing on the elderly, those aged over 70 years, were excluded)
- with cognitive impairment caused by illness other than psychotic disorders (including those with mental retardation, brain injury)
- with epilepsy
- who were critically, physically ill[6] (Wagner and O'Hara, 1997), including patients in non-psychiatric Intensive Care Units (ICU's)
- who were healthy volunteers not presenting with symptoms of behavioural dyscontrol
- who were not randomly allocated into treatment condition;

concerned:

- pharmacological relaxation to facilitate rapid sequence intubation
- sedation for surgical procedures
- rapid neuroleptisation or psychotolysis
- treatment of alcohol withdrawal, sleep disorders, panic disorders, migraine, depression
- general anaesthetics including ketamine, propofoletomidate, barbiturates
- opioids such as morphine
- reversal agents such as flumazenil
- anti-cholinergic agents (such as benztropine, procyclidine)
- anti-convulsants (excluding valproic acid derivatives)
- zuclopenthixol acetate (a longer acting drug effective for up to 72 hours with a delayed onset of antipsychotic effect).
- drug/s being evaluated which were administered beyond 72 hours (where administered for up to three days, outcomes were only considered in this review where measured within 24 hours of the initial treatment dose).

2.2 SEARCH STRATEGY

A systematic method of literature searching and selection was employed in the preparation of this review.

[6] Drugs that in other settings may be considered short-acting often have significantly altered onset and duration in critically ill patients (Wagner & O'Hara, 1997).

Searches were limited to English language material published from 1980 onwards. The searches were completed on 31 October, 2000.

The preliminary search strategy was peer reviewed by Andrew Booth, Director of Information Services at the School of Health & Related Research at the University of Sheffield and his suggestions were incorporated in the subsequent searches.

Principal sources of information

The following databases were searched (using the search strategy outlined in **Appendix 1**):

Bibliographic databases

- Medline
- Embase
- Current Contents
- Healthstar
- Science Citation Index
- Social Science Citation Index
- International Pharmaceutical abstracts
- PsychInfo
- Cinahl

Review databases

- Cochrane Library
- Database of Abstracts of Reviews of Effectiveness
- NHS Economic Evaluation database
- Health Technology Assessment database
- Best Evidence

Library Catalogues

- US National Library of Medicine
- New Zealand National Bibliographic Database
- British Library

Websites

- Websites of New Zealand, Canadian, British, Australian and United States government and provincial health departments, professional associations and colleges of psychiatry and emergency medicine, and mental health organisations were scanned for relevant publications, guidelines, or consensus statements.

Other

- Hand search of NZHTA print collection.
- Internet search using Copernic 2000 meta-search engine.
- Scan of reference sections of retrieved papers for relevant publications.
- Search of Science Citation Index to identify any relevant papers that had cited included papers published from 1990 onwards.

Hand searching of journals, contacting of drug manufacturers, or contacting of authors for unpublished research was not undertaken in this review. A complete list of the sources searched for this review is given in **Appendix 2.**

Search terms used

- Index terms from Medline/Healthstar (MeSH terms): central nervous system depressants, antipsychotic agents, anti-anxiety agents, lorazepam, droperidol, haloperidol, diazepam, benzodiazepines, benzodiazepinones, flunitrazepam, loxapine, emergency services-psychiatric.
- Index terms from Embase: emergency medicine, emergency health service, emergency treatment, exp neuroleptic agent, loxapine, diazepam, haloperidol, droperidol, lorazepam, clonazepam, midazolam, benzodiazepines.
- Additional index terms used for International Pharmaceutical Abstracts: tranquilisers.
- Additional index terms used for PsychInfo: exp neuroleptic drugs, emergency services, crisis intervention services.
- The above index terms were used as keywords in databases where they were not available and in those databases without controlled vocabulary.
- Additional keywords (not standard index terms) were used in all databases: (Rapid* short or emergenc* or fast) near (tranquil* or sedat*); (rapid or quick or fast or short) near (onset or acting); chemical* near restrain*; pharmacologic* near restrain*; acute near (mania or psycho* or agitat* or distress* or aggress*).

The search was done in two major sections reflecting stages in the development of the review scope. The initial batch of searches looked at literature published from 1995 onwards using a broad search without exclusions or filters for study design. Refinement of selection criteria led to a second series of searches of the literature from 1980-1994. These searches were limited to those studies that were randomised controlled trials or controlled clinical trials. A number of exclusions were also used in this section using the following keywords if present in the title of the article:

Dementia, brain injur*, epilepsy, seizure, elderly, aged, mental retard*, anaesthetic, anesthetic, alcohol withdrawal, intubation, ventilation, status epilepticus

2.3 SELECTION AND APPRAISAL

Approximately 800 articles were identified in the search. From reading abstracts, the reviewer (MB) identified 39 research studies as potentially eligible for inclusion and which were retrieved as full text. The inclusion and exclusion criteria were applied to select the final group of 12 primary studies and two systematic reviews for critical appraisal and inclusion in the evidence tables. Included studies and other cited publications (e.g. those providing background material) are presented in the References. Excluded retrieved studies (n=25) are presented in **Appendix 2**.

2.4 APPRAISAL OF STUDIES

Systematic reviews and meta-analyses were described and critiqued in terms of their search strategy, inclusion/exclusion criteria, data synthesis and interpretation. Note that such papers were considered principally as background information.

Evidence tables for primary research studies of clinical effectiveness employed column headings described below.

- **Source of the study** including authors, year published, and country of origin.
- **Study design** including study "blinding"; that is, whether the "clinician" (or other health professional) administering the drug and measuring the intervention, and the "patient" (the study participant receiving the intervention) were unaware of (blinded to) the study group to which they were allocated.

- **Study setting** such as psychiatric in-patient ward, or psychiatric emergency room.
- **Sample** including number of participants, description of their eligibility in terms of behavioural dyscontrol, sample characteristics including demographic and clinical variables, any comparisons between intervention groups on these variables at baseline, and exclusion criteria.
- **Interventions (transmission route) and dose** including the drugs being compared, their transmission route (intramuscular, or oral), dose, and whether and how frequently drugs were re-administered.
- **Outcomes** relevant to drug effectiveness and safety (see section 2.5 below), as well as the timing of when outcomes were measured relative to the initial administration of the drug.
- **Results** relevant to drug effectiveness and safety, including statistically tested comparisons, and any information on adverse events and specifically extrapyramidal side effects.
- **Comments** including key study limitations and authors' conclusions.

2.5 KEY OUTCOME MEASURES FOR PRIMARY STUDIES

Key quantitative outcomes relating to effectiveness and/or safety of the drug treatments considered are listed below.

Effectiveness

Effectiveness could be measured by degree of reduction over time in behavioural dyscontrol, or the rapidity of onset of, or duration of, a specified therapeutic end-point.

Safety

Safety could be measured by the incidence or severity of *adverse events* such as hypotension, seizures, blurred vision, dry mouth, neuroleptic malignant syndrome, and extreme or over-sedation (sometimes regarded as a therapeutic end-point), and specifically by *extrapyramidal side effects* (EPS) such as acute dystonia, akathisia and parkinsonism.

2.6 LIMITATIONS OF THE REVIEW

This study has used a structured approach to review the literature. However, there were some inherent limitations with this approach.

This review has been limited by the restriction to English language studies and references presented in the database, cited by these papers, or suggested by individuals consulted during preparation of this review. In addition, the review has been limited to the published academic literature and has not appraised unpublished work.

Papers published pre-1980 were not considered as these tended to concern outdated drugs and practices. This cut-off was also employed by another major systematic review of managing imminent violence in users of mental health services (Wing et al., 1998).

The studies included in this review were all conducted outside New Zealand and therefore their generalisability to the New Zealand population and context may be limited.

The review scope was developed with the assistance of Ministry of Health staff. It had the goal of providing information that was relevant to urgent sedation within the context of New Zealand's Guidelines for Medical Practitioners using Sections 110 and 110A of the Mental Health (Compulsory Assessment and Treatment) Act 1992.

This review has greatly benefited from the advice provided by the consultant peer reviewer. However, it has not been exposed to wider peer review.

For a detailed description of interventions and evaluation methods and results used in the studies appraised, the reader is referred to the original papers cited.

Chapter 3: Results

3.1 SECONDARY RESEARCH

The search strategy identified two relevant reviews. The methods and conclusions are described in **Table 1 (p.14)**.

The review of the efficacy and side effects of the antipsychotic droperidol in urgent sedation by Chambers and Druss (1999) did not appear to be systematic in its identification, appraisal or synthesis of material and employed a limited search strategy (Medline only, using search term of droperidol). However, it provides a useful summary of the history of use of droperidol as well as referencing recent trials, including two RCT's appraised in the present review (Resnick and Burton, 1984; Thomas et al., 1992). The authors conclude that droperidol, which has not been widely used for acute sedation in the United States, may be superior to other typical high potency antipsychotics such as haloperidol because of a shorter latency of onset and a comparable side effect profile. Interestingly, the authors suggest that droperidol may have been stigmatised for use in psychiatric emergencies by its association with non-psychiatric settings such as medical emergency rooms and with surgical cases, which may have given practitioners the false impression that it was an anaesthetic.

A systematic review produced by the UK's Royal College of Psychiatrists' Research Unit (Wing et al., 1998) considered the management of imminent violence by adult users of mental health services. Pharmacological interventions were considered within a wider review encapsulating restraint and seclusion practices. The comprehensive review was based on research published between 1980 and 1997 and included a wide variety of study designs. Only four randomised controlled trials were identified with only one (Thomas et al., 1992) meeting specified design criteria. Due to the lack of high quality research considered, the authors concluded that it was not possible to draw strong evidence-based conclusions. However, they observed that several papers suggest that if rapid tranquillisation (urgent sedation) is indicated, benzodiazepines or an antipsychotics alone can be used with a reasonable degree of safety for managing violent behaviour. However, they argued that there was no evidence to suggest that a combination of several medications or higher than standard doses recommended in the UK produced better results.

Table 1. Secondary research appraised

Source	Search method	Criteria for inclusion/exclusion	Results	Conclusions
(Chambers and Druss, 1999)	Search: 1966 – 1998. Databases searched: Medline literature from "psychiatry related ", "internal medicine or emergency medicine related", and "anaesthesia and pharmacological" literature published in British and North American Journals. European literature "that seemed particularly relevant or illustrative to some points in the review" were also considered, as were papers identified from references of included papers (A. Chambers, *personal communication*, December 2000). Search term: droperidol	Considered English language literature only. Considered papers relevant to psychiatric indications, side effect profile, pharmaco-kinetic properties, and early pre-clinical and clinical European experience with droperidol. Included animal studies.	28 studies identified relevant to droperidol. Summarised the use of droperidol in urgent sedation in the psychiatric and emergency room setting. Included two RCT's appraised in this review (Resnick and Burton, 1984; Thomas et al., 1992).	The authors' concluded: "As the primary treatment in acute psychiatric settings becomes more focussed on control of dangerous behaviour, there is a greater need for an optimal injectable neuroleptic that has a short latency of onset so as to prevent injury to patients and staff. In these clinical situations, droperidol should be considered a candidate as the therapeutic drug of choice, as supported by the studies outlined in this review".
(Wing et al., 1998) Royal College of Psychiatrists' Research Unit (UK)	Search: 1966 – 1997, but excluded papers relating to pharmacological interventions that were published prior to 1980. Databases searched: Cochrane library, Embase, Medline, PsychLIT. Also searched reference lists of identified studies, and contacted experts in the field to identify further references.	Randomised controlled trials, controlled trials, cohort studies, descriptive studies, meta-analyses and reviews which focused on the management of imminent violence by adult users of mental health services. Included pharmacological interventions in this wider review. Considered outcomes of effectiveness and safety. Excluded studies involving elderly people, people with learning disorders, people with problems due to personality disorders or substance abuse, people receiving domicilliary visits and those attending general practice surgeries.	19 studies appraised relevant use of pharmacological interventions including 4 randomised controlled trials, 7 controlled studies, 1 review of controlled studies, 2 cohort and 5 descriptive studies. Only one trial satisfied all design criteria (Thomas et al., 1992). Many provided no evidence for claims of randomisation or for clinicians being blind to treatment allocation.	Not possible to draw strong evidence-based conclusions from these studies due to methodological concerns. Several papers suggest that if rapid tranquillisation (urgent sedation) is indicated, benzodiazepines alone, or an antipsychotic alone, can be used with a reasonable degree of safety for managing violent behaviour. No evidence to suggest that a combination of several medications or higher than standard doses produce better results. Suggest that controlled studies of the use of atypical and short-acting depot psychotics are needed.

3.2 PRIMARY RESEARCH: STUDY DESIGNS AND QUALITY

The search identified 12 eligible primary research studies. Below is an overview of study designs and aspects of quality represented by these studies.

Study design

Meeting requirements for eligibility for this review, all studies were randomised controlled trials published no earlier than 1980 and involving samples of at least 20 participants. One study was a multi-centre trial (Battaglia et al., 1997). Of the 12 studies reviewed, nine reported being double blind; that is, where neither the clinicians/health professionals administering the drug treatments nor the patient receiving the interventions were aware of which drug/s had been administered. Two studies specifically reported that they were double blind *except* for the administration of the drug by the clinician.

Study setting

Six studies were set in psychiatric emergency rooms, including the multi-centre trial involving five psychiatric emergency departments (Battaglia et al., 1997). One study was situated in a general emergency department (ED) (Thomas et al., 1992). Five studies involved psychiatric in-patients, one of which was set in a locked psychiatric intensive care ward.

Samples

Studies tended to include mixed samples of participants with a range of psychiatric disorders. Studies varied widely in terms of psychiatric condition represented, whether acute or chronic, and whether or not participants were already receiving medication for their disorder. The study of ED admissions included mostly intoxicated patients.

Most studies (n=10) involved samples of participants exhibiting extremely agitated behaviour or broadly aggressive, unmanageable behaviour. The degree of behavioural dyscontrol varied greatly across the 12 studies appraised and a wide range of descriptors were employed. Behaviour ranged from restless, uncooperative, disorganised, disruptive, or overactive to hostile, combative, violent, destructive, and assaultive. Some participants were described as requiring physical restraint, or as in imminent danger of causing harm to themselves or others.

How inclusion criteria were defined and measured varied. Some criteria were defined by minimum scores on scales (e.g. visual analogue scales of agitation or hostility, Overt Aggression Scale, Combativeness Scale) or scale items (e.g. hostility and uncooperativeness items of the Brief Psychiatric Rating Scale (BPRS). However, most studies relied on the judgement of staff as to whether patients required urgent sedation.

Two studies described participants only in terms of their being acutely disturbed or agitated. Eligibility for inclusion in these studies was defined by a minimum score on selected items from the Brief Psychiatric Rating Scale (BPRS) which included some or all of the following attributes: anxiety, excitement, conceptual disorganisation, tension, hostility, suspiciousness, hallucinatory behaviour, uncooperativeness, unusual thought content, or mannerisms and posturing. Participants were not required to score highly on all items and therefore it is possible that some were included for exhibiting symptoms of their underlying mental illness unrelated to the necessity for urgent sedation.

Exclusion criteria were described in nine studies. Most studies excluded physical illnesses such as haematologic, cardiovascular, renal, and hepatic impairment. Other exclusions specified less frequently included: drug and alcohol intoxication, pregnancy, mental retardation and neurologic disorders, use of prescribed psychotropic medications shortly prior to the study, known sensitivity to the drugs being used, glaucoma, severe hypo- or hyper- tension, CNS depression, delirium, neuroleptic malignant syndrome, or airway obstruction.

Interventions

Five papers **(Table 2, p.22)**, including four published before 1987, compared antipsychotic drugs alone.

Seven papers **(Table 3, p.27)**, all published since 1989, reported statistical comparisons between an antipsychotic and a benzodiazepine (n=5) and/or comparisons between solo drugs and combinations of antipsychotic and benzodiazepine drugs (n=3). One study also included combination of an antipsychotic and a hypnosedative as an intervention (Garza-Trevino et al., 1989).

Antipsychotics used as solo agents included: haloperidol, droperidol, loxapine, clothiapine and molindine. Benzodiazepines investigated as solo agents included lorazepam and flunitrazepam. Combined medications of an antipsychotic and benzodiazepine included lorazepam and haloperidol, and lorazepam and thiothixene. The study, including administration of a combination of an antipsychotic and a non-benzodiazepine hypnosedative, concerned haloperidol and phenobarbital sodium (Garza-Trevino et al., 1989). Of these, haloperidol, droperidol, loxapine (oral administration), lorazepam (oral), thiothixene (oral) and phenobarbital sodium are currently available in New Zealand.

The drug transmission route was intramuscular (IM) for nearly all interventions considered, with oral concentrate as the alternative in one study (Foster et al., 1997).

Effectiveness outcomes

Outcomes were measured within the following periods post initial dose: 30 minutes - 2 hours (n=3), 3 - 4 hours (n=5), 12 hours (n=1), and 24 hours (n=3).

Outcomes employed included the following: Clinical Global Impression (CGI) scale (n=6 studies), selected items from or the whole Brief Psychiatric Rating Scale (BPRS) (n=6), Overt Aggression Scale (OAS) (n=4), Visual Analogue Scales (VAS) reflecting agitation and/or hostility (n=2), Agitated Behaviour Scale (ABS) (n=1), Combativeness Scale (n=1), and the Target Symptom Rating Scale (TSRS) (n=1). Outcomes were usually measured as changes in these measures over time, however, four studies investigated the proportion of patients responding to treatment (defined as a minimum scale score), or the time to reach this therapeutic end-point post drug administration. In one study the outcome employed was whether a second injection was required based on whether a maximum score threshold on the BPRS had been met (Resnick and Burton, 1984).

Ratings of the onset or degree of sedation were applied in four studies, including one employing a visual analogue scale. Extreme sedation marked by sleep was either regarded as a therapeutic end-point or as an indicator of oversedation.

Safety outcomes

Adverse events including extrapyramidal side effects (EPS) were generally monitored at the same time as effectiveness outcomes and reported unsystematically or using checklists.

Quantitative measures were rare although one study measured EPS using the Simpson Angus Scale (SAS). Side effects were sometimes recorded within 24 hours of first drug administration. In one study (Thomas et al., 1992), side effects were assessed from medical records at least one week post discharge for any patient returning to the hospital.

3.3 PRIMARY RESEARCH: STUDY RESULTS

Full details of the 12 papers appraised, including methods, key results, limitations and conclusions, are provided in evidence **Table 2** (including studies reporting comparisons between antipsychotics alone) and **Table 3** (including studies reporting comparisons between benzodiazepines, antipsychotics and hypnosedatives). Studies are presented in reverse chronological order of publication within each table.

Comparisons between antipsychotics

Five studies, mostly published prior to 1987, compared the administration of one antipsychotic with another **(see Table 2, pages 22-26)**.

A study of 47 combative and agitated general emergency department users (Thomas et al., 1992), most of whom were intoxicated on entrance to the trial, compared the effects of haloperidol (5 mg IM) with droperidol[7] (5 mg IM). Results were reported for 38 patients receiving a single dose. There were five assessments over the one-hour follow-up period revealing a reduction in combativeness for patients receiving either antipsychotic. However, there was a greater reduction for patients receiving droperidol after 10, 15 and 30 minutes compared with those receiving haloperidol. For the sub-sample of patients admitted and for whom side effects data was therefore available (more of whom were in the haloperidol group), there were six cases of hypotension, though there was no difference between groups in its incidence. One patient in the haloperidol group returned to hospital after 18 hours with an acute dystonic reaction. Results suggest that droperidol may lead to more rapid management of behavioural dyscontrol, and the authors suggest that this may be due to faster absorption by the IM route for droperidol compared with haloperidol.

In a psychiatric emergency department setting, 54 hostile and uncooperative patients with schizophrenia were offered either haloperidol (5 mg IM) or loxapine (25 mg IM) in flexible doses as required (PRN), with an average of 25mg of haloperidol and 83 mg of loxapine received within the first 24 hours (Tuason, 1986). Drug administration was not clinician-blinded although assessment of outcomes was. Whilst there were improvements on the Clinical Global Impressions (CGI) scale and hostility and uncooperativeness items of the BPRS for both groups, there were no differences between groups in effectiveness outcomes. Nearly all patients were asleep within 12 hours of initial administration, regarded as a desirable outcome in this study. The number of adverse events did not differ between the groups though data on this outcome is confounded by the 10-day oral phase of treatment that followed three days of IM administration.

Dubin and colleagues (1986) compared the use of loxapine (25 mg IM) with thiothixene (10 mg IM) administered PRN in a sample of 58 acutely disturbed patients from a psychiatric emergency service. On average, three doses were administered for each group every 30 minutes until sedation or maximum dose was achieved (i.e. within two hours of baseline). As with the Tuason et al. (1986) study above, drug administration was not clinician-blinded, though assessment of outcomes was. There were improvements for both groups on the CGI and the BPRS. However, there appeared to be a more rapid response for loxapine compared to thiothixene. More patients in the loxapine group reached a therapeutic end-point after receiving their first injection than the thiothixene group (62% cf. 14%, respectively), and more loxapine patients reached this end-point after 90 minutes than those receiving thiothixene (79% cf. 50%, respectively). There were minimal side effects during the 24-hour IM phase of this trial with no difference between groups in adverse events.

A study of 27 acutely agitated patients recruited from an emergency department and psychiatric crisis unit by Resnick and colleagues (1984) compared the administration of haloperidol (5 mg IM) with droperidol (5 mg IM). Comparisons between groups at baseline were not reported and therefore it is not clear whether randomisation was effective in this small sample. After 30 minutes, more patients receiving haloperidol required a second injection (81%) (based on a high BPRS score) compared with those receiving droperidol (36%). One patient in the haloperidol group manifested dysarthia and tongue protrusion 18 hours post administration during the 24-hour follow-up period.

A small trial of 24 acutely agitated, aggressive patients from a psychiatric treatment unit (Binder and McNiel, 1999) compared haloperidol (5 mg IM) with molindone (5 mg IM), administered hourly PRN. Scores on the Target Symptom Rating Scale (TSRS) improved for both groups over time. Of many comparisons performed, improvements were found to be greater for the haloperidol group three hours post administration compared with the molindone group. Sedative effects and the number of adverse events did not differ between groups although this outcome included an extended oral phase of treatment following the brief IM phase of the study reported here. Erythema around the injection site was more common for the haloperidol group than the molindone group.

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[7] (Patients could also receive their medication intravenously; whilst route of transmission was not randomised, scores on the Combativeness Scale at baseline were the same in IM and IV groups)

Summary

These studies support the use of antipsychotics for urgent sedation. However, the limitations of the research make it difficult to make clear conclusions about relative effectiveness of particular antipsychotic drugs. Apart from small sample sizes and methodological flaws, it is not always clear how relevant the study populations are to urgent sedation. Inclusion criteria employed in these studies e.g. Dubin and Weiss, (1986); Resnick and Burton, (1984)) such as items on the BPRS suggest that some participants may not necessarily have required urgent behavioural control. Moreover, the outcomes considered were often more relevant to treatment of psychotic symptoms generally than to aggressive, acutely agitated and potentially violent behaviour e.g. Binder and McNiel, (1999).

Therefore, there is insufficient evidence to describe the relative *effectiveness* of loxapine, haloperidol, thiothixene and molindone for use in urgent sedation. However, there is some evidence that droperidol may lead to more rapid control of behaviour than haloperidol (Resnick and Burton, 1984; Thomas et al., 1992), possibly due to faster absorption by the IM route for droperidol (Thomas et al., 1992).

It is also not possible to comment conclusively about the relative *safety* of these antipsychotics with each other due to factors which include small sample sizes, short follow-up, or longer follow-up being confounded by extended treatment beyond the scope of this review.

Comparisons between antipsychotics and benzodiazepines

Five papers reported on statistical comparisons between an antipsychotic drug and a benzodiazepine **(see Table 3, pages 27-28, 30-32)**.

A study by Dorevitch and colleagues (1999) compared single doses of haloperidol (5 mg IM) with flunitrazepam (1 mg IM) in a small sample of 28 aggressive, disruptive or agitated in-patients already receiving treatment with antipsychotics. Both groups exhibited significant reductions in overt aggression (measured by the OAS) within 90 minutes of drug administration. Whilst there was no difference in ratings of aggression between treatment groups by this time, maximal effect was achieved more quickly (after 30 minutes) for flunitrazepam compared with haloperidol. There were no acute EPS observed in the short follow-up period of two hours. Extreme sedation was noted in three patients in each group.

Foster and colleagues (1997) compared haloperidol (5 mg IM or oral concentrate) with lorazepam (2 mg IM or oral concentrate) in a sample of 37 highly agitated and potentially dangerous in-patients in a psychiatric emergency room. Doses were administered PRN every 30 minutes, either intramuscularly or orally, though usually by one route per person. Over the four-hour follow-up period, BPRS scores decreased by about a third, as did the CGI scores, though there were no differences in these outcomes between treatment groups, nor in the number of doses, or route of transmission used. Whilst the IM route did not appear to be more effective than the oral concentrate route of transmission, this conclusion is confounded by the fact that patients with initially more severe CGI ratings were given their drug using the IM route. No EPS were observed during the brief follow-up period of four hours. Extreme sedation was observed for five patients overall, approximately equally in each group.

Again, in a psychiatric emergency room setting, Subramaney and colleagues (1998) investigated the effectiveness of clothiapine (40 mg IM) and lorazepam (4 mg IM) in a sample of 60 patients admitted with “aggressive and disorganised” behaviour, who were already being treated with an antipsychotic (haloperidol, 10 mg PO). Patients received doses every six hours PRN. At the (only) assessment 24 hours post initial drug administration, aggression (measured by the OAS) was decreased in the majority of patients. There were no differences between treatment groups in scores or rate of onset of sedative effect. The authors claim that there were fewer EPS (measured by the SAS) for the lorazepam group compared with the clothiapine group after 24 hours though conflicting data presented between table and text makes this finding difficult to confirm.

The largest study considered in this review was conducted by Battaglia and colleagues (1997). It involved 98 patients newly enrolled into any of five psychiatric emergency departments exhibiting agitated and aggressive behaviour. Thirty-five patients received haloperidol (5 mg IM), 31 received lorazepam (2 mg IM) and the remainder received a combination of both drugs (comparisons involving combination drugs are discussed in the next section). Patients could receive up to six doses within 12

hours though most received no more than three. Both drugs led to a significant reduction in agitation (measured by the ABS) over the 12-hour treatment period. No differences in agitated behaviour (ABS), CGI or the modified BPRS were found between the single drug groups at any time-point. However, at three hours post first injection, more patients were asleep in the lorazepam group (61%) compared with the haloperidol group (32%). There was no difference between groups in incidence of adverse events. However, there were more EPS observed for patients in the haloperidol group (n=7, 20%) than the lorazepam group (n=1, 3%).

A study set in a locked psychiatric intensive care unit by a team led by Salzman (1991) also compared the administration of (usually a single dose of) haloperidol (5 mg IM) with lorazepam (2 mg IM) in a sample of 60 "aggressive" in-patients. Most patients were already receiving prescribed antipsychotics and possibly other medications for their illness. Aggression (measured by the OAS) scores reduced by around 90% for both groups after two hours. There were no differences between groups in this reduction. There were also no differences between groups after 24 hours on the OAS or the BPRS. More instances of EPS (akathisia and acute dystonia) were observed in the group receiving haloperidol compared with the lorazepam group (50% compared with 4%, respectively).

Summary

All five studies comparing an antipsychotic with a benzodiazepine found strong decreases in behavioural dyscontrol during post administration follow-up regardless of medication used. In all studies, including the three where patients were reported as already receiving on-going antipsychotic treatment, there were no clear differences between groups in effectiveness within 24 hours post initial drug administration in terms of aggressiveness, agitated behaviour, and psychotic symptoms. Studies where follow-up was brief (up to four hours) reported no significant EPS. However, in three studies where side effects were monitored beyond 24 hours, there was some evidence for fewer EPS occurring after the administration of a benzodiazepine (lorazepam) compared with that of an antipsychotic (haloperidol or clothiapine).

Comparisons between solo and combination drugs

Three papers, describing four studies, reported on statistical comparisons between a drug administered on its own (i.e. a solo drug) with more than one drug type administered concurrently (i.e. a combination drug) **(see Table 3 pages 29, 31, 33)**.

In a psychiatric emergency room service, Bieniek and colleagues (1998) investigated the effectiveness of lorazepam (2 mg IM) and a combination of haloperidol (5 mg IM) and lorazepam (2 mg IM) for a small sample of 20 acutely agitated and aggressive patients. The medication was provided as a single dose for all but two patients (in the lorazepam-only group) who received a second injection after 30 minutes. Assessments were half-hourly over three hours. Both regimens led to a significant reduction in aggression (measured by the OAS) (by 75%), the CGI (45%) and the visual analogue scales (VAS) reflecting agitation and hostility (50%) after 60 minutes. No significant group differences were found using ANOVA's statistical tests. Non-parametric statistical tests suggested a greater proportion of participants in the combined group compared with the lorazepam-only group reached the improvement criterion after 60 minutes for both the OAS and the VAS, with no difference on the CGI. Survival analyses suggested a shorter time to improvement on the OAS for patients receiving the combined versus the solo drug treatment. No adverse effects were noted during the short follow-up period. One needs to be cautious about these results given the extremely small sample size, and the number of tests performed without adjustment to the level of significance accepted.

The multi-centre trial by Battaglia's team (1997) considered a sample of 98 newly enrolled patients displaying agitated and aggressive behaviour recruited from five psychiatric emergency departments. The study compared two solo drugs, haloperidol (5 mg IM) and lorazepam (2 mg IM), with a combination of both drugs (i.e. haloperidol, 5 mg IM, and lorazepam, 2 mg IM). Patients could receive up to six doses within 12 hours; most (78%) received no more than three doses. All medications led to a significant reduction in aggression (measured by the OAS) over the 12-hour follow-up period. The only treatment difference observed for the ABS was at one-hour post initial injection such that the combination drug led to a greater reduction in aggression than the lorazepam-only drug. For the modified BPRS, patients in the combination group received a greater reduction in scores at two and three hours post injection compared with those in the solo drug groups. There were no differences in

the CGI between groups. At three hours post first injection, more patients were asleep in the combination group (61%) compared with the haloperidol group (32%). Whilst there was no difference between groups in incidence of adverse events generally, there were more EPS observed for the haloperidol group (n=7, 20%) compared with the combination group (n=2, 6%). These results suggest that there is a possibility that the combination medication may have been more effective in the early hours post initial treatment, with fewer side effects than the haloperidol-only group. However, as with the previous study, there were many analyses conducted for the hourly assessments, which increases the risk of reporting differences due to chance alone.

In two studies, Garza-Trevino and colleagues (1989) investigated administration of various drug regimens for agitated or assaultive psychotic in-patients in a psychiatric hospital. In Study 1 involving 68 patients, single doses of haloperidol (5 mg IM) and lorazepam (4 mg IM) were compared with the combination of these drugs (i.e. haloperidol, 5 mg IM, and lorazepam, 4 mg IM). (Notably a larger dose of lorazepam is given here than the usual 2 mg suggested in most other studies reviewed). Repeat doses were administered PRN and assessments were made at 30, 60 and "after 60" minutes (within 3.5 hours) after first dose. More patients "responded" (reached the criterion level of sedation) within 30 minutes in the combination group (75%) than for those receiving either of the component drugs (36%). Study 2 involved 53 patients, and compared the combination of an antipsychotic (haloperidol, 5 mg IM) and a non-benzodiazepine hypnosedative (phenobarbital sodium, 130 mg IM), with the combination of an antipsychotic (thiothixene, 5 mg IM) and a benzodiazepine (lorazepam, 4 mg IM). Just over half of patients responded within each group within 30 minutes. Four patients failed to respond after the third dose. This study suggests that other drug combinations may be effective though unfortunately did not compare them with the more commonly applied haloperidol-lorazepam combination or solo drug medications in the same sample. In both studies there were few indications of over-sedation or dystonic reactions, though follow-up was limited to fewer than 3.5 hours. It is also important to note that both studies were neither clinician- nor patient- blinded which may introduce bias into the way that the drugs were administered, received and outcomes coded.

Summary

These three papers' findings are consistent with the possibility that combined antipsychotics and benzodiazepines may be more effective in the early hours following first dose of treatment compared with solo drug regimens of lorazepam and haloperidol. Notably, these studies all concerned patients who were not receiving ongoing antipsychotic treatment. Care should be taken in making conclusions given limitations of sample size and follow-up in two studies, and the mixed nature of results generally after many comparative analyses have been performed. Such approaches without adjustment to the p value accepted increase the risk of erroneously finding differences by chance alone.

Effectiveness and safety results are complicated in studies comparing combination drugs with solo drugs by the issue of whether doses are of equivalent potency in each arm of the trial. Apparent superiority of a combination treatment to component alternatives may be due to the former involving a greater total dose of drug in those studies where number of injections were equivalent between arms. This was the case for two studies where single doses were uniformly administered in all arms of the trial (Bieniek et al., 1998; Garza-Trevino et al., 1989).

In the multi-centre trial (Battaglia et al., 1997), this issue is further complicated by a varying number of injections. In the combination group, 91% of patients received three or fewer injections compared with 74% and 71% of patients in the solo drug groups, lorazepam and haloperidol respectively. That fewer doses were required for the combination group may be due to a greater total dose being given than with each solo drug. However, the authors of this trial argued that combination antipsychotic-benzodiazepine regimens might have additive sedative effects due to their different neurochemical action (benzodiazepines having gamma-aminobutyric acid-facilitating effects and antipsychotics acting as dopamine-blocking agents).

Despite apparent increased effectiveness for the combined group, there were fewer side effects in the combined haloperidol and lorazepam versus the haloperidol-only group in this trial (Battaglia et al., 1997), although the other two studies were not able to confirm this finding due to a short follow-up period. It has been suggested that the anti-convulsant effect of benzodiazepines such as lorazepam may offset the lowering of seizure threshold engendered by antipsychotics (Kerr and Taylor, 1997).

Conclusion

These studies support the use of antipsychotics and benzodiazepines as effective and safe in urgent sedation. However, the limitations of the small research base make it difficult to make robust conclusions about relative effectiveness and safety of particular drug regimens. Results are discussed more fully in the next chapter.

Table 2. Evidence table of primary research studies comparing antipsychotics

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Thomas et al., (1992)	RCT Clinician-blinded Patient-blinded	Emergency department	N=47 violent or markedly agitated adults requiring physical restraint and scoring 1 on the combativeness scale. Physical restraint used on all patients initially until no longer required. No significant difference between the groups in age, blood alcohol levels, or rates of admission. Excluded: known allergy to the drug, low blood pressure (below 110/60 mm Hg), received other prescribed psychotropic medications prior to study.	Antipsychotic - Haloperidol (IM) 5 mg Antipsychotic - Droperidol (IM) 5 mg Route of transmission (IM or IV) was chosen at discretion of attending physician and only those receiving the drug IM only (n=47) are reported here. Patients could receive a second dose after 30 minutes if first dose is ineffective. In this case, outcomes from *initial* 30 minutes reported only. Fewer participants at the 60-minute assessments as 5/21 haloperidol and 4/26 droperidol were withdrawn after requiring another dose/medication.	Combativeness Scale (ranging 1-5 from violently agitated, fully restrained, and requiring constant attention to no agitation, no supervision required, may be asleep). Vital signs recorded. Timing: 5, 10, 15, 30, 60 minutes post drug administration. Side effects assessed from medical records at least 1 week post-discharge for any patient returning to hospital.	Effectiveness: Both drugs led to a reduction in combativeness over time. However, there was a more rapid response for those receiving droperidol than haloperidol, with significant group differences at 10, 15, and 30 minutes post administration. More patients receiving haloperidol were admitted as in-patients than those in the droperidol group. Safety: Hypotension (drop in blood pressure to 90/60 mm Hg or less) noted in 6 patients, none of whom were hospitalised. No difference between groups in heart rate and blood pressure changes. One patient from haloperidol group returned in 18 hours with acute dystonic reaction. No adverse events noted for admitted patients.	Limitations: - route of transmission was not randomised and more of the droperidol group received the IM route than the IV route (26 cf. 9) than in the haloperidol group (21 cf 12). However, no differences in demographic variables or Combativeness Scale at baseline. - Combativeness Scale not psychometrically tested. - patients not admitted (n=21) were lost to follow-up relating to side effects. - "most patients were intoxicated" though substantial missing data on this variable. Author's conclusions: In equal IM doses, droperidol results in more rapid control of agitated patients than haloperidol, without any increase in undesirable side effects. Argue that there may be more rapid absorption by IM route for droperidol than for haloperidol.

Table 2. Evidence table of primary research studies comparing antipsychotics *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Tuason, (1986) USA	RCT Drug administration not blinded, assessments were clinician-blind Patient-blinded	Psychiatric emergency department	N=54 acutely psychotic schizophrenic in-patients who were hostile, aggressive, uncooperative or unmanageable, with score on hostility and uncooperativeness items of the Brief Psychiatric Rating Scale (BPRS) of at least 8. Psychiatric condition: all with schizophrenia (confirmed after sufficiently controlled). Age range: 18 – 65 years. No significant difference between the groups in race, sex, diagnosis, or duration of current episode. Patients in haloperidol group were older by about 6 years and had a longer duration of schizophrenic illness than in the loxapine group. Excluded: metabolic impairment, history of epilepsy or neurologic disorder, mental retardation, organic brain syndrome, obvious senility.	Antipsychotic - Haloperidol (IM) 5 mg Antipsychotic - Loxapine (IM) 25 mg After initial dose, given hourly as flexible doses within limits (mean on day 1: 25 mg haloperidol or 83 mg loxapine). Received drugs IM for 24-72 hours followed by oral dose for 10 days (report effectiveness results to 24 hours only here).	Clinical Global Impressions (CGI) Scale, and BPRS ratings of hostility and uncooperativeness. Ratings of sedation. Adverse events measured in terms of severity, duration, and treatment given. Timing: CGI and BPRS at 24 hours post first administration. Sedation, hostility and uncooperativeness measured at 30 minutes, 1, 2, 3, 4, 8, 12, and 24 hours after first administration.	Effectiveness: Significant improvement in outcomes from baseline at each assessment for both groups, but no significant group differences. Extreme sedation, regarded as therapeutic end-point, noted in the first hour for "most patients". Within 12 hours, 24/25 loxapine patients and 22/27 haloperidol patients were asleep. Safety: Most frequently reported adverse events over the whole study period (10 days, including oral phase) were dystonia (n=14) and akathisia (n=14). Four removed from the study due to adverse events, 2 in loxapine group (increased blood pressure, tachycardia), 2 in haloperidol group (severe akathisia and severe dystonia). Number of adverse events did not differ between groups.	Limitations: - drug administration was not blinded - medication history of patients not known/reported - side effects may be due to oral phase of treatment. Author's conclusions: Loxapine and haloperidol are comparably effective in the initial management of hostile and aggressive schizophrenic patients.

Table 2. Evidence table of primary research studies comparing antipsychotics *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Dubin and Weiss, (1986) USA	RCT Administration not blind, assessments of outcome were clinician-blinded Patient-blinded	Psychiatric emergency service.	N=58 acutely disturbed, psychotic patients admitted as a psychiatric emergency with a score of least 6 ("severe") in 3 or more items of the Brief Psychiatric Rating Scale (BPRS): anxiety, excitement, conceptual disorganisation, tension, hostility, suspiciousness, hallucinatory behaviour, uncooperativeness, unusual thought content. Psychiatric condition: chronic schizophrenia (37), acute schizophrenia (12), bipolar disorder, manic (9). Age range: 18 - 65 years. No difference in age, sex, diagnosis, race, or severity of illness between groups. Excluded: drug hyper-sensitivity, pregnancy or lactating mother, haematologic, cardiovascular, renal, hepatic impairment, convulsive disorder, urinary retention, glaucoma, mental retardation, received antipsychotic, hypnosedative, or anti-anxiety drugs in past 24 hours.	Antipsychotic - Thiothixene (IM) 10 mg Antipsychotic - Loxapine (IM) 25 mg After initial dose, given at 30 minute intervals as needed until therapeutic end-point of sedation, or until maximum dose administered (or if adverse event required ceasing drug administration). Mean dose in 24 hours was 75 mg for patients receiving loxapine (3.10 doses) and 31 mg for those receiving thiothixene (3.07 doses). Received drugs IM for 24 hours followed by oral dose for 5 days (report effectiveness results to 24 hours only here).	Clinical Global Impressions (CGI) scale, and the BPRS. Time to therapeutic end-point: scored no more than "mild" on the three items of the BPRS initially recorded as at least "severe". Timing: CGI, BPRS and any side effects recorded at 30-minute intervals until after *last* dose (usually within 2 hours of first administration).	Effectiveness: Significant improvement in outcomes from baseline for both groups. After first injection, 62% in the loxapine group and 14% in the thiothixene group had reached therapeutic end-point. By 90 minutes, therapeutic end-point achieved in 79% of the loxapine group and in 50% in the thiothixene group. Manic and schizophrenic patients responded similarly. Safety: Minimal side effects during the IM phase, 3 had dystonic reactions (1 in loxapine group, 2 in thiothixene group), and 2 were unduly sedated (thiothixene group). Number and severity of adverse events did not differ between groups.	Limitations: - administration was not blinded - not clear that all patients necessarily required urgent sedation, though sample was described ir the paper's conclusion as "agitated". Author's conclusions: Median time to tranquillisation was significantly less with loxapine (60 min) than with thiothixene (95 min) in the initial management of hostile and aggressive schizophrenic patients.

Table 2. Evidence table of primary research studies comparing antipsychotics *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Resnick and Burton, (1984) USA	RCT Clinician-blinded Patient-blinded	Emergency department and Psychiatric Crisis Unit.	N=27 acutely agitated, patients admitted as a psychiatric emergency and displaying symptoms of acute agitation with a score of at least 17 on a subset of items of the Brief Psychiatric Rating Scale (BPRS): anxiety, tension, hostility, mannerisms and posturing, uncooperativeness, and excitement. Excluded: intoxicated, known sensitivity to drugs being used, evidence of active renal, hepatic or cardiac disease.	Antipsychotic - Haloperidol (IM) 5 mg Antipsychotic - Droperidol (IM) 5 mg After initial dose, given at 30 minute intervals as needed until BPRS score less than 17.	Outcome was whether a second injection was required (based on BPRS score at 30 minutes following the first dose). Side effects noted, and blood pressure, pulse rate, and respiratory rate monitored. Timing: BPRS recorded 15 minutes after administration, then at 30 minute intervals for 3 hours. EPS noted for 24 hour follow-up phase.	Effectiveness: After 30 minutes, more patients treated with haloperidol required a second injection (81%, n=13/16) compared with those in droperidol group (36%, n=4/11). Safety: one patient in haloperidol group manifested dysarthia and tongue protrusion 18 hours after administration of drug, which was treated successfully.	Limitations: - small sample - demographic and clinical details at baseline not described or compared between groups - target behaviour and outcomes considered were not restricted to aggression/agitation requiring urgent sedation. Author's conclusions: Droperidol appears to be as at least as efficacious and perhaps more effective than haloperidol in achieving rapid control of "anxiety tension, bizarre behaviour, hostility, and excitement", though requires larger study to confirm.

Table 2. Evidence table of primary research studies comparing antipsychotics *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Binder and McNiel, (1999) USA	RCT Clinician-blinded Patient-blinded	Psychiatric treatment unit	N=24 acutely agitated, psychotic patients consecutively admitted and who were overactive, aggressive, assaultive, and for whom urgent sedation was required. Psychiatric diagnosis: schizophrenia (23), reactive psychosis, unspecified (1). Age range: 19 – 57 years. Severity of mental illness at baseline according to the Brief Psychiatric Rating Scale (BPRS), Target Symptom Rating Scale (TSRS), and Clinical Global Impressions (CGI) scale did not differ between groups. No difference in groups for sex, race, age. Excluded: not reported.	Antipsychotic - Haloperidol (IM) 5 mg Antipsychotic - Molindone (IM) 25 mg After initial dose, given every hour as clinically needed. Received drugs IM for 24 hours followed by oral dose for 5 days (report effectiveness results to 24 hours only here).	TSRS Adverse events noted. Timing TSRS recorded prior to each injection and 1 and 3 hours after last injection. Side effects measured up to 5 days post baseline.	Effectiveness: In general, improvements on TSRS were significant for both groups. Improvements on the TSRS score 3 hours post administration was greater for the haloperidol group than the molindone group. Sedative effects not different between groups. Safety: Erythema at the injection site more common for the haloperidol group (25%) than for the molindone group (14%). No difference between groups in the *number* of patients with adverse side effects after 5-day treatment period, though side effects were more severe in the haloperidol group (not statistically compared).	Limitations: - small sample - no objective measure of behaviour on entry into the study - target behaviour and outcomes considered were not restricted to aggression/agitation requiring urgent sedation - many comparisons performed with no adjustment to p value - side effects may be due to oral phase of treatment. Author's conclusions: Molindone appears to be comparable in efficacy to haloperidol in acutely agitated psychotic patients (note that these conclusions also refer to administration and follow-up beyond one day).

Key:
RCT: randomised controlled trial IM: Intra-muscular injection (route of transmission) EPS: extrapyramidal side effects
Ns: not significant

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Dorevitch et al., (1999) Israel	RCT Clinician-blinded Patient-blinded	Acute ward for psychiatric inpatients	N=28 inpatients with active psychosis presenting with disruptive or aggressive behaviour, pronounced psychomotor agitation, or violent outbursts. Patients were already under treatment with antipsychotics. Psychiatric condition: schizophrenia (19), schizoaffective disorder (7), and bipolar disorder (2). Two groups did not differ in diagnostic classification, or severity of psychotic symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression scale (CGI). Exclusions: not reported.	Antipsychotic - Haloperidol (IM) 5 mg Benzodiazepam - Flunitrazepam (IM) 1 mg Single doses.	Response defined as reduction of 50% or more in Overt Aggression Scale (OAG) score at 90 minutes post drug administration. Duration of response (length of time the reduced aggression level lasted following drug administration). Timing: 15, 30, 45, 60, 90, 120 minutes post drug administration.	Effectiveness: Both drugs led to a significant reduction in OAS scores with 80% in flunitrazepam group and 92% in haloperidol group responding within 90 minutes. The effect lasted for at least 120 minutes post administration. No significant difference in anti-aggressive response at 90 minutes between the two groups. However, drug X time interaction such that flunitrazepam achieved maximal anti-aggressive effect in less time (30 minutes post administration) than haloperidol. Safety: No acute extrapyramidal side effects observed in either group. Marked sedation induced in 3 patients in each drug group.	Limitations: - small sample size - short follow-up - no objective measure of behaviour on entry into the study. Author's conclusions: From this small trial, flunitrazepam appears to be a satisfactory alternative to haloperidol as a rapid, effective and safe adjunct to antipsychotics in rapid sedation in emergency psychiatric settings.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Foster et al., (1997) USA	RCT Clinician-blinded Patient-blinded	Psychiatric emergency room service	N=37 highly agitated in-patients exhibiting psychotic symptoms who were judged to be an imminent danger to themselves, required 4 point physical restraints, scored higher than 4 on at least three items of the Brief Psychiatric Rating Scale (BPRS), and scored at least 4 on the Clinical Global Impression scale (CGI). Age range: 18 - 61 years. Psychiatric condition: schizophrenia (13), schizoaffective disorder (4), bipolar disorder (13), and psychotic, not otherwise specified (7). Two groups did not differ in drug or alcohol history, sex, race, age, BPRS or CGI scores. More patients with bipolar disorder received lorazepam, and more patients with unspecified psychotic disorder received haloperidol, compared to the alternative intervention group. Exclusions: physical illness.	Antipsychotic - Haloperidol (IM or oral concentrate) 5 mg Benzodiazepam - Lorazepam (IM or oral concentrate) 2 mg Most patients received drug by one transmission route (73%), 33% of these by IM. Four patients received both, usually IM first. Doses administered as needed (until patient was sedated or no longer of danger to themselves or others) every 30 minutes for 4 hours.	BPRS and the CGI. EPS noted. Extensive training given to four raters of outcomes to enhance inter-rater reliability. Timing: 1, 2, 3 and 4 hours post first administration.	Effectiveness: Both drugs led to a significant reduction in BPRS scores (haloperidol: 10% after 1 hour, 35% after 4 hours; lorazepam: 14% after 1 hour, 36% after 4 hours) and CGI scores (haloperidol: 5% after 1 hour, 29% after 4 hours; lorazepam: 11% after 1 hour, 35% after 4 hours). No drug X time interactions. No difference in number of doses, or route of transmission (IM or oral) between groups. Heart rate or systolic or diastolic blood pressure decreased over time, with no difference between groups. Safety: No extrapyramidal side effects observed in either group during 4-hour study period. Extreme sedation (marked by sleep) observed in 2 patients receiving haloperidol and 3 receiving lorazepam.	Limitations: - small sample size - transmission route varied - short follow-up period - questionable additional exploratory analyses performed - possible that longer intervals between doses may have produced similar results. Author's conclusions: No advantage of IM over oral concentrate administration though confounded by IM being used for patients with more severe CGI ratings. Given *potential* for severe side effects of haloperidol, authors suggest lorazepam "may be the preferred approach" in the rapid sedation of acutely agitated psychotic patients in emergency room settings. Suggest there is a need for more dose-response studies.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
(Bieniek et al., 1998) USA	RCT Clinician-blinded Patient-blinded	Psychiatric emergency service	N=20 acutely agitated, newly-admitted patients with a serous degree of aggressive or agitated behaviour as shown by a score of at least 4 on the Overt Aggression Scale (OAS), and 2 or more on at least one item. Also required a rating of at least 50 on a 100-point visual analogue scale reflecting agitation and hostility (VAS). Complete blood count and physical examination performed at baseline. Age range: 18 - 50 years. Psychiatric condition: bipolar/manic disorder (9), psychosis not otherwise specified (4), schizophrenia (3), substance-induced (2), brief reactive psychosis (1), undifferentiated schizophrenia (1). No significant difference between the groups in demographic and diagnostic variables at baseline. Exclusions: not reported.	Benzodiazepam - Lorazepam (IM) 2 mg Combination - Haloperidol (IM) 5 mg plus lorazepam (IM) 2 mg Single doses except two participants in the lorazepam-only group who received a second injection after 30 minutes.	OAS, VAS, Clinical Global Impression scale (CGI), and adverse events. Degree of sedation also rated by visual analogue scale. Improvement defined as decrease of 4 or more on OAS, and decrease of 40 or more on visual analogue scales within 60 minutes of first administration. CGI was an additional improvement criterion. Inter-rater reliability was assessed prior to the trial. The same physician rating the baseline rated subsequent assessments for the same patients. Timing: 30, 60, 120, 180 minutes post first administration.	Effectiveness: Both drugs led to a significant reduction after 60 minutes for OAS (15/20=75%), VAS 10/20=50%), and CGI (9/20=45%). No significant group differences were found in ANOVA's. In non-parametric tests, greater proportion of participants improved 60 minutes post first dose on OAS in the combined group (9/9=100%) compared with lorazepam-only group (6/11=55%), and on VAS in the combined (7/9=78%) compared with lorazepam-only group (3/11=27%). No group differences for CGI. Survival analyses suggested shorter time to improvement on the OAS for the combined compared with the lorazepam-only group, a similar trend for the VAS (p=.071), and no relationship for the CGI. No difference between groups in time to sedation. Safety: No serious adverse events occurred.	Limitations: - very small sample size - short follow up period - many comparisons performed with no adjustment to p value - 2 patients receiving a 2nd injection in the lorazepam-only group not excluded though this would disadvantage the combination group. Author's conclusions: Combination of lorazepam and haloperidol superior to lorazepam alone. However, suggest that a higher injection of lorazepam (say, 4 mg) may have similar effect to combination drug.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Subramaney et al., (1998) South Africa	RCT Clinician-blinded Patient-blinded	Psychiatric emergency room service	N=60 patients already treated with haloperidol (10 mg orally) consecutively admitted with aggressive and disorganised behaviour. Age range: 18 - 45 years. Psychiatric condition: organic (psychoactive substance) hallucinosis or delusional disorder (24), schizophrenia (16), bipolar disorder (14). No significant difference between groups in demographic and diagnostic variables at baseline. Exclusions: physical illness, pregnancy, and abnormal blood tests.	Antipsychotic - Clothiapine (IM) 40 mg Benzodiazepam - Lorazepam (IM) 4 mg Doses administered every 6 hours if clinically warranted.	Overt Aggression Scale (OAS) and EPS by the Simpson Angus Scale (SAS). Onset of sedation. Timing: OAS 24 hours after admission/initial drug administration. SAS measured 1 and 3 days post admission (though table suggests 3 and 7 days).	Effectiveness: OAS decreased in both groups (by 69% for lorazepam and 80% for clothiapine). No significant difference between the groups in OAS, or onset of sedation. Safety: Lorazepam reported as associated with fewer EPS than clothiapine according to SAS though this difference is not reflected by the p value in Table 2.	Limitations: - no short term measures of outcome - no objective measure of behaviour on entry into the study - conflicting reporting in the results makes some findings questionable. Author's conclusions: Lorazepam and clothiapine are of equivalent efficacy in the control of acutely behaviourally disturbed patients when combined with an antipsychotic. Lorazepam was associated with fewer EPS.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Battaglia et al., (1997) USA	RCT Multi-centre trial Clinician-blinded Patient-blinded	Five psychiatric emergency departments	N=98 newly-admitted patients enrolled during an 18-month period, with psychosis, and exhibiting agitated, aggressive, destructive, assaultive, or restless behaviour capable of harming themselves or others. Urine drug screen, physical examination and psychiatric history taken. Age range: 18 - 50 years. Psychiatric condition (multiple codes allowed): schizophrenia (47), psychosis not otherwise specified (27), psychoactive substance abuse (16), mania (13), schizophrenia form disorder (1). No significant difference between the groups in demographic variables. Excluded: alcohol intoxication, allergic hypersensitivity, CNS depression, delirium, neuroleptic malignant syndrome, airway obstruction, severe hypo- or hyper- tension, pregnancy, glaucoma, benzodiazepine or neuroleptic in 24 hours.	Antipsychotic - Haloperidol (IM) 5 mg Benzodiazepam - Lorazepam (IM) 2 mg Combination - Haloperidol (IM) 5mg plus lorazepam (IM) 2 mg Patients received 1 – 6 injections within maximum of 12 hours, based on clinical need, the first three at least 1 hour apart, and the remainder 2 hours apart. Most received 3 doses or fewer.	Agitated Behaviour Scale (ABS), 11 psychosis/anxiety items of the modified Brief Psychiatric Rating Scale (MBPRS), Clinical Global Impression scale (CGI), and side-effects checklist. Means adjusted by ANCOVA statistical text for baseline levels. Timing: hourly post administration until 12 hours post first dose, if awake according to the Alertness Scale.	Effectiveness: All drugs led to a significant reduction in ABS and MBPRS over time. No differences between solo drug groups. There was a significantly greater reduction at one hour for combination compared with lorazepam-only groups (trend compared with the haloperidol-only group, p=.064). Greater reduction in the MBPRS at hours 2 and 3 for the combination group compared with solo drug groups. There were no differences between groups in the CGI at any time-point. At 3 hours, more patients were asleep in the lorazepam-only (65%) and combination groups (61%) than in the haloperidol-only group (32%). Safety: No differences between groups in incidence of adverse events. More EPS in the haloperidol-only group (n=7, 20%) than the lorazepam-only (n=1) or combination group (n=2).	Limitations: - no objective measure of behaviour on entry into the study - many comparisons performed with no adjustment to p value Considered sleep as a therapeutic end-point and therefore regard combination and lorazepam as superior to haloperidol-only group on this outcome. Author's conclusions: Lorazepam and haloperidol are equally effective, but the combination of lorazepam and haloperidol are superior to lorazepam or haloperidol alone.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Salzman et al., (1991) USA	RCT Clinician-blinded Patient-blinded	Locked intensive care unit for psychotic patients	N=60 in-patients requiring medication to control aggressive, assaultive, or disruptive behaviour (after other therapeutic attempts have failed). Most patients already receiving antipsychotics and a minority also received other medication including lithium, anti-convulsants, beta-blockers, and benzodiazepines. Results for these sub-groups did not differ and therefore analyses reported for total sample. Psychiatric condition: schizophrenia (26), bipolar disorder (11), schizo-affective (4), organic mental disorder (6), and other psychosis (14). No significant difference between groups in age. More patients in haloperidol group with bipolar disorder. Excluded: those with known substance abuse by positive toxicology on admission.	Antipsychotic - Haloperidol (IM) 5 mg Benzodiazepam - Lorazepam (IM) 2 mg Patients usually required only one injection (mean=1.10 for haloperidol; mean=1.13 for lorazepam).	Overt Aggression Scale (OAS), Clinical Global Impressions (CGI) scale, and the Brief Psychiatric Rating Scale (BPRS). Side effects and sedation rated and statistically compared. Timing: OAS at 2 and 24 hours post administration, BPRS and CGI ratings at 24 hours (also at 48 hours not reported here). Side effects and sedation assessed 1 and 24 hours by independent clinicians.	Effectiveness: Significant reduction in OAS scores over time with reduction in scores of 91% for lorazepam and 88% for haloperidol. No group differences at 2 or 24 hours in OAS using ANOVA. Questionable chi-squared analyses also conducted on proportion of individuals with greater than mean decreases. No significant difference between groups for BPRS or CGI at 24 hours. Safety: EPS (akathisia and dystonia) 11 times more prevalent in haloperidol group (9/18) than lorazepam group (1/22, RR=11). Extreme sedation (marked by sleep) observed in similar numbers in each group (haloperidol: 7/26. Lorazepam: 8/27).	Limitations: - no objective measure of behaviour on entry into the study - significant amount of missing data (though similar in each group) at 24 hours, reportedly due to high drop-out rate from discharge and transfer from unit. Author's conclusions: Based on chi-squared analyses, conclude that lorazepam added to ongoing antipsychotic treatment may be superior to haloperidol added to ongoing antipsychotic treatment for rapid control of severely psychotic aggressive patients. Lorazepam associated with fewer acute EPS.

Table 3. Evidence table of primary research studies comparing antipsychotics, benzodiazepines and combination drug regimens *(continued)*

Source	Study design	Setting	Sample	Interventions	Outcomes	Results	Comments
Garza-Trevino et al., (1989) USA	RCT Not blinded	Acutely psychotic in-patients in a general psychiatric hospital	N=68 patients (STUDY 1) and 53 patients (STUDY 2) requiring immediate treatment for agitated or assaultive behaviour with drugs, seclusion or both. Patients needed to score at least 50 of 100 in visual analogue scale of agitation for entry into the study. Psychiatric condition: manic patients (22), schizophrenia (16), atypical psychotic patients (16), and 14 miscellaneous. No significant difference between groups in diagnoses, or age. In study 1, more women in haloperidol-only group than lorazepam-only or combined. Excluded: No patient had received a dose of a centrally acting depressant medication for at least 2 hours before baseline.	STUDY 1 Antipsychotic - Haloperidol (IM) 5 mg Benzodiazepam - Lorazepam (IM) 4 mg Combined - Haloperidol (IM) 5 mg and lorazepam (IM) 4 mg Repeat doses given if required. STUDY 2 Antipsychotic/hypnosedative - Haloperidol (IM) 5mg and phenobarbital sodium (IM) 130 mg. Antipsychotic/ benzodiazepine combination - thiothixene (IM) 5 mg and lorazepam (IM) 4 mg.	Degree of agitation measured by visual analogue scale (VAS). Time to respond (to reach criterion tranquillisation) measured as being in either 30 minutes, 60 or more minutes, or more than 60 minutes. Timing: 30, 60, "more than 60" minutes (usually within 3.5 hours) after first administration.	STUDY 1 Effectiveness: Combination treatment was more likely to lead to tranquillisation within 30 minutes (18/24=75%) than either of the single component drugs (16/44=36%) in chi-squared analyses. Finding was replicated in ANOVA's after statistical correction for baseline agitation. STUDY 2 Effectiveness: Number of patients responding within 30 minutes of first injection was the same for both groups (15/27 =55% haloperidol/phenobarbital sodium group, and 15/26=58% thiothixene/lorazepam group). Three patients in former group, and one in the latter group, failed to reach tranquillisation after third dose. Safety: "Few indications of oversedation or dystonic reactions".	Limitations: - very short follow up period. - side effects not described - not double blind. Author's conclusions: STUDY 1 Combination appeared to be superior in efficacy to either component alone but "we cannot be sure that such superiority would have been evident if the doses of the single components had been adjusted to be equivalent to those in the combination". STUDY 2 Argue that combination of antipsychotic and hypnosedative drugs provides excellent control of agitated behaviour, suggesting that results of Study 1 could be generalised to other high potency antipsychotics and to hypnosedatives for which IM route of drug administration is feasible

Key:
RCT: randomised controlled trial IM: Intra-muscular injection (route of transmission) EPS: extrapyramidal side effects
Ns: not significant

Chapter 4: Summary and conclusions

4.1 SUMMARY OF EVIDENCE

This report systematically reviewed the international evidence for the effectiveness and safety of drug treatments for urgent sedation of individuals in psychiatric emergencies.

Approximately 800 articles were identified by the search strategy. From 39 articles identified as potentially eligible for inclusion, a final group of 14 papers were selected for appraisal, including 12 randomised controlled trials and two systematic reviews. Main results are presented below.

- A systematic review by Wing and colleagues (1998) considered pharmacological interventions within a wider review of the management of imminent violence by adult users of mental health services. It was concluded that due to the lack of high quality research available it was not possible to draw strong evidence-based conclusions. However, several papers suggested that if urgent sedation is indicated, benzodiazepines or an antipsychotic alone could be used with a reasonable degree of safety for managing violent behaviour (Chambers and Druss, 1999). It was also concluded that there was no evidence to suggest that a combination of several medications or higher than standard doses produced better results.
- From the present review, there is insufficient evidence to suggest that particular antipsychotics have an advantage in terms of effectiveness. There is some evidence that droperidol may lead to more rapid control of behaviour than haloperidol, possibly due to faster absorption by the IM route for droperidol (Thomas et al., 1992). Intramuscular droperidol also has the advantage in urgent sedation of a shorter half-life (2 hours) compared with haloperidol (10-19 hours) (Glow, 1997) which allows for psychiatric assessment sooner and better titration with repeat dosing. Such evidence has led authors of a review of droperidol to conclude that droperidol may be superior to other typical high potency antipsychotics such as haloperidol because of a shorter latency of onset and a comparable side effect profile. It is not possible to comment conclusively about the relative safety of antipsychotics.
- Studies of different solo drug regimens also suggest no clear benefit in terms of effectiveness of antipsychotics over benzodiazepines. In studies of these drugs, side effects were extremely rare in the hours shortly following initial drug administration. However, beyond 24 hours, there was some evidence for fewer extrapyramidal side effects occurring after the administration of a benzodiazepine (lorazepam) compared with that of an antipsychotic (haloperidol or clothiapine).
- Whilst there was some support for increased effectiveness of combined regimens (antipsychotics and benzodiazepines) compared with single drug regimens, these studies were severely limited in terms of small sample sizes, brief follow-up, mixed results, dosage variations, and the risk of spurious results due to excessive analyses performed. A single study (Battaglia et al., 1997) suggested that there may be fewer side effects for patients in the combined haloperidol and lorazepam treatment group compared with the haloperidol-only group.

4.2 LIMITATIONS OF CURRENT RESEARCH BASE

Further research should address limitations in study design demonstrated in this review. Key issues are described below.

- No studies appraised were set in the wider community. Instead, studies were conducted in psychiatric emergency department/in-patient settings. These contexts were likely to have involved more experienced psychiatric staff than one may expect to find in community settings where medical practitioners relatively rarely employ urgent sedation strategies.
- Definitions of behavioural dyscontrol required for entry into a study varied widely. In some studies, earlier ones in particular, patients were not selected for their aggressive behaviour per se

but instead were selected due to minimal scores on the BPRS scale at baseline. This measure of psychotic symptoms may include an item reflecting hostility, which can manifest itself as overt physical aggression if rated highly. However, it was generally not a condition of eligibility that a high score on this particular item was given. Similarly, agitation may not necessarily equate with being behaviourally "out of control" and requiring urgent sedation. The meaning of terms used such as "disturbed" or "difficult" are also rarely defined (Wing et al., 1998).

- It was not always clear how patients were recruited into the trials or whether biases may have been evident in the selection of patients. Exceptions are three studies involving patients consecutively enrolled over a specified period upon admission (Battaglia et al., 1997; Binder and McNiel, 1999; Subramaney et al., 1998).
- A wide variety of samples were considered including intoxicated patients, and those already receiving ongoing treatment for their disorder. The range of illness witnessed in community settings is likely to be comparable to patients recruited through emergency departments. However, the ability to determine the specificity of drug effectiveness for particular patient groups (e.g. manic, schizophrenic) was limited by the heterogeneity of diagnosis represented in many samples.
- The overall advantage of treatment by various drug regimens considered cannot be determined without placebo controls, though these are likely to be regarded as unethical given that urgent sedation is generally only considered after other non-pharmacological management alternatives have been attempted without success. Some differences over time may be partially due to the act of administering the intervention, increased staff attention, or a natural quietening over time (Salzman et al., 1991).
- The relationship between drug treatments for urgent sedation and other ameliorating factors such as ward morale, pre-emptive psychosocial interventions, restraint or seclusion, have not been considered in research in this field (Wing et al., 1998).
- Whilst most studies claimed to be fully randomised and double-blind, methods for ensuring blinding and randomisation were rarely described and it was not always clear how reliably these procedures had been carried out. For example, whether both the administration of the drug and recording of the outcomes by the clinician/health professional were blind was frequently unclear.
- Outcome measures were not always psychometrically tested and validated, or appropriate for measuring effectiveness in terms of reduction in behavioural dyscontrol as opposed to rapid treatment of psychotic symptomatology.
- It was frequently difficult in studies to determine whether equipotent doses of drugs were being administered in each arm of a trial, especially when many studies involved individualised drug dose determinations administered PRN.
- It was not always clear whether effects found when drugs were routinely given every 30 minutes could have been achieved with less frequent administration. It has been suggested that it does not make pharmaco-dynamic sense to readminister antipsychotics at 30 minute intervals if it takes longer to reach peak sedation levels (Hillard, 1998).
- Whilst some side effects tend to manifest themselves within a few hours of drug administration (such as dystonias), other side effects such as parkinsonian symptoms generally appear between three and nine days after initiation of treatment (Kamin et al., 2000). Such medium-term indicators of drug safety are not likely to be detected in studies with only limited follow-up assessments. Patients were rarely followed up beyond 24 hours in the studies appraised in this review, and when they were the safety outcomes were often confounded by continuing treatment (e.g. by oral dosing).
- Most studies were severely hampered by small sample sizes that reduced the statistical power required to be sensitive to group differences, particularly for rare events such as side effects. Conversely, the type and number of statistical tests employed was frequently inappropriate for studies involving such small numbers of participants and in some studies was likely to have led to spurious findings by chance alone.

4.3 CONCLUSIONS

Because acutely disturbed or violent behaviour may result from a number of conditions, there are many different drugs available for use in urgent sedation and little consensus on which is the most effective approach (Kerr and Taylor, 1997). Guidelines are also challenged by the wide-ranging settings and patient conditions for which urgent sedation can be used, as well as the variation in practitioner attitudes that is evident internationally. There are few well-conducted, comparative trials in this field, and only a small range of drugs and settings are represented in the studies appraised in this review. This limits the ability to make specific conclusions to cover the many situations in which urgent sedation may be warranted. In the absence of a strong evidence base, much guidance in this area is based on pharmacological reasoning and clinical experience.

The conclusions described below are based on the current evidence available from this report's systematic review of international literature published from 1980 onwards on the effectiveness and safety of drug treatments for urgent sedation of individuals in psychiatric emergencies. Studies were included for review if they reported randomised controlled trials comparing the use of benzodiazepines or other hypnosedatives, antipsychotics and valproic acid derivatives (valproate, divalproex) or a combination of these administered intramuscularly or orally for urgent sedation.

- Studies appraised support the effective and reasonably safe use of antipsychotics and benzodiazepines for urgent sedation.
- Research was conducted in applied settings; that is, involving in-patients in psychiatric wards and admissions to (generally, psychiatric) emergency departments. No studies in the wider community met conditions for inclusion in the review. The applicability of the research considered here to mentally disordered people in the community is limited, given variations in the experience of staff with urgent sedation practices in that setting. However, the range of illness represented in the community is likely to be comparable to patients recruited through emergency departments in studies reviewed here.
- From the appraisal of 12 research papers reporting on randomised controlled trials in psychiatric and emergency room settings, drug treatments for urgent sedation appear to be both effective and reasonably safe.
- The limitations of the small research base make it difficult to make robust conclusions about relative effectiveness of particular drugs in applied settings. Comparisons between particular drug regimens suggest no conclusive benefit in terms of *effectiveness* of one antipsychotic over another, antipsychotics over benzodiazepines, or combination drugs (of antipsychotics, benzodiazepines and hypnosedatives) over single drug regimens. There is some evidence to suggest that droperidol has a shorter latency of onset whilst offering comparable effectiveness and safety profile to alternative antipsychotics which may be of advantage for urgent sedation.
- There is currently limited availability of drugs for urgent sedation in New Zealand, particularly those available intra-muscularly. Of those included in studies appraised in this review, only haloperidol, droperidol, loxapine (oral administration), lorazepam (oral), thiothixene (oral) and phenobarbital sodium are currently available in New Zealand. Moreover, the benzodiazepine clonazepam is only available for oral or intravenous administration.
- No studies were appraised which considered valproate or atypical antipsychotics and therefore their potential effectiveness for urgent sedation cannot be commented on.
- Side effects were extremely rare in the hours shortly following initial drug administration and urgent sedation appears to be reasonably safe. Given small sample sizes and the shortness of follow-up there was limited scope for conclusive research into the longer-term safety of the drugs considered for urgent sedation in real-world settings. There was some evidence for fewer extrapyramidal side effects occurring after the administration of a benzodiazepine (lorazepam) compared with administering an antipsychotic (haloperidol or clothiapine), and for fewer side effects after treatment with a combined antipsychotic and benzodiazepine regimen (haloperidol and lorazepam) than for an antipsychotic (haloperidol) alone.
- These conclusions are broadly consistent with a systematic review of the management of imminent violence by adult users of mental health services conducted by Wing and colleagues (1998), based on research published between 1980 and 1997.

- High quality, randomised controlled trials are required investigating the utility of available drugs for urgent sedation (including atypical antipsychotics), employing larger samples, situated in community settings, and systematically manipulating dosage and frequency of drug administration.

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List of abbreviations and acronyms

ANOVA	—	Analysis of Variance
ANCOVA	—	Analysis of Co-variance
Cinahl	—	Cumulative Index to Nursing and Allied Health Literature
DAO	—	Duly Authorised Officer
ED	—	Emergency Department
EPS	—	extrapyramidal side effects
IM	—	intramuscular (route of administration of drug)
MOH	—	Ministry of Health (NZ)
NHS	—	National Health Service (UK)
NZHTA	—	New Zealand Health Technology Assessment (The Clearing House for Health Outcomes and Health Technology Assessment)
PO	—	oral (route of administration of drug)
PRN	—	as needed (from Latin translation)
RCT	—	randomised controlled trial
RR	—	relative risk

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Glossary

Akathisia A condition of motor restlessness in which there is a feeling of muscular quivering, an urge to move about constantly, and an inability to sit still often exhibited as pacing or rocking. Often accompanied by sensations of muscular discomfort, dysphoria and agitation.

Analysis of variance (ANOVA) A statistical analysis involving the comparison of variance reflecting different sources of variability.

Bias Deviation of results or inferences from the truth, or processes leading to such deviation.

Blinded study A study in which observers and/or subjects are kept ignorant of the group/intervention to which they are assigned.

Cohort study The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed in different degrees, to a factor or factors (e.g. receiving a screening test for cervical cancer) hypothesised to influence the probability of occurrence of a given disease or other outcome (e.g. positive biopsy). Studies usually involve the observation of a large population, for a prolonged period (years), or both.

Confounder A third variable that indirectly distorts the relationship between two other variables, because it is independently associated with each of the variables.

Dysarthia Impaired articulation of speech due to disturbances of muscular control.

Dystonia Prolonged and unintentional muscular contractions of voluntary or involuntary muscles. It most often affects the large axial muscles of the trunk and limb girdles.

Erythemia Redness of the skin produced by congestion of the capillaries.

Extrapyramidal side effects (EPS) Primarily neurological adverse events involving voluntary and involuntary musculature, including dystonias, parkinsonism, and akathisia.

Hypertension Abnormally high blood pressure.

Hypotension Abnormally low blood pressure.

Meta-analysis Any systematic method that uses statistical analysis to integrate the data from a number of independent studies.

Neuroleptic malignant syndrome Major acute side effect of antipsychotics (neuroleptics) characterised by severe muscular rigidity, fever, an altered level of consciousness, and an autonomic instability.

Parenteral Administering a medication by injection through a route other than by alimentary canal (e.g. intramuscularly or intravenously).

Parkinsonism A group of neurological disorders characterised by hypokinesia, tremor, and muscular rigidity. Antipsychotic induced parkinsonism is generally characterised by the triad of resting tremor, muscular rigidity, and bradykinesia (manifested as a mask-like facial expression or reduction of accessory limb movement or as a problem of initiating movements). Other side effects include slowed cognition, worsening of negative symptoms, shuffling gait, and excessive salivation.

Polypharmacy The administration of two or more drugs together.

Randomised controlled trial An epidemiologic experiment in which subjects in a population are randomly allocated into groups to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre or intervention. The groups are compared prospectively. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology.

Selection bias Error due to systematic differences in characteristics between those who are selected for inclusion in a study and those who are not (or between those compared within a study and those who are not).

Systematic review Literature review reporting a systematic method to search for, identify and appraise a number of independent studies.

Tachycardia Excessive rapidity in the action of the heart; the term is usually applied to a heart rate of above 100 beats per minute.

This glossary was prepared with reference to various sources (Dorland, 1994; Kamin et al., 2000; Last, 1995; New Zealand Ministry of Health, 2000).

Appendix 1

SEARCH STRATEGIES 1995-2000

Medline

1 (psychiatric adj3 emergenc:).mp. (1044)
2 (chemical: adj3 restrain:).mp. (187)
3 ((rapid: or acute or short-acting or fast-acting or emergenc:) adj3 (sedat: or tranquil:)).mp. (538)
4 emergency services, psychiatric/ (1017)
5 or/1-4 (2241)
6 animal/ (3053817)
7 5 not 6 (2041)
8 limit 7 to english (1543)
9 limit 8 to yr=1995-2000 (479)
10 haloperidol/ (10859)
11 droperidol/ (1515)
12 lorazepam/ (1606)
13 flunitrazepam/ (2199)
14 clonazepam/ (1555)
15 midazolam/ (3051)
16 exp diazepam/ (13846)
17 exp benzodiazepines/ (36050)
18 exp benzodiazepinones/ (26378)
19 exp loxapine/ (456)
20 exp antipsychotic agents/ (61861)
21 or/10-20 (95109)
22 emergenc:.mp. (88692)
23 emergency service, hospital/ (12663)
24 22 or 23 (88692)
25 21 and 24 (929)
26 limit 25 to english (755)
27 limit 26 to yr=1995-2000 (284)
28 27 not 6 (255)
29 (acute: adj2 (agitat: or psycho:)).mp. (2819)
30 29 and 21 (599)
31 30 not 6 (584)
32 limit 31 to english (469)
33 limit 32 to yr=1995-2000 (100)
34 33 or 28 or 9 (760)
35 from 34 keep (SELECTION OF ARTICLES)
36 from 34 keep (SELECTION OF ARTICLES)
37 from 36 keep (SELECTION OF ARTICLES)
38 from 36 keep (SELECTION OF ARTICLES)
39 from 38 keep (SELECTION OF ARTICLES)
40 35 or 37 or 39 (SELECTION OF ARTICLES)
41 from 40 keep (SELECTION OF ARTICLES)
42 from 41 keep (SELECTION OF ARTICLES)
43 ((acute: adj distress:) or (acute adj psycho:) or acute mania).mp. (1243)
44 21 and 43 (289)
45 (acute: adj agitat:).mp. (37)
46 44 or 45 (325)
47 (rapid: or quick-acting or short-acting or fast-acting).mp.
48 (distress: or agitat: or mania).mp. (33528)
49 47 and 48 (1682)
50 21 and 49 (134)

51 (sedat: or tranquil:).mp. (29780)
52 48 and 51 (662)
53 48 and 51 and 47 (93)
54 psycho:.mp. (267304)
55 47 and 54 and 21 (521)
56 46 or 50 or 53 or 55 (898)
57 limit 56 to english (783)
58 limit 57 to yr=1995-2000 (226)
59 58 not 34 (151)
60 21 and 51 and 47 (578)
61 ((rapid or quick or fast or short) adj2 onset).mp. (4240)
62 61 and 21 (227)
63 60 or 62 (729)
64 56 or 63 (1395)
65 limit 64 to english (1213)
66 limit 65 to yr=1995-2000 (341)
67 66 not 34 (250)
68 67 not 6 (190)
69 from 68 keep (SELECTION OF ARTICLES)

Embase

1 emergency medicine/
2 emergency health service/
3 emergency treatment/
4 emergenc:.ti.
5 (chemical: adj restrain:).mp.
6 ((rapid: or short or fast or quick) adj3 (acting or onset)).mp.
7 (sedat: or tranquil:).mp.
8 (agitat: or aggress: or distress: or acute psycho:).mp.
9 (rapid: or quick or fast or short).mp.
10 or/1-4
11 and 10
12 and 7
13 and 9
14 13 and 8
15 and 8
16 8 and 10
17 or 12 or 14 or 15 or 16
18 limit 17 to english
19 limit 18 to yr=1995-2000
20 haloperidol/
21 droperidol/
22 flunitrazepam/
23 lorazepam/
24 clonazepam/
25 midazolam/
26 benzodiazepines/
27 benzodiazepinones/
28 loxapine/
29 diazepam/
30 exp neuroleptic agent/
31 or/20-30
32 31 and 10
33 31 and 13
34 31 and 8 and 7
35 31 and 8 and 9
36 or/32-35
37 limit 36 to english
38 limit 37 to yr=1995-2000

39 human/
40 38 and 39
41 (anesthesia or surgical procedure: or imaging).mp.
42 insomnia.mp.
43 41 or 42
44 40 not 43
45 from 44 keep (SELECTION OF ARTICLES)

International Pharmaceutical Abstracts

1 (chemical: adj restrain:).mp. (9)
2 ((rapid: or short or fast or quick) adj3 (acting or onset)).mp.
3 (rapid: or short or fast or quick).mp. (14419)
4 (sedat: or tranquil:).mp. (8820)
5 3 and 4 (736)
6 tranquilizers.mp.
7 2 and 6 (17)
8 emergenc:.mp.
9 6 and 8 (26)
10 (agitat: or aggress: or distress: or acute psycho:).mp. (2067)
11 6 and 10 (128)
12 haloperidol/ (573)
13 droperidol/ (104)
14 lorazepam/ (452)
15 flunitrazepam/ (117)
16 clonazepam/ (221)
17 midazolam/ (321)
18 benzodiazepines/ (1111)
19 benzodiazepinones/ (0)
20 loxapine/ (47)
21 antipsychotic agents/ (590)
22 or/12-21 (3201)
23 22 and 10 (159)
24 22 and 8 (55)
25 22 and 5 (168)
26 2 and 22 (37)
27 1 or 5 or 7 or 9 or 23 or 24 or 25 or 26 (953)
28 limit 27 to yr=1995-2000 (159)
29 limit 28 to english (147)
30 from 29 keep (SELECTION OF ARTICLES)

Psychinfo

1 (chemical: adj restrain:).mp. (38)
2 ((rapid: or short or fast or quick) adj3 (acting or onset)).mp.
3 (rapid: or short or fast or quick).mp. (56166)
4 (sedat: or tranquil:).mp. (6762)
5 3 and 4 (580)
6 tranquilizers.mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers](1132)
7 2 and 6 (8)
8 emergenc:.mp.
9 6 and 8 (26)
10 (agitat: or aggress: or distress: or acute psycho:).mp.
11 6 and 10 (66)
12 haloperidol/ (3011)
13 droperidol/ (0)
14 lorazepam/ (330)
15 flunitrazepam/ (0)
16 clonazepam/ (157)
17 midazolam/ (203)
18 benzodiazepines/ (2690)

19 benzodiazepinones/ (0)
20 loxapine/ (49)
21 antipsychotic agents/ (0)
22 or/12-21 (6300)
23 22 and 10 (372)
24 22 and 8 (62)
25 22 and 5 (102)
26 2 and 22 (94)
27 1 or 5 or 7 or 9 or 23 or 24 or 25 or 26 (1101)
28 limit 27 to yr=1995-2000 (274)
29 limit 28 to english (266)
30 emergency services/ or crisis intervention services/ (2032)
31 exp neuroleptic drugs/ (8879)
32 exp neuroleptic drugs/ (8879)
33 droperidol.mp. (63)
34 flunitrazepam.mp. (234)
35 22 or 31 or 33 or 34 (14335)
36 30 and 35 (26)
37 35 and 10 (839)
38 35 and 8 (165)
39 35 and 5 (157)
40 5 and 30 (11)
41 or/36-40 (1105)
42 limit 41 to english (985)
43 limit 42 to yr=1995-2000 (396)
44 43 or 29 (513)
45 from 44 keep (SELECTION OF ARTICLES)

Cinahl

1 (psychiatric adj3 emergenc:).mp. (127)
2 (chemical: adj3 restrain:).mp. (47)
3 ((rapid: or acute or short-acting or fast-acting or emergenc:) adj3 (sedat: or tranquil:)).mp. (44)
4 haloperidol/ (86)
5 droperidol/ (33)
6 lorazepam/ (42)
7 flunitrazepam/ (5)
8 clonazepam/ (13)
9 midazolam/ (190)
10 exp diazepam/ (89)
11 exp benzodiazepines/ (645)
12 exp antipsychotic agents/ (694)
13 emergenc:.mp. (17000)
14 (acute: adj2 (agitat: or psycho:)).mp. (112)
15 (psychiatr: adj2 emergenc:).mp. (214)
16 emergency care/ or emergency service/ (6312)
17 or/1-3 (217)
18 or/4-12 (1291)
19 or/13-16 (17096)
20 18 and 19 (93)
21 17 or 20 (300)
22 limit 21 to yr=1995-2000 (180)
23 limit 22 to english (177)
24 from 23 keep (SELECTION OF ARTICLES)
25 from 24 keep (SELECTION OF ARTICLES)
26 from 25 (SELECTION OF ARTICLES)(45)
27 ((fast or quick or rapid) adj onset).mp. (56)
28 acute mania.mp. (1)
29 27 or 28 (57)
30 from 29 keep 12 (1)

31 from 30 keep 1 (1)
32 26 or 31 (45)
33 (rapid: or fast acting or short acting or emergenc:).mp.
34 18 and 33 (121)
35 34 not 21 (29)
36 from 35 keep 16, 19 (2)
37 32 or 36 (47)

Current Contents

1 ((rapid or quick or fast) adj (onset or acting)).mp. [mp=abstract, title, author keywords, keywords plus]
2 (sedat: or tranquil:).mp. [mp=abstract, title, author keywords, keywords plus]
3 1 and 2
4 from 3 keep 10
5 (chemical: adj3 restrain:).mp. [mp=abstract, title, author keywords, keywords plus]
6 from 5 keep (SELECTION OF ARTICLES)
7 (psychiatr: and emergenc:).mp. and 2 [mp=abstract, title, author keywords, keywords plus]
8 from 7 keep (SELECTION OF ARTICLES)
9 (agitat: or distress: or aggressi:).mp. [mp=abstract, title, author keywords, keywords plus]
10 2 and 9
11 3 or 5 or 7
12 10 not 11
13 limit 12 to english
14 from 13 keep (SELECTION OF ARTICLES)
15 4 or 6 or 8 or 14
16 emergenc:.mp. [mp=abstract, title, author keywords, keywords plus]
17 2 and 16
18 limit 17 to english
19 11 or 13
20 18 not 19
21 from 20 keep (SELECTION OF ARTICLES)
22 (haloperiodol or droperidol or lorazepam or flunitrazepam or clonazepam).mp. [mp=abstract, title, author keywords, keywords plus]
23 (diazepam or midazolam or loxapine or benzodiazepine: or benzodiazepinones or antipsychotic:).mp. [mp=abstract, title, author keywords, keywords plus]
24 22 or 23
25 and 2
26 rapid.mp. [mp=abstract, title, author keywords, keywords plus]
27 25 and 26
28 (((quick or fast or short) adj onset) or acting).mp. [mp=abstract, title, author keywords, keywords plus]
29 25 and 28
30 27 or 29
31 limit 30 to english
32 not 19
33 not 20
34 from 33 keep (SELECTION OF ARTICLES) or 8 or 14 or 21 or 34

Healthstar

1 (psychiatric adj3 emergenc:).mp. (881)
2 (chemical: adj3 restrain:).mp. (74)
3 ((rapid: or acute or short-acting or fast-acting or emergenc:) adj3 (sedat: or tranquil:)).mp. (318)
4 emergency services, psychiatric/ (1101)
5 or/1-4 (1809)
6 animal/ (141514)
7 5 not 6 (1799)
8 limit 7 to english (1404)
9 limit 8 to yr=1995-2000 (462)
10 haloperidol/ (1759)

11 droperidol/ (561)
12 lorazepam/ (820)
13 flunitrazepam/ (447)
14 clonazepam/ (403)
15 midazolam/ (1735)
16 exp diazepam/ (2961)
17 exp benzodiazepines/ (10068)
18 exp benzodiazepinones/ (6474)
19 exp loxapine/ (170)
20 exp antipsychotic agents/ (12826)
21 or/10-20 (22066)
22 emergenc:.mp. (68480)
23 emergency service, hospital/ (12918)
24 22 or 23 (68480)
25 21 and 24 (542)
26 limit 25 to english (450)
27 limit 26 to yr=1995-2000 (202)
28 27 not 6 (200)
29 (acute: adj2 (agitat: or psycho:)).mp. (1806)
30 29 and 21 (413)
31 30 not 6 (411)
32 limit 31 to english (341)
33 limit 32 to yr=1995-2000 (78)
34 33 or 28 or 9 (672)
35 ((acute: adj distress:) or (acute adj psycho:) or acute mania).mp. (777)
36 21 and 35 (201)
37 (acute: adj agitat:).mp. (24)
38 36 or 37 (224)
39 (rapid: or quick-acting or short-acting or fast-acting).mp.
40 (distress: or agitat: or mania).mp. (21147)
41 39 and 40 (959)
42 21 and 41 (102)
43 (sedat: or tranquil:).mp. (11339)
44 40 and 43 (448)
45 40 and 43 and 39 (75)
46 psycho:.mp. (151916)
47 39 and 46 and 21 (310)
48 38 or 42 or 45 or 47 (562)
49 limit 48 to english (503)
50 21 and 43 and 39 (306)
51 ((rapid or quick or fast or short) adj2 onset).mp. (1470)
52 51 and 21 (108)
53 50 or 52 (369)
54 48 or 53 (782)
55 limit 54 to english (687)
56 limit 55 to yr=1995-2000 (232)
57 56 not 34 (159)
58 57 not 6 (153)
59 34 or 49 or 53 (1334)
60 limit 59 to nonmedline (25)
61 from 60 keep (SELECTION OFARTICLES)

Combined (cross-database) follow-up searches of Medline, Embase, IPA, Cinahl, Psychinfo

1 (pharmacologic: adj restrain:).mp. (25)
2 from 1 keep 7,15,17-18 (4)
3 (acut: adj agitat:).mp. (115)
4 limit 3 to english (104)
5 from 4 keep (SELECTION OF ARTICLES)

6 remove duplicates from 5 (33)
7 (acute adj episode).mp. (1808)
8 acute mania.mp. (624)
9 acute delirium.mp. (151
10 or/7-9 (2581)
11 remove duplicates from 10 (1719)
12 limit 11 to yr=1995-2000 (644)
13 limit 12 to english (482)
14 (dement: or alzheimer:).mp. (109224)
15 13 not 14 (478)
16 15 not (1 or 3) (478)
17 from 16 keep (SELECTION OF ARTICLES) (15)
18 6 or 17 (48)
19 limit 18 to yr=1995-2000 (24)
20 from 19 keep (SELECTION OF ARTICLES)
21 from 19 keep (SELECTION OF ARTICLES)
22 exp central nervous system depressants
23 exp anti-anxiety agents
24 22 or 23
25 restrain:.mp.
26 24 and 25
27 remove duplicates from 26
28 limit 27 to yr=1995-2000-12-11
29 28 not 14
30 (rapid: or fast acting or short acting or emergenc:).mp.
31 ((fast or quick or rapid) adj onset).mp.
32 30 or 31
33 24 and 32
34 31 and 26
35 (fast acting or short acting).mp.
36 35 and 26
37 (rapid: or emergenc:).mp.
38 26 and 37
39 24 and 35
40 24 and 37
41 (mental: or psychiatr: or psycho:).tw.
42 (39 or 40) and 41
43 limit 42 to yr=1995-2000
44 43 not 16
45 44 not 14
46 from 45 keep 1-400
47 remove duplicates from 46
48 from 45 keep 401-882
49 remove duplicates from 48
50 34 or 36 or 38 or 47 or 49
51 limit 50 to yr=1995-2000
52 from 51 keep 1-500
53 remove duplicates from 52
54 from 51 keep 501-874
55 remove duplicates from 54
56 53 or 55
57 limit 56 to english
58 from 57 keep (SELECTED ARTICLES)

Cochrane Library

1 (((RAPID or QUICK) or FAST) or SHORT)
2 (TRANQUIL* or SEDAT*)
(#1 and #2)
3 #3

4 (CHEMICAL and RESTRAIN)
5 (CHEMICAL* and RESTRAIN*)
6 (PSYCHIATR* and EMERGENC*)
7 (#7 not #3)
8 #8
9 ((AGITAT* or DISTRESS*) or PSYCHO*)
10 EMERGENC*
11 (#10 and #11)
12 #12
13 (#8 or #4)
14 (#13 not #14)
15 HALOPERIDOL*:ME
16 DROPERIDOL*:ME
17 LORAZEPAM*:ME
18 FLUNITRAZEPAM*:ME
19 CLONAZEPAM*:ME
20 MIDAZOLAM*:ME
21 DIAZEPAM*:ME
22 BENZODIAZEPINES*:ME
23 BENZODIAZEPINONES*:ME
24 LOXAPINE*:ME
25 ANTIPSYCHOTIC-AGENTS*:ME
26 (((((#16 or #17) or #18) or #19) or #20) or #21)
27 (((((#22 or #23) or #24) or #25) or #25) or #26)
28 (#27 or #28)
29 #29 AND ##3
30 (#29 and #3)
31 (#29 and #10)
32 (#29 and #11)
33 ((AGITAT* or AGGRESSI*) or DISTRESS*)
34 (#29 and #34)
((#31 or #33) or #35)

SEARCH STRATEGIES 1980-1994

A second series of searches using the above strategies were undertaken looking at the literature from 1980-1994. These searches were limited to randomised controlled trials (subject heading or publication type) or controlled clinical trials (subject heading of publication type). Additionally, articles were excluded if any of the following words appeared in the **title**:

> Dementia, elderly, aged, epilepsy, seizure, status epilepticus, anesthetic, anaesthetic, surgical procedure*, mental retard*, brain injur*, alcohol withdrawal

SEARCHES FROM OTHER SOURCES

In databases and all other sources without controlled vocabulary combinations of the index terms and additional keywords from the above strategies were used in the search.

Appendix 2

SOURCES SEARCHED

Bibliographic databases

Medline

Embase

International Pharmaceutical Abstracts

Cinahl

Healthstar

Psychinfo

Science Citation Index

Social Science Citation Index

Current Contents

Index New Zealand

Review databases

Cochrane Library

Best Evidence

Database of Abstracts of Reviews of Effectiveness

NHS Economic Evaluation database

Health Technology Assessment database

Evidence-based collections

TRIP - Turning Research into Practice (University of Wales College of Medicine)

US National Guidelines Clearing House

Scottish Intercollegiate Guidelines Network

Canadian Medical Association guidelines

E-BMJ resources

US Agency for Health Research Quality

OMNI - Organised Medical Networked Information (University of Manchester)

Primary Care Clinical Practice Guidelines (University of San Francisco)

Professional colleges/associations

American Psychiatric Association

American Academy of Child & Adolescent Psychiatry

Australasian College of Psychiatrists

University of Oxford Department of Psychiatry

Maudsley Hospital (UK)

Royal College of Psychiatry (UK)

American College of Emergency Physicians

Australasian College for Emergency Medicine

British Association of Accident & Emergency Medicine

Canadian Association of Emergency Physicians

International Association of Emergency Psychiatry

Government/state websites

Australian Department of Health & Family Services

Australian state health departments (ACT, New South Wales, Northern Territory, Queensland, South Australia, Tasmania, Victoria, West Australia)

Canadian provincial health departments (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland/Labrador, NW Territories, Nova Scotia, Ontario, Prince Edward Island, Quebec, Saskatchewan, Yukon)

Health Canada

New Zealand Ministry of Health

US National Institute of Mental Health

New Zealand Mental Health Commission

Other websites

Current Controlled Trials

Controlled Trials.gov

NZ Mental Health Foundation

US Center for Mental Health Services

British Library OPAC - reports and monographs section

US National Library of Medicine

NZ bibliographic database

Search engines

Searchnz

Copernic 2000 (meta-search engine)

Google

Appendix 3

RETRIEVED STUDIES EXCLUDED FOR REVIEW

Ainsworth, C., & Catts, S. V. (1997). A rapid tranquillization protocol. *Schizophrenia Research*, 24, 204.

Anonymous (1992). Droperidol vs haloperidol for agitation. *Nurses Drug Alert*, 16, 53.

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Edwards, R., Stephenson, U., & Flewett, T. (1991). Clonazepam in acute mania: a double blind trial. *Australian & New Zealand Journal of Psychiatry*, 25, 238-42.

Fenton, M., Bowers, L., Jones, J., Lakeman, R., & Morrison, E. (2000). Containment strategies for those with serious mental illness (protocol for a Cochrane review). *Cochrane Library*, Issue 3.

Herrera, J. N., Sramek, J. J., Costa, J. F., Roy, S., Heh, C. W., & Nguyen, B. N. (1988). High potency neuroleptics and violence in schizophrenics. *Journal of Nervous and Mental Disease*, 176, 558-61.

Hogan, T. P., & Awad, A. G. (1992). Subjective response to neuroleptics and outcome in schizophrenia: a re-examination comparing two measures. *Psychological Medicine*, 22, 347-52.

Janicak, P. G., Bresnahan, D. B., Sharma, R., Davis, J. M., Comaty, J. E., & Malinick, C. (1988). A comparison of thiothixene with chlorpromazine in the treatment of mania. *Journal of Clinical Psychopharmacology*, 8, 33-7.

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Kelwala, S., Ban, T. A., Berney, S. A., & Wilson, W. H. (1984). Rapid tranquilization: a comparative study of thiothixene and haloperidol. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 8, 77-83.

Martucci, N., Manna, V., & Agnoli, A. (1987). A clinical and neurophysiological evaluation of clotiazepam, a new thienodiazepine derivative. *International Clinical Psychopharmacology*, 2, 121-8.

McGowan, W. A., Dundee, J. W., Clarke, R. S., & Howard, P. J. (1980). Comparison of the subjective effects and plasma concentrations following oral and i.m. administration of flunitrazepam in patients. *British Journal of Anaesthesia*, 52, 447-51.

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Sailas, E., & Fenton, M. (2000). Seclusion and restraint for people with serious mental illnesses (Cochrane review). *Cochrane Library*, Issue 3.

Shields, J. R., Hovey, J. K., & Fuller, S. S. (1980). A comparison of physostigmine and meperidine in treating emergence excitement. *MCN, American Journal of Maternal Child Nursing*, 5, 170-5.

Stanislav, S. W., & Childs, A. (2000). Evaluating the usage of droperidol in acutely agitated persons with brain injury. *Brain Injury*, 14, 261-5.

Wyant, M., Diamond, B. I., O'Neal, E., Sloan, A., & Borison, R. L. (1990). The use of midazolam in acutely agitated psychiatric patients. *Psychopharmacology Bulletin*, 26, 126-9.

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