

Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine

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ABSTRACT

Objective To determine whether haloperidol alone results in swifter and safer tranquillisation and sedation than haloperidol plus promethazine.

Design Pragmatic randomised open trial (January-July 2004).

Setting Psychiatric emergency room, Rio de Janeiro, Brazil.

Participants 316 patients who needed urgent intramuscular sedation because of agitation, dangerous behaviour, or both.

Interventions Open treatment with intramuscular haloperidol 5-10 mg or intramuscular haloperidol 5-10 mg plus intramuscular promethazine up to 50 mg; doses were at the discretion of the prescribing clinician.

Main outcome measures The primary outcome was proportion tranquil or asleep by 20 minutes. Secondary outcomes were asleep by 20 minutes; tranquil or asleep by 40, 60, and 120 minutes; physically restrained or given additional drugs within 2 hours; severe adverse events; another episode of agitation or aggression; additional visit from the doctor during the subsequent 24 hours; overall antipsychotic load in the first 24 hours; and still in hospital after 2 weeks.

Results Primary outcome data were available for 311 (98.4%) people, 77% of whom were thought to have a psychotic illness. Patients allocated haloperidol plus promethazine were more likely to be tranquil or asleep by 20 minutes than those who received intramuscular haloperidol alone (relative risk 1.30, 95% confidence interval 1.10 to 1.55; number needed to treat 6, 95% confidence interval 4 to 16; $P=0.002$). No differences were found after 20 minutes. However, 10 cases of acute dystonia occurred, all in the haloperidol alone group.

Conclusions Haloperidol plus promethazine is a better option than haloperidol alone in terms of speed of onset of action and safety. Enough data are now available to change guidelines that continue to recommend treatments that leave people exposed to longer periods of aggression than necessary and patients vulnerable to distressing and unsafe adverse effects.

Trial registration Current Controlled Trials
ISRCTN83261243.

INTRODUCTION

Agitated and violent behaviour can occur in many different clinical settings. It arises in 10% of psychiatric emergencies and is most commonly associated with psychosis or substance misuse.^{1,2} For control of the acute phase, guidelines in the United States and United Kingdom recommend the use of intramuscular haloperidol, lorazepam, both combined, or olanzapine.^{3,4} However, little information on comparative effectiveness or safety is available. Some people consider it prudent to routinely combine haloperidol with an anticholinergic agent or an antihistamine such as promethazine,^{4,6} although this is not specifically recommended in the guidelines.

The above drugs, with the exception of intramuscular olanzapine, are potentially accessible in low and middle income countries,⁷ and they are relatively inexpensive. Haloperidol alone, or the combination of haloperidol with lorazepam, is commonly and widely used.^{5,8,9} In Brazil and India, however, many people consider it standard practice to add promethazine to haloperidol.¹⁰ Promethazine is a sedative antihistamine with anticholinergic properties.

To date, although four randomised trials have compared lorazepam with haloperidol (total $n=223$), only two report relevant data (total $n=90$; relative risk not sedated by four hours 1.00, 95% confidence interval 0.44 to 2.23).¹¹ One trial compared lorazepam with haloperidol plus promethazine ($n=200$, relative risk not tranquil/asleep by 30 minutes 0.26, 0.10 to 0.68).¹² The combination of lorazepam plus haloperidol has been compared with haloperidol alone in only one randomised trial ($n=67$, relative risk needing additional injection by four hours 0.95, 0.79 to 1.15).¹¹ Olanzapine has been compared with haloperidol twice ($n=482$, relative risk no response by two hours 1.00, 0.73 to 1.38) and with lorazepam twice ($n=355$, relative risk no response by two hours 0.92, 0.66 to 1.30).¹³ Finally, midazolam has been compared

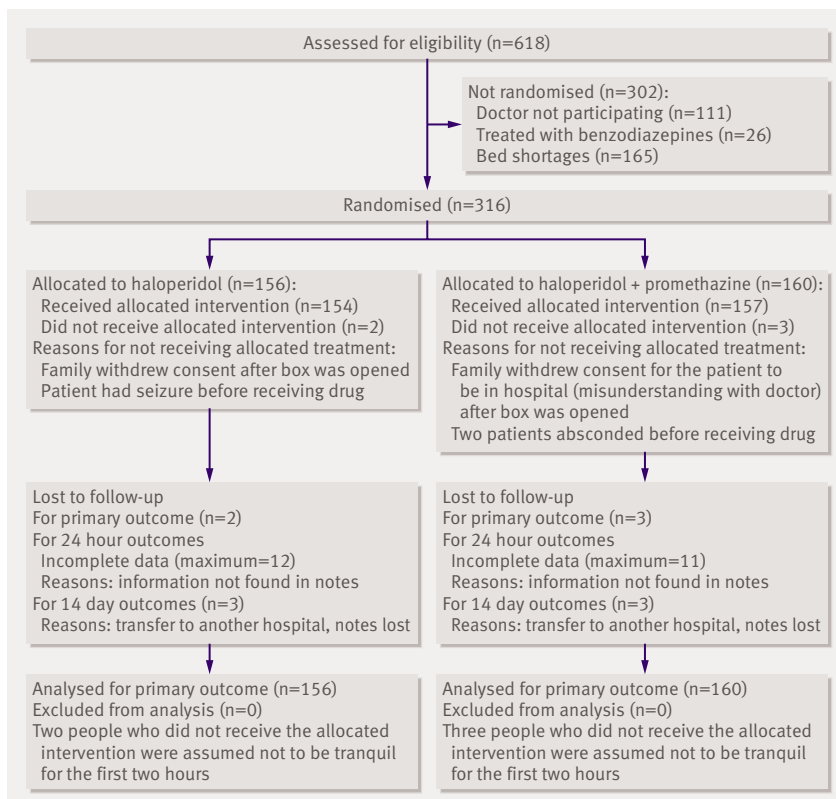
with the haloperidol-promethazine mix once ($n=301$, relative risk not tranquil/asleep by 30 minutes 2.9, 1.75 to 4.8), but respiratory depression is a particular problem with this benzodiazepine.¹⁴ Haloperidol alone was used for the control group in seven trials (279 people).

Our two TREC-I trials,^{10,15} described as “the only large studies of high methodological quality” in the area,⁴ are the only randomised trials that used haloperidol plus promethazine as the control (501 people). (TREC stands for tranquilização rápida-ensaio clínico, translated as rapid tranquillisation-clinical trial.) This combination treatment was both effective and safe in comparison with midazolam or lorazepam but has never been compared head to head with intramuscular haloperidol alone. This study uses similar methods and aimed to determine whether haloperidol alone has any advantage or disadvantage compared with haloperidol plus promethazine for managing agitated/aggressive patients presenting to a psychiatric emergency room.

METHODS

Selection of participants

We did this TREC trial of Rio de Janeiro, Brazil (TREC-Rio-2) in a single public psychiatric hospital (Instituto Municipal Philippe Pinel) with a catchment of approximately 1.5 million people. The busy psychiatric emergency room is open 24 hours a day.



Flow of participants through trial

We designed the trial so that it would not interfere with the routine care of participants—eligibility criteria were simple and data collection was minimised.

Patients were eligible for the trial if they clearly needed acute intramuscular sedation because of agitation, dangerous behaviour, or both and the clinician was not already committed to use the haloperidol plus promethazine mix or haloperidol alone. People were ineligible if the clinician believed that one of the treatment options represented an additional risk for the patient.

Most patients eligible for the study were brought to the hospital by the police without relatives and were not able to give consent. If relatives were present, they were fully informed and their verbal consent requested, required, and recorded. A full explanation of the study was available for participants after the acute episode.

Randomisation and allocation concealment

The UK collaborator (CEA) generated the randomisation sequence, by using MS Excel to randomly generate even numbers of less than 10 for the block size. These blocks were then applied to a table of random numbers. To help to ensure concealment of allocation, CEA sent a list of the allocation sequence without the block size to a Brazilian colleague, who packed trial boxes independently of the trial team. Boxes were consecutively numbered, sealed, opaque, and identical in appearance and weight; on the outside was a form with questions to be completed by the attending doctor while “blind” to the contents of the box. As well as the interventions determined by the randomisation list (see below), the boxes contained one disposable syringe and needle and study follow-up forms. No-one with clinical involvement in the study had any indication of what drugs were in the boxes until they were opened.

Interventions

We compared open giving of haloperidol alone with the standard treatment of haloperidol plus intramuscular promethazine. Doses of the drugs were at the doctor’s discretion. Interventions were supplied as either two ampoules of haloperidol 5 mg or two ampoules of haloperidol 5 mg plus one of promethazine 50 mg.

Procedures

When a person met the eligibility criteria, the clinician took the next consecutive box and, before opening the trial box, still blind to the allocated treatment, completed a form printed on its top. The form recorded the doctor’s assessment of the severity and cause of the episode. This constituted trial entry. The number and contents of the box were recorded and emailed to the UK for verification of the sequence of allocation.

Once the form on the outside of the box was completed, the doctor opened the box, gave the drug, and set a timer to ring every 20 minutes for the first hour. Once the rating of the severity of the episode was

complete, the TREC boxes were opened and treatment thereafter was not blind. When the clock rang, the attending nurse, who was not necessarily blind to the intervention, assessed outcome. A TREC collaborator who was not involved in randomisation or assessment of the main outcome extracted other data from the patient's notes. We checked the severity of episode at trial entry for a randomly selected sample of 42 (13%) patients and the accuracy of assessment of primary outcome in another randomly selected sample of 68 (22%) patients, by using a rater who was blind to treatment allocation and who used a stopwatch to access time to tranquillisation/sedation.

Outcomes

In our previous study,¹⁵ clinicians in the emergency room chose "tranquillisation or asleep by 20 minutes" as the primary outcome. Although time to tranquillisation/sedation would also have been of interest, this was primarily of concern to researchers and not to frontline clinicians, and this outcome would have added complexity to the pragmatic design that had already been successful. People were considered to be tranquillised when they were felt to be calm and peaceful—that is, neither agitated nor restless and not displaying threatening verbal behaviour or physical aggression against objects, other people, or themselves. Secondary outcomes were as follows: asleep by 20 minutes; tranquil or asleep by 40, 60, and 120 minutes; physically restrained or given additional drugs within two hours; severe adverse events as defined by the frontline clinicians; another episode of agitation/aggression; needing additional visits from

the doctor during the subsequent 24 hours; overall antipsychotic load in the first 24 hours; and still in hospital after two weeks. We decided against using rating scales, as these were not requested by clinicians, would have devalued the real world ethos of the trial, and are difficult to interpret.

Sample size

We estimated that 67% of people would be expected to be tranquillised 20 minutes after receiving the haloperidol plus promethazine.¹⁵ Therefore, to detect a relative difference of at least 20% between haloperidol alone and the haloperidol-promethazine mix, at 5% level of significance (α error) and 80% power, we needed to randomise 650 patients. Emergency room clinicians chose the absolute difference of at least 20% as the difference that would cause them to change practice.

Statistical analysis

We compared sociodemographic and clinical characteristics between groups at trial entry. For primary and secondary outcomes, we used intention to treat analysis to calculate relative risk, risk difference, and number needed to treat and their 95% confidence intervals. We used the Mantel-Haenszel method when relative risk needed to be adjusted by a single factor and κ statistics for estimating inter-rater agreement for the primary outcome and severity of episode. We entered data in Epi-Info 6.04 and analysed them with SPSS12.0.

Data and safety monitoring

We planned an interim analysis when 300 participants had been recruited and presented the results in confidence to the Data Monitoring Committee. Reasons for stopping the trial were based on effectiveness and adverse effects.¹⁶ When this multiple testing procedure was used with $\alpha=0.05$, $P\leq 0.006$ was needed for the committee to advise the Steering Group to stop the study.

RESULTS

Recruitment was from 6 January 2004 to 1 July 2004. After seeing the results of the interim analysis, the Data Monitoring Committee advised that the study should be stopped. During this period, 6433 people attended the emergency room. Of these, 618 presented some degree of violent behaviour and, when collaborating doctors were in attendance 100% (316) were randomised—160 to haloperidol plus promethazine and 156 to haloperidol alone (figure). All boxes were opened in consecutive order. People randomised were similar to those who were not in terms of age (mean 40.1 years randomised, 39.8 years not randomised) and sex (53.8% men randomised, 54.0% men not randomised). Most recruitment (87%) was between 6 00 am and 10 00 pm, and primary outcome data were available for 311 (98.4%) participants.

Table 1 | Characteristics of participants by treatment group. Values are numbers (percentages) unless stated otherwise

Characteristic	Haloperidol group (n=156)	Haloperidol plus promethazine group (n=160)
Male sex	75 (48)	95 (59)
Severity:		
Moderate	50 (32)	62 (39)
Intense	82 (53)	73 (46)
Extreme	24 (15)	25 (16)
Cause:		
Psychosis	125 (80)	119 (74)
Substance misuse	25 (16)	33 (21)
No information	3 (2)	0
Others	3 (2)	8 (5)
First attendance:		
Yes	33 (21)	26 (16)
No	104 (67)	120 (75)
No information	19 (12)	14 (9)
Mean (SD) age (years)	39.3 (13.1)	40.2 (12.7)
Did not receive allocated treatment	2 (1)	3 (2)
Dose of drug:		
Haloperidol 5 mg	44 (28)	80 (50)
Haloperidol 10 mg	109 (70)	79 (50)
Promethazine 25 mg	0	8 (5)
Promethazine 50 mg	0	150 (94)

Baseline characteristics were similar between the two treatment groups. However, the proportion of men was higher in the haloperidol plus promethazine group (table 1). Behavioural disturbance was rated as intense or extreme for 62% of participants. The underlying cause was thought to be psychosis for 77% of people. Agreement for severity of episode was good (weighted $\kappa=0.85$, 95% confidence interval 0.73 to 0.98).

Five people (two haloperidol alone, three haloperidol plus promethazine) did not receive the allocated intervention (figure). Of people allocated haloperidol alone, 29% received 5 mg and the rest 10 mg, and of those allocated haloperidol plus promethazine, half received 5 mg of haloperidol and the rest 10 mg.

Primary outcome

In absolute terms, 17% (95% confidence interval 6% to 27%) more patients were tranquil or asleep after

20 minutes in the haloperidol plus promethazine group than in the intramuscular haloperidol alone group (relative risk 1.30, 95% confidence interval 1.10 to 1.55; number needed to treat 6, 4 to 16; $P=0.002$) (table 2). Inter-rater agreement on time from injection to tranquillisation or sleep was good ($\kappa=0.83$, 0.67 to 0.99); the biggest disagreement was no more than 16 minutes. We did two post hoc analyses, controlling for sex and dose of haloperidol and using Mantel-Haenszel methods. The relative risk for the primary outcome remained stable in both analyses (relative risk controlling for sex 1.29, 1.08 to 1.53; relative risk for those receiving 5 mg haloperidol 1.31, 0.96 to 1.31; relative risk for those receiving 10 mg haloperidol 1.29, 1.05 to 1.59).

Secondary outcomes

The difference for the outcome of tranquil or asleep at 20 minutes was no longer apparent by 40, 60, and

Table 2 | Main results. Values are numbers (percentages) unless stated otherwise

	Haloperidol plus promethazine group (n=160)	Haloperidol group (n=156)	Relative risk (95% CI)	Difference in risk (95% CI)
By 20 minutes				
Tranquil/asleep (primary outcome)	115 (72)	86 (55)	1.30 (1.10 to 1.55)	16.7 (6.3 to 27.2)
Asleep	31 (19)	13 (8)	2.33 (1.26 to 4.27)	11.0 (3.5 to 18.5)
Unknown	3 (2)	2 (1)		
By 40 minutes				
Tranquil/asleep	129 (81)	118 (76)	1.07 (0.95 to 1.20)	5.0 (-4.1 to 14.1)
Asleep	57 (36)	54 (35)	1.03 (0.76 to 1.39)	1.0 (-9.5 to 11.5)
Unknown	3 (2)	2 (1)		
By 60 minutes				
Tranquil/asleep	139 (87)	127 (81)	1.07 (0.97 to 1.17)	5.5 (-2.6 to 13.5)
Asleep	77 (48)	77 (49)	0.98 (0.78 to 1.22)	-1.2 (-12.3 to 9.8)
Unknown	3 (2)	2 (1)		
By 120 minutes				
Tranquil/asleep	146 (91)	138 (89)	1.03 (0.96 to 1.11)	2.8 (-3.9 to 9.4)
Asleep	97 (61)	94 (60)	1.01 (0.84 to 1.20)	0.4 (-10.4 to 11.2)
No additional tranquillising drugs	152 (95)	143 (92)	1.04 (0.98 to 1.10)	3.3 (-2.2 to 8.8)
Restraints not needed	122 (76)	111 (71)	1.07 (0.94 to 1.22)	5.1 (-4.6 to 14.8)
Unknown	3 (2)	2 (1)		
Within 24 hours				
No other episode of aggression	129 (81)	124 (80)	1.01 (0.91 to 1.13)	1.1 (-7.7 to 10.0)
Unknown	6 (4)	12 (8)		
Doctor not called to see patient	123 (77)	102 (65)	1.18 (1.02 to 1.36)	11.5 (1.7 to 21.4)
Unknown	7 (4)	11 (7)		
Accept oral drugs*	132 (84)	129 (84)	0.97 (0.88 to 1.06)	-3.0 (-10.9 to 4.9)
Unknown	11 (7)	11 (7)		
Mean (SD) chlorpromazine equivalents (mg)	245 (194)	234 (182)	Mann-Whitney U=11885.500; P=0.46	
Serious adverse effect†	1 (1)	11 (7)	0.09 (0.01 to 0.68)	-6.4 (-10.6 to -2.2)
By 2 weeks				
Discharged	62 (39)	73 (47)	0.83 (0.64 to 1.07)	-8.0 (-18.9 to 2.8)
Unknown	3 (2)	3 (2)		

*Two patients in each group excluded as not prescribed oral drugs.
 †Patients with unknown outcome excluded from analysis.

120 minutes (table 2). We found no difference between the interventions for the use of additional tranquillising drugs or use of restraints within the first two hours. For outcomes occurring by 24 hours after injection, we found no differences for another episode of agitation or refusing to take oral medication. Nevertheless, doctors were called more frequently to see patients allocated haloperidol alone than those in the combination treatment group. This may at least in part have been accounted for by attending to people with the acute serious adverse effect of dystonia (table 3), as after these people were removed from the analysis the difference was no longer significant ($n=304$; relative risk 1.18, 0.96 to 1.26; $P=0.16$). Acute dystonia is sustained, often painful muscular spasms, producing twisting abnormal postures. It is both distressing and frightening and can be dangerous.

Important adverse effects were reported for 12 people (table 3). Two people had seizures (one haloperidol plus promethazine, one haloperidol alone). Nine people had acute dystonia; all of these had been allocated to haloperidol alone. One person had both of these adverse events (haloperidol alone). The dystonia was successfully treated in all cases with promethazine, as is standard in Brazil. We reanalysed these data, controlling for haloperidol dose. The relative risk for any important adverse effect remained almost the same, changing from 0.09 to 0.07 (95% confidence interval 0.01 to 0.75). The proportion of people with acute dystonia who had been given 5 mg of haloperidol (2.4%) was similar to that of those given 10 mg (3.8%; $P=0.75$, Fisher exact test).

DISCUSSION

This trial sought to investigate whether following international guidelines and changing routine care in Brazil from haloperidol plus promethazine to haloperidol alone for managing agitated/aggressive patients presenting to a psychiatric emergency room offered

any benefit. We found no evidence of benefit and significant evidence of harm.

Routine care in Rio de Janeiro, as described elsewhere,¹⁷ is not so different from many situations worldwide as to render the results of this study impossible to generalise. The pragmatic design helped to ensure a remarkably complete dataset, and the high reliability of agreement in rating of the primary outcome between blinded and non-blinded raters suggests that, for this particular outcome, observation bias as a result of raters being unblinded was small. We have found no reason for the uneven sex distribution other than the play of chance and see no plausible link to outcome.

We found no benefit in using haloperidol alone and significant disadvantages that have, to this point, not been obvious for several reasons. A simple pragmatic randomised trial of adequate power affords an opportunity to properly compare the clinical effects of treatment strategies for agitated or mentally ill people. Such trials are rare and, in everyday care, where services are more dispersed, important effects can easily go unnoticed. Haloperidol alone does swiftly tranquillise aggressive psychotic people; it is just not as fast nor as safe as when it is combined with promethazine. Its continued use exposes people to the dangers of aggression for longer, but this would be difficult to notice outside a well designed trial.

The high frequency of acute movement disorders, however, should have been more obvious. The rate of 6.4% (95% confidence interval 3.3% to 11.8%) in the haloperidol alone group in this study is in keeping with estimates from other sources.^{2,18} Of the 279 people allocated to haloperidol in the randomised trials already identified in relevant systematic reviews,^{11,13} 32 (12%, 95% confidence interval 8% to 16%) had acute dystonia or “acute extrapyramidal symptoms.” Several of these poorly classified movement disorders are probably acute dystonia. These 32 events, however, were distributed over seven trials with different

Table 3 | Incidence of important adverse reactions in first 24 hours

Allocated intervention	Type of reaction	Time after administration (hours:minutes)	Treatment*
Haloperidol (10 mg)	Acute dystonia	0:15	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	0:33	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	1:20	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	1:50	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	15:00	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	15:30	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	18:20	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	20:45	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	22:50	Diazepam (10 mg) plus promethazine oral (25 mg)
Haloperidol (10 mg)	Acute dystonia plus seizure	0:30	Diazepam (10 mg) plus promethazine (50 mg)
Haloperidol (10 mg)	Seizure	16:55	Diazepam (10 mg)
Haloperidol (5 mg) plus promethazine (25 mg)	Seizure	1:30	Clonazepam oral (2 mg)

*Intramuscular unless stated otherwise.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Rapid tranquillisation of people with aggressive behaviour due to mental illness is sometimes necessary

Guidelines are often influenced by local practice, have limited evidence, and vary in which drugs they recommend

The combination of haloperidol plus promethazine has been shown to be effective and safe in pragmatic trials in Brazil and India

WHAT THIS STUDY ADDS

Around 60% of participants given either drug regimen were tranquillised or sedated within 20 minutes of administration, and 90% by two hours

Haloperidol caused 55% of participants to be tranquil or asleep within 20 minutes, compared with 72% with haloperidol-promethazine

Because of the high incidence (7%) of serious adverse effects, administering intramuscular haloperidol alone for emergency treatment of acutely aggressive mentally ill people is no longer justifiable

comparisons, and the results of our larger study highlight what is less obvious from previous research. Combining lorazepam with haloperidol does not clearly offset the dystonia (two trials, $n=41$; 5% incidence, 0.9% to 18%). Managing these acute movement disorders in the midst of an acute aggressive episode is, at the very least, problematic. Guidelines recommend access to anticholinergic drugs if haloperidol is to be used alone,³⁴ but evidence from this and other studies suggests that routine use of a more sedative drug with anticholinergic properties has advantages.^{10 15}

Strengths and limitations

This study is one in a series testing treatments commonly used in routine care worldwide, recruiting large numbers of participants, with nearly complete follow-up for both primary and secondary outcomes, and not funded by industry. Because of the design of the study, a treatment that has been in common use for 50 years in the emergency situation, haloperidol alone, has been evaluated with adequate power for the first time, and as a result the recommendations of international guidelines should be reconsidered.

The open evaluation of the treatments could have resulted in the introduction of bias. Allocation was, however, fully concealed and randomisation was successful; intervention doses were monitored for differences that could have resulted from open giving, and no differences were found; and a sample of outcomes were blindly verified with excellent levels of agreement.

Conclusions

Sole use of intramuscular haloperidol is not an acceptable way of managing acute aggression as it leaves people exposed to the dangers of violence for longer than necessary and carries with it the avoidable risk of acute dystonia. Haloperidol routinely combined with promethazine is swiftly effective and safe and is the treatment for acute aggression due to psychosis for which most trial based evidence exists.

The pragmatic design of a randomised trial in emergency psychiatry is feasible and informative. With the combined data from other studies,¹⁴ intramuscular haloperidol plus promethazine is now a well researched, safe, and effective benchmark treatment for managing aggression/violence due to psychosis.

New atypical antipsychotics are now being used in the emergency situation, although trials are few.¹³ Before guidelines recommend these drugs, they should be compared with well evaluated, accessible benchmark treatments that are more effective and safe than sole use of haloperidol and in trials not funded by bodies with a pecuniary interest in the results.

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