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- 1 Nolan T, Angos P, Cunha AJ, Muhe L, Qazi S, Simoes EA, et al. Quality of hospital care for seriously ill children in less-developed countries. *Lancet* 2001;357:106-10.
- 2 Zucker JR, Lackritz EM, Ruebush TK, Hightower AW, Adungosi JE, Were JB, et al. Childhood mortality during and after hospitalization in

western Kenya: effect of malaria treatment regimens. *Am J Trop Med Hyg* 1996;55:655-60.

- 3 Veirum JE, Sodemann M, Biai S, Jensen H, Juul S, Aaby P. Increased mortality among children discharged from a paediatric ward in Bissau, Guinea Bissau, 1991-97. *Acta Paediatr* (in press).
- 4 Sodemann M, Veirum J, Biai S, Nielsen J, Bale C, Jakobsen MS, et al. Reduced case fatality among hospitalised children during a war in Guinea-Bissau: a lesson in equity. *Acta Paediatr* 2004;93:959-64.
- 5 Van Lerberghe W, de Béthune X, De Brouwere V. Hospitals in sub-Saharan Africa: why we need more of what does not work as it should. *Trop Med Int Health* 1997;8:799-808.

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Rapid tranquillisation in psychiatric emergency setting in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine

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ABSTRACT

Objective To compare the effect of intramuscular olanzapine with intramuscular haloperidol plus promethazine on rapid tranquillisation of agitated or violent adults with mental illness.

Design Pragmatic, allocation concealed, randomised controlled trial.

Setting Emergency services of a general hospital psychiatry department in Vellore, south India.

Participants 300 adults with agitated or violent behaviour as a result of mental illness; 150 randomised to intramuscular olanzapine and 150 randomised to intramuscular haloperidol plus promethazine.

Interventions Open treatment with intramuscular olanzapine or intramuscular haloperidol plus promethazine.

Main outcome measures Primary outcome was proportion of patients who were tranquil or asleep at 15 minutes and 240 minutes. Secondary outcomes were proportion of patients who were tranquil, asleep, restrained, absconding, or clinically improved at 15, 30, 60, 120, and 240 minutes; additional medical interventions and adverse effects over four hours; and compliance with oral drugs and adverse effects over two weeks.

Results Of 300 people randomised to receive either intramuscular olanzapine or intramuscular haloperidol plus promethazine, follow-up data were available for primary outcomes for 298 (99%). Both treatments resulted in similar proportions of people being tranquil or asleep at 15 minutes (olanzapine 131/150 (87%), haloperidol plus promethazine 136/150 (91%); relative risk 0.96, 95% confidence interval 0.34 to 1.47) and 240 minutes (olanzapine 144/150 (96%), haloperidol plus promethazine 145/150 (97%); relative risk 0.99, 0.95 to 1.03). However, more people given olanzapine than those given haloperidol plus promethazine required additional drugs over four hours (65/150 (43%) v 31/150

(21%); relative risk 2.07, 1.43 to 2.97). Adverse effects were uncommon with both treatments.

Conclusions Intramuscular olanzapine and intramuscular haloperidol plus promethazine were effective at rapidly tranquillising or sedating agitated or violent adults with mental illness but the combination resulted in fewer additional medical interventions within four hours of intervention.

Trial registration Clinical trials NCT00455234.

INTRODUCTION

As rates of mental illness are similar worldwide¹ it is reasonable to presume that the management of aggressive or violent behaviour is an important problem and a mental health priority in low and middle income countries, where most of the world's people live, and particularly in countries with large populations, such as India. Non-pharmacological strategies are recommended to manage violence in the emergency psychiatry setting, but rapid tranquillisation with drugs to reduce agitation may be unavoidable.²⁻⁴ Guidelines and clinical practice vary widely on the choice of drugs to manage violence in psychiatric emergencies.²⁻⁵

Two trials by the TREC Collaborative Group (tranquilização rápida-ensaio clínico [rapid tranquillisation-clinical trial]), carried out in India⁶ and Brazil,⁷ proved the efficacy and safety of combined intramuscular haloperidol and promethazine in agitated or violent people compared with intramuscular benzodiazepines. Although guidelines from the UK National Institute for Health and Clinical Excellence² commended the quality of the trials, it stopped short of recommending the routine use of combined haloperidol and promethazine in the United Kingdom owing to insufficient data, particularly on safety, and the preference for calming rather than for sedation. Intramuscular olanzapine is

one of the drugs recommended by NICE for treating violence.²

The problems in extrapolating the results from these studies to real life are that the studies were sponsored and authored by the drug industry; used rating scales to evaluate outcomes, which, although validated, are not routinely used in busy emergency settings, at least in low and middle income countries; and excluded people with comorbid alcohol or drug dependence, those with violence towards others, and those who needed restraints. We compared intramuscular olanzapine with intramuscular haloperidol plus promethazine for the management of agitated and violent adults in psychiatric emergency settings.

METHODS

Our study was carried out in the psychiatric unit of Christian Medical College, Vellore, south India. Between September 2005 and July 2006 we assessed consecutive patients for trial entry if the attending doctor thought that intramuscular sedation was indicated because of agitation or violent behaviour and that neither intervention posed an additional risk for the patient.

We randomised patients according to a computer generated random numbers list in varying sized blocks of fewer than 10 to intramuscular olanzapine or to intramuscular haloperidol plus promethazine.

Identical boxes were produced containing either two ampoules of haloperidol (5 mg each, recommended dose 10 mg) plus one ampoule of promethazine (50 mg), or one vial of olanzapine (10 mg) and distilled water for dilution (5 ml); one disposable syringe; a needle; and forms for follow-up. Staff with clinical involvement in the study had no indication of the drugs until the boxes were opened.

The duty doctor completed a form on patients' details, including the initial diagnosis (international classification of diseases, 10th revision)⁸ and the severity of aggression and violence (severity subscale of the clinical global impressions scale).⁹ The doctor then opened the box to deliver the intervention. The patient was followed up at 15 minutes, 240 minutes, and two weeks by the first author (NSR) and at 30, 60, and 120 minutes by the doctor or nurse.

Participants were considered to be tranquil when they were calm and not exhibiting agitated or dangerous behaviour. They were considered to be asleep if they appeared asleep and were not aroused by ambient disturbances; for data analysis we dichotomised sleep into asleep or not asleep. We assessed inter-rater reliability before and during the trial.

Secondary outcomes were proportion of patients tranquil or asleep, asleep, restrained, absconding, or clinically improved on the improvement subscale of the clinical global impressions scale⁹ at 15, 30, 60, 120, and 240 minutes; the proportion requiring the doctor to be recalled; the use of additional medical interventions; and adverse effects over four hours. Compliance with oral drugs and adverse effects were further assessed at two weeks. We rated participants for adverse effects at all assessment points on the

Simpson–Angus extrapyramidal side effects rating scale¹⁰ and the Barnes akathisia scale.¹¹ Additional measures, such as blood pressure, and investigations were undertaken as indicated by routine practice.

Statistical analysis

We used double data entry and analysed data using SPSS version 11.0. We calculated relative risks, the number needed to treat, and their 95% confidence intervals using intention to treat analysis. We assumed any participant not available at any of the assessment points to have not improved, not to be tranquil, and not to be asleep.

We also used repeated measures analysis of variance to compare mean scores for improvement between groups across various time points, with being asleep entered as a covariate at follow-up points. We compared mean times to tranquillisation and sedation using the Mann-Whitney U test. We used the κ statistic to evaluate agreement for treatment allocation and improvement.

RESULTS

Between 17 September 2005 and 20 July 2006 364 eligible adults presenting with aggressive or violent behaviour as a result of mental illness were screened (see bmj.com). Overall, 150 patients were randomised to intramuscular olanzapine and 150 to intramuscular haloperidol plus promethazine. The groups were similar for baseline characteristics (see bmj.com).

In total, 148 people in the combined drug arm received 10 mg haloperidol and 50 mg promethazine and two received 5 mg haloperidol and 25 mg olanzapine. Two people in the olanzapine arm received 5 mg and 148 received 10 mg.

NSR correctly guessed allocation in 50% of those randomised to olanzapine and 51% of those randomised to haloperidol plus promethazine ($\kappa=0.13$).

Olanzapine and haloperidol plus promethazine were equally effective for the primary outcome of tranquillisation or sedation at 15 minutes and 240 minutes after intervention, with 87% of patients in the olanzapine arm and 91% in the combined drug arm being either tranquil or asleep at 15 minutes; these increased to 96% and 97% at four hours (table). Haloperidol plus promethazine sedated patients more rapidly, however, with 14% more patients being asleep at 15 minutes (number needed to treat (NNT) for one extra patient to sleep=8, 95% confidence interval 4 to 36). The proportion of patients asleep favoured the combined drug at all assessment points. At four hours 16% more people given the combined drug were asleep (NNT=7, 4 to 18). Ratings for improvement did not differ significantly 15 minutes after intervention, but significantly greater proportions of patients given haloperidol plus promethazine compared with olanzapine were rated as improved from 30 minutes to four hours after intervention.

Seventy eight patients were restrained within the four hours after intervention. Although the differences between groups were not significant, it may be

clinically significant that 6% more people given olanzapine were restrained in the four hours after intervention.

Olanzapine rapidly calmed patients but the effects did not last long, and 17% more patients given olanzapine compared with those given haloperidol plus promethazine required the recall of doctors (NNT=6, 4 to 13). Additional drugs to control aggression over the four hours were prescribed for 20% more people given olanzapine than given the combined drug (NNT=6, 3 to 10). Combined haloperidol and promethazine both calmed and sedated patients rapidly

and this effect lasted throughout the four hours. The interventions did not differ in proportions of patients requiring additional drugs in the first hour (olanzapine 37 (25%), combined drug 30 (20%); relative risk 1.23, 95% confidence interval 0.81 to 1.89). Between one hour and four hours, however, 49 (33%) of those given olanzapine needed additional drugs compared with 20 (13%) given the combined drug (relative risk 2.45, 1.53 to 3.91; NNT=6, 4 to 10). Four people given olanzapine and one given the combination were never tranquil or asleep and were rated as not improved throughout the four hours.

Outcomes for patients randomised to intramuscular olanzapine or intramuscular haloperidol plus promethazine for agitation or violence as a result of mental illness. Values are numbers (percentages) of patients unless stated otherwise

Outcomes	Olanzapine group (n=150)	Haloperidol plus promethazine group (n=150)	Relative risk (95% CI)	Risk difference (95% CI)
Tranquil or asleep after injection (minutes):				
15*	131 (87)	136 (91)	0.96 (0.34 to 1.47)	3.3 (-3.7 to 10.4)
30	140 (93)	144 (96)	0.97 (0.92 to 1.03)	2.7 (-2.4 to 7.7)
60	141 (94)	149 (99)	0.95 (0.91 to 0.99)	5.3 (1.3 to 9.4)
120	141 (94)	146 (97)	0.97 (0.92 to 1.01)	3.3 (-1.26 to 7.9)
240*	144 (96)	145 (97)	0.99 (0.95 to 1.03)	0.67 (-3.6 to 4.9)
Asleep after injection (minutes):				
15*	65 (43)	86 (57)	0.76 (0.60 to 0.95)	14.0 (2.8 to 25.2)
30	95 (63)	114 (76)	0.83 (0.72 to 0.97)	12.6 (2.4 to 23.0)
60	99 (66)	120 (80)	0.83 (0.72 to 0.95)	14.0 (4.1 to 23.9)
120	91 (61)	120 (80)	0.76 (0.65 to 0.88)	19.3 (9.2 to 29.4)
240*	88 (59)	112 (75)	0.79 (0.67 to 0.93)	16.0 (5.5 to 26.5)
Improved† after injection (minutes):				
15	98 (65)	109 (73)	0.90 (0.77 to 1.05)	2.8 (-7.7 to 13.3)
30	110 (73)	127 (85)	0.87 (0.77 to 0.98)	11.3 (2.2 to 20.5)
60	120 (80)	138 (92)	0.87 (0.79 to 0.95)	12.0 (4.3 to 19.7)
120	118 (79)	136 (91)	0.87 (0.79 to 0.99)	12.0 (4.0 to 20.1)
240	131 (87)	141 (94)	0.91 (0.86 to 1.00)	6.7 (0.2 to 13.2)
In restraints after injection (minutes):				
15	45 (30)	43 (29)	1.05 (0.74 to 1.49)	1.3 (-9.0 to 11.6)
30	42 (28)	43 (29)	0.98 (0.68 to 1.40)	0.7 (-9.5 to 10.9)
60	38 (25)	37 (25)	1.03 (0.69 to 1.52)	0.7 (-9.1 to 10.5)
120	34 (23)	27 (18)	1.26 (0.80 to 1.89)	4.7 (-4.4 to 13.8)
240	24 (16)	15 (10)	1.60 (0.88 to 2.93)	6.0 (-1.6 to 13.6)
Other outcomes in 4 hours:				
Doctor called back	49 (33)	23 (15)	2.13 (1.37 to 3.31)	17.3 (7.9 to 26.8)
Additional drugs used	65 (43)	31 (21)	2.07 (1.43 to 2.97)	20.0 (10.0 to 30.0)
Adverse effects	3 (2.0)	1 (0.6)	3.00 (0.32 to 28.05)	1.3 (-1.3 to 3.9)
Absconded	5 (3.4)	0	—	1.0 (-0.1 to 2.7)
After 4 hours:				
Admitted	47 (31)	38 (25)	1.24 (0.86 to 1.78)	6.0 (-4.2 to 16.2)
Discharged	65 (43)	70 (47)	0.93 (0.72 to 1.19)	3.3 (-8.0 to 14.6)
Further observation	36 (24)	42 (28)	0.93 (0.58 to 1.26)	4.0 (-5.9 to 13.9)
Lost to follow-up	2 (1)	0	—	1.3 (-0.5 to 3.2)
At 2 weeks:				
Lost to follow-up	10 (7)	14 (9)	0.71 (0.33 to 1.6)	2.7 (-3.5 to 8.8)
No serious adverse effects	149 (99)	150 (100)	0.99 (0.98 to 1.0)	0.7 (-0.6 to 2.0)
Taking oral drugs	138 (92)	133 (89)	1.04 (0.96 to 1.12)	3.3 (-3.3 to 10.0)

*Primary outcomes.

†Rated on clinical global impression—improvement subscale.

The mean (standard deviation) time for haloperidol plus promethazine to produce tranquillisation was less than that with olanzapine (12.8 (16.7) minutes *v* 20.5 (34.5) minutes); the same was true for time to sedation (26.2 (32.2) minutes *v* 34.9 (42.2) minutes). These differences were not significant ($P=0.4$ and $P=0.2$).

Scores on the improvement scale were subjected to repeated measures analysis of variance (see bmj.com). The differences on the ratings over time and between interventions remained significant when being asleep was entered as a covariate at each assessment point.

Two patients in the olanzapine group developed akathisia and one patient reported nausea after four hours. One patient in the haloperidol plus promethazine group who was dehydrated as a result of psychosis developed transient hypotension within 15 minutes of the injection, but this had resolved by 30 minutes.

No significant differences were found in the proportion of patients accepting oral drugs in either group at two weeks. No patient in the combined drug arm experienced any serious adverse events over two weeks. One patient in the olanzapine arm who had been prescribed clozapine developed intestinal obstruction, which resolved with conservative management.

DISCUSSION

Intramuscular olanzapine and intramuscular haloperidol plus promethazine are effective in the rapid tranquillisation of agitated or violent adults as a result of mental illness. Important differences were, however, found in the effects of the two interventions. Olanzapine produced a calming effect within an hour, but this seemed to wear off and additional medical attention and interventions were required, particularly after an hour. Combined haloperidol and promethazine had a rapid calming effect but also put most patients to sleep rapidly, and this was maintained better over four hours than with olanzapine, reducing the need for additional medical involvement and intervention. The addition of promethazine facilitated sedation and prevented significant extrapyramidal adverse effects, particularly dystonia. This trial was not, however, adequately powered to confirm the safety of either intervention.

Sleep is often not considered a desirable end point of rapid tranquillisation,² and calming patients without producing sleep is considered the ideal. In an analysis of industry sponsored trials of olanzapine,¹¹ the drug was considered to produce a calming effect distinct from sedation. In our trial, however, over 60% of patients given olanzapine were asleep within an hour.

Haloperidol and promethazine are both on the World Health Organization's list of essential drugs.¹² The combined drug costs nearly a third less than injectable olanzapine in India. If the costs of the additional drugs used and the utilisation of additional resources were totalled, the difference is likely to favour haloperidol plus promethazine.

In India it is common to place violent people in restraints in addition to using drugs. The interventions did not result in significant differences in proportions of patients restrained, although fewer people given haloperidol plus promethazine were restrained at all assessment points.

Strengths and limitations of the study

The major strengths of this trial are the use of central random allocation to minimise selection bias, adequate measures to preserve allocation concealment, adequacy of blinding for the principal outcomes, sufficient power to detect significant differences in the main outcomes, multiple measures of outcome, and the pragmatic nature of the design that mimicked routine clinical practice.

Because concurrent drug use was uncontrolled, the use of additional drugs early in the trial may have influenced ratings. As more people randomised to olanzapine received additional drugs, however, subtracting the effects of this from the outcomes would increase the superiority of haloperidol plus promethazine.

Assessments between 30 minutes and 120 minutes were done by people not blind to treatment allocation, although allocation itself was concealed. The primary outcomes were, however, rated blind to treatment allocation, the reliability of blinding was satisfactory, and outcomes were assessed in different ways with satisfactory inter-rater reliability pre-established.

We avoided using specific aggression scales as these are cumbersome and time consuming, are not used routinely in clinical care, and provide continuous measures of outcome that are difficult to interpret clinically. The outcomes used in the study are the ones most likely to be used in routine clinical practice and were chosen after discussion with doctors as being the most appropriate to guide clinical practice.

The study was powered only for primary outcomes for which the interventions did not differ, and we used several secondary outcomes, some of which favoured haloperidol plus promethazine over olanzapine; these must be interpreted with caution.

No patient in the combined drug arm developed dystonia or other extrapyramidal adverse effects. One patient in the olanzapine arm with pre-existing dehydration as a result of psychosis developed transient hypotension, which resolved uneventfully.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Guidelines for rapid tranquillisation of aggressive people with mental illness are often influenced by local practice, have limited evidence, and vary for recommended drugs. Combined haloperidol and promethazine was shown to be effective in pragmatic trials carried out in Brazil and India.

WHAT THIS STUDY ADDS

Around 90% of adults given olanzapine or haloperidol plus promethazine were tranquillised or sedated within 15 minutes and 96% by four hours.

Additional interventions were used within four hours for 43% of those given olanzapine and 21% of those given haloperidol plus promethazine.

Neither intervention produced serious adverse effects but the trial was not designed to evaluate the safety of these interventions.

Conclusions

Olanzapine and haloperidol plus promethazine were effective in controlling aggressive or violent behaviour as a result of mental illness by producing rapid tranquillisation and sedation. Patients given the combined drug required less medical attention or additional drugs within four hours of intervention than those given olanzapine.

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Competing interests: None declared.

Ethical approval: This study was approved by the institutional review board of the Christian Medical College, Vellore.

- Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper J, et al. Schizophrenia: manifestations, incidence and course in different cultures. A world health organization ten-country study. *Psychol Med Monogr Suppl* 1992;20:1-97.
- National Institute for Health and Clinical Excellence (NICE). *Violence: clinical practice guidelines. The short-term management of*

- disturbed/violent behaviour in in-patient psychiatric settings and emergency departments.* London: Royal College of Nursing, 2005.
- Hillard JR. Emergency treatment of acute psychosis. *J Clin Psychiatry* 1998;59(suppl 1):57-61.
 - Expert Consensus Guideline Group. Treatment of schizophrenia. The expert consensus guideline series. *J Clin Psychiatry* 1999;60(suppl 11):3-80.
 - Binder RL, McNiel DE. Emergency psychiatry: contemporary practices in managing acutely violent patients in 20 psychiatric emergency rooms. *Psychiatr Serv* 1999;50:1553-4.
 - Alexander J, Tharyan P, Adams CE, John T, Mol C, Philip J. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting: a pragmatic randomised trial of intramuscular lorazepam versus haloperidol plus promethazine. *Br J Psychiatry* 2004;185:63-9.
 - TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003;327:708-13.
 - World Health Organization. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines.* Geneva: WHO, 1992.
 - Guy W. *ECDEU assessment manual for psychopharmacology*, revised edn. Rockville, MD: National Institute of Mental Health, 1976.
 - World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. 2002. www.wma.net/e/policy/b3.htm (accessed 24 Jan 2007).
 - Battaglia J, David SR, Alaka K, Meehan K, Wright P. Calming versus sedative effects of IM olanzapine in agitated patients. *Schiz Res* 2002;53(suppl 1):183.
 - World Health Organization. The WHO model list of essential drugs (EDL 1999). www.who.int/medicines/organization/par/edl/infedmain.shtml (accessed 3 Jan 2005).

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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.