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.

We thank the doctors and nurses who helped assess the clinical outcomes during the trial and the staff of the department of psychiatry at the Christian Medical College. Members of the Rapid Tranquilisation-India II Collaborative Group were Joncy Philip, Ravi Nesan, Jai Shankar, Sialan Selvaraj, Rajesh Gopalakrishnan, Naveen Thomas, Titus Samson Premkumar, Susan Jayabal, Thangadurai P, Basanth Kumar, Anto Praeved Rajkumar, Satyavijay, Helen Charles, Sheeba Chandy, Devakumar K P, Karunakaran K P, P Raja RSK, Kasthuri Narasimhan, Parameswaran R, Bindu Sam, Bhavani, Geetha R, Ida Priscilla.

Contributors: See bmj.com.

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


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

Gisele Huf,1 E S F Coutinho,2 C E Adams3

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
For control of agitated and violent behaviour in clinical settings, guidelines in the United States and United Kingdom recommend the use of intramuscular haloperidol, lorazepam, both combined, or olanzapine. However, little information on comparative effectiveness or safety is available. Haloperidol alone, or the combination of haloperidol with lorazepam, is widely used. In Brazil and India, many people consider it standard practice to add promethazine to haloperidol. Promethazine is a sedative antihistamine with anticholinergic properties.

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

Our two TREC-I trials are the only randomised trials that used haloperidol plus promethazine as the control. This combination treatment was both effective and safe in comparison with midazolam or lorazepam but has never been compared with intramuscular haloperidol alone. This study 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.

Table 1 | Main results. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol plus promethazine group (n=160)</th>
<th>Haloperidol group (n=156)</th>
<th>Relative risk (95% CI)</th>
<th>Difference in risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 20 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquil/asleep (primary outcome)</td>
<td>115 (72)</td>
<td>86 (55)</td>
<td>1.30 (1.10 to 1.55)</td>
<td>16.7 (6.3 to 27.2)</td>
</tr>
<tr>
<td>Asleep</td>
<td>31 (19)</td>
<td>13 (8)</td>
<td>2.33 (1.26 to 4.27)</td>
<td>11.0 (3.5 to 18.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 40 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquil/asleep</td>
<td>129 (81)</td>
<td>118 (76)</td>
<td>1.07 (0.95 to 1.20)</td>
<td>5.0 (-4.1 to 14.1)</td>
</tr>
<tr>
<td>Asleep</td>
<td>57 (36)</td>
<td>54 (35)</td>
<td>1.03 (0.76 to 1.39)</td>
<td>1.0 (-9.5 to 11.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 60 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquil/asleep</td>
<td>139 (87)</td>
<td>127 (81)</td>
<td>1.07 (0.97 to 1.17)</td>
<td>5.5 (-2.6 to 13.5)</td>
</tr>
<tr>
<td>Asleep</td>
<td>77 (48)</td>
<td>77 (49)</td>
<td>0.98 (0.78 to 1.22)</td>
<td>-1.2 (-12.3 to 9.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 120 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquil/asleep</td>
<td>146 (91)</td>
<td>138 (89)</td>
<td>1.03 (0.96 to 1.11)</td>
<td>2.8 (-3.9 to 9.4)</td>
</tr>
<tr>
<td>Asleep</td>
<td>97 (61)</td>
<td>94 (60)</td>
<td>1.01 (0.86 to 1.20)</td>
<td>0.4 (-10.6 to 11.2)</td>
</tr>
<tr>
<td>No additional tranquilising drugs</td>
<td>152 (95)</td>
<td>143 (92)</td>
<td>1.04 (0.98 to 1.10)</td>
<td>3.3 (-2.2 to 8.8)</td>
</tr>
<tr>
<td>Restraints not needed</td>
<td>122 (76)</td>
<td>111 (71)</td>
<td>1.07 (0.94 to 1.22)</td>
<td>5.1 (-4.6 to 14.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No other episode of aggression</td>
<td>129 (81)</td>
<td>124 (80)</td>
<td>1.01 (0.91 to 1.13)</td>
<td>1.1 (-7.7 to 10.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (4)</td>
<td>12 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor not called to see patient</td>
<td>123 (77)</td>
<td>102 (65)</td>
<td>1.18 (1.02 to 1.36)</td>
<td>11.5 (1.7 to 21.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (4)</td>
<td>11 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accept oral drugs*</td>
<td>132 (84)</td>
<td>129 (84)</td>
<td>0.97 (0.88 to 1.06)</td>
<td>-3.0 (-10.9 to 4.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (7)</td>
<td>11 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) chlorpromazine equivalents (mg)</td>
<td>245 (194)</td>
<td>234 (182)</td>
<td>Mann-Whitney U=11885.500; P=0.46</td>
<td></td>
</tr>
<tr>
<td>Serious adverse effect†</td>
<td>1 (1)</td>
<td>11 (7)</td>
<td>0.09 (0.01 to 0.68)</td>
<td>-6.4 (-10.6 to -2.2)</td>
</tr>
<tr>
<td>By 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>62 (39)</td>
<td>73 (47)</td>
<td>0.83 (0.64 to 1.07)</td>
<td>-8.0 (-18.9 to 2.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

RESULTS
Recruitment was from 6 January 2004 to 1 July 2004. 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 (mean age 40.1 years)—160 to haloperidol plus promethazine and 156 to haloperidol alone. Primary outcome data were available for 311 (98.4%) participants.

Baseline characteristics were similar between the two treatment groups. However, the proportion of men was higher in the haloperidol plus promethazine group. 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).

Of people allocated haloperidol alone, 29% received 5 mg and the rest 10 mg. 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 1). Inter-rater agreement on time from injection to tranquillisation or sleep was good ($\kappa=0.83$, 0.67 to 0.99). We did two post hoc analyses, controlling for sex and dose of haloperidol. 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 120 minutes (table 1). 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. Doctors were called more frequently to see patients allocated haloperidol alone than those in the combination treatment group. When patients with acute dystonia were removed from the analysis the difference was no longer significant ($n=304$; relative risk 1.18, 0.96 to 1.26; $P=0.16$).

Important adverse effects were reported for 12 people (table 2). 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). 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).

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...
A study tested a treatment commonly used in routine care worldwide, recruited large numbers of participants, with nearly complete follow-up, and was not funded by industry. 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 leaves people exposed to the dangers of violence for longer than necessary and carries with it the 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.

New atypical antipsychotics are now being used in the emergency situation, although trials are few.9 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.

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Funding: Brazilian Research Council (CNPq).

Competing interests: None declared.

Ethical approval: Ethics committees from Escola Nacional de Saúde Pública Fundação Oswaldo Cruz, Instituto Philippe Pinel, the members of the consumer advocate group of Rio de Janeiro (SOSINTRA)—society of family and friends of the mentally ill in Rio de Janeiro), National Council of Ethics in Research, Brazil.

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