Haloperidol IM vs Haloperidol + Promethazine IM for Acute Agitation/Aggression: A Randomized Controlled Trial (Trec-Rio-II: ISRCTN83261243)

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Background

In 2003, in the largest randomised trial of its kind, this team found that haloperidol + promethazine IM was safe and effective for rapid tranquilisation of aggressive people with psychosis (n=301, 99% follow up).[1]

In 2004, our second team showed haloperidol + promethazine IM to be considerably more effective and safe than lorazepam for a similar population (n=200, 99% follow up).[2]

In 2005 these two trials were described as follows:

What NICE have said about our trials in 2005

Conclusions

Unlike most of the other studies in this review both these were large studies of a high methodological quality.

Violence: The Short-Term Management of Disturbed/Violent Behaviour in Psychiatric In-patient and Emergency Departments Guideline – NICE 2005

In 2005, the Brazil-UK team wished to compare the haloperidol + promethazine mix, now the most evaluated approach for rapid tranquilisation, with another APA and NICE recommendation for acutely disturbed people thought to have psychosis – the use of haloperidol alone.

TREC-Rio*

***Tranquilização Rápida-Ensaio Clínico**
[Translation: Rapid Tranquillisation-Clinical Trial]

Design

- Pragmatic, randomised
- Real-world participants
- Regularly used, available interventions
- Routinely recorded outcomes
- Designed with the help of staff of the Psychiatric Emergency Rooms of Rio, carers and advocate groups in Rio, trialists with experience in the area of emergency medicine

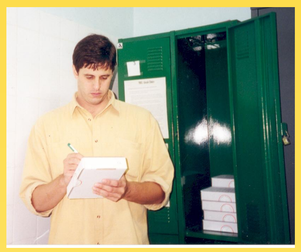
Protocol

Eligible if the person needs acute intramuscular sedation because of disturbed and dangerous behaviour and clinician is uncertain about the benefits and risks of haloperidol plus promethazine versus haloperidol alone.

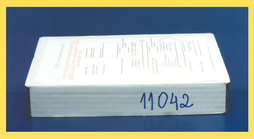
Exclude if clinician believes that one treatment represents an additional risk for the patient.

Trial entry treatment allocated by taking consecutive TREC boxes stored in the

emergency drug cupboard.



The box has two questions on the outside.



and contains

- Either haloperidol (2 X 5mg ampules) + promethazine (2 X 50mg ampules) OR haloperidol (2 X 5mg ampule). All doses are at the discretion of the doctor.
- One syringe, one needle, two swabs, one plaster.
- TREC form to be filled out by the attending doctor/nurse.
- TREC stickers for the patient's notes.

Outcomes

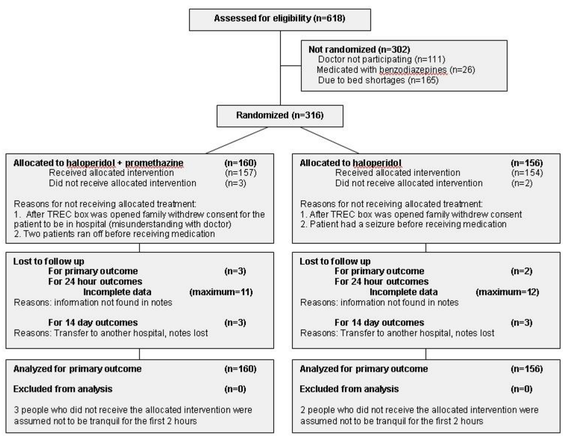
Primary outcome is tranquil or sedated at 20 minutes.

Data for up to two weeks were extracted from the notes on clinical state, hospital status, sedation, use of additional medications and adverse reactions.

Results

- The Data Monitoring Committee (DMC) recommended that the Steering Committee halt the trial early.
- 316 randomised
- 99% follow up

CONSORT diagram for TREC-Rio-II



Relative risk, number needed to treat for primary and secondary outcomes

	Haloperidol + promethazine (n=160)	Haloperidol (n=156)	Relative Risk (95% CI)	Difference in risk (95% CI)	NNT (p value)
By 20 minutes					
Tranquil/asleep	115 (71.9)[1]	86 (55.1)	1.30 (1.10-1.55)	16.7 (6.3-27.2)	6 9.5 (0.002)
Asleep	31 (19.4)	13 (8.3)	2.33 (1.26-4.27)	11.0 (3.5-18.5)	
Serious adverse effect[2]	1 (0.6)	11 (7.2)	0.09 (0.01-0.73)	- 6.0 (- 10.0; -2.0)	17 8.21 (0.004)
Unknown	3 (1.9)	2 (1.3)			
By 40 minutes					
Tranquil/asleep	129 (80.6)	118 (75.6)	1.07 (0.95-1.20)	5.0 (- 4.1- 14.1)	
Asleep	57 (35.6)	54 (34.6)	1.03 (0.76-1.39)	1.0 (- 9.5- 11.5)	
Unknown	3 (1.9)	2 (1.3)			
By 60 minutes					
Tranquil/asleep	139 (86.9)	127 (81.4)	1.07 (0.97-1.17)	5.5 (- 2.6- 13.5)	
Asleep	77 (48.1)	77 (49.4)	0.98 (0.78-1.22)	- 1.2 (- 12.3- 9.8)	
Unknown	3 (1.9)	2 (1.3)			
By 120 minutes					
Tranquil/asleep	146 (91.3)	138 (88.5)	1.03 (0.96-1.11)	2.8 (-3.9- 9.4)	
Asleep	97 (60.6)	94 (60.3)	1.01 (0.84-1.20)	0.4 (-10.4- 11.2)	
No additional tranquillising drugs	152 (95.0)	143 (91.7)	1.04 (0.98-1.10)	3.3 (- 2.2- 8.8)	
Not needing restraints	122 (76.3)	111 (71.2)	1.07 (0.94-1.22)	5.1 (-4.6- 14.8)	
Unknown	3 (1.9)	2 (1.3)			
Within 24 hours					
No other episode of aggression	129 (80.6)	124 (79.5)	1.01 (0.91-1.13)	1.1 (- 7.7- 10.0)	
Unknown	6 (3.7)	12 (7.7)			
Doctor not called to see patient	123 (76.9)	102 (65.4)	1.18 (1.02-1.36)	11.5 (1.7-21.4)	
Unknown	7 (4.4)	11 (7.1)			
Accepting oral medication[3]	132 (83.5)	129 (83.8)	0.97 (0.88-1.06)	- 3.0 (- 10.9- 4.9)	
Unknown	11 (6.9)	11 7.1)			
By 2 weeks					
Discharged	62 (38.8)	73 (46.8)	0.83 (0.64-1.07)	- 8.0 (-18.9- 2.8)	
Unknown	3 (1.9)	3 (1.9)			

[1] Number of people (%)
[2] patients with unknown outcome excluded from analysis
[3] 2 patients excluded in each group for not being prescribed oral medication

Adverse effects in first 24 hours

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

Results

IM haloperidol + promethazine is again shown to be rapid and safe.

The high incidence of adverse effects for the haloperidol alone group is not related to use of higher doses of the drug.

Because of the clear findings the Brazilian DMC felt it unethical to continue using the APA-NICE recommended intervention.

Conclusions

More acutely aggressive psychotic people have been randomised to IM haloperidol/promethazine than any other approach to rapid tranquilisation.

The trials are recognised to be of the highest quality.

Although haloperidol may often be given with other drugs, the use of haloperidol alone is one of the recommendations of the APA and NICE.

In the light of these new data these recommendations should be amended.

References
1. BMJ 2003;327:708-13 2. BJPsych 2004; 185: 63-9