

Rapid tranquillisation in mental health settings: promethazine hydrochloride

Evidence summary

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[nice.org.uk/guidance/esuom28](https://www.nice.org.uk/guidance/esuom28)

Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

A Cochrane review ([Huf et al. 2009](#); 4 randomised controlled trials [RCTs], n=1117) provides limited evidence that intramuscular haloperidol plus promethazine is effective for the rapid tranquillisation of people with agitation or aggression associated with mental illness. However, it is difficult to draw any firm conclusions because the results are [heterogeneous](#). In addition, the results were not relevant to UK clinical practice because the primary objective of the studies was sleep, whereas in the UK the primary objective is to calm the person to enable other psychosocial techniques to be used. Safety analyses in the Cochrane review and 2 small RCTs ([Baldaçara et al. 2011](#) [n=150] and [Mantovani et al. 2013](#) [n=100]) do not provide conclusive evidence that the combination of promethazine with haloperidol is safer than other intramuscular treatments, or that it reduces the adverse effects of antipsychotics when used for rapid tranquillisation.

Regulatory status: off-label

This topic was prioritised because there was a high volume of requests from the NHS for information on this topic and there is uncertainty about the balance of risks and benefits when promethazine is used for rapid tranquillisation in mental health conditions.

Effectiveness	Safety
<ul style="list-style-type: none"> • A Cochrane review (4 RCTs, n=1117) found that, compared with intramuscular haloperidol plus promethazine: <ul style="list-style-type: none"> – more people using intramuscular midazolam were tranquil or asleep by 30 minutes – fewer people using intramuscular lorazepam were tranquil or asleep by 30 minutes – fewer people using intramuscular haloperidol alone were tranquil or asleep by 20 minutes. • There was no significant difference between haloperidol plus promethazine and intramuscular olanzapine in the proportions of people who were tranquil or asleep at 15 or 30 minutes. <p>* Statistically significant difference.</p>	<ul style="list-style-type: none"> • Promethazine (Phenergan injection) is contraindicated in people with central nervous system depression and those who have taken monoamine oxidase inhibitors within the past 14 days. • Cautions include respiratory conditions, coronary artery disease, epilepsy and hepatic and renal insufficiency. • Combination of promethazine with an antipsychotic may involve additional risks. For example, the adverse effects of intramuscular haloperidol include extrapyramidal and cardiovascular adverse effects. • In 3 of the RCTs (n=801) included in the Cochrane review, a total of 7 serious adverse events were seen. • The fourth RCT (n=298 in the safety analysis) was stopped early because statistically significantly more people experienced serious adverse events with haloperidol alone compared with haloperidol plus promethazine (number needed to harm [NNH] 15).

Patient factors	Resource implications
<ul style="list-style-type: none"> The NICE clinical guideline on violence advises that oral medication should be offered for rapid tranquillisation whenever possible. Promethazine is administered intramuscularly for this indication. Many people may prefer oral treatment. 	<ul style="list-style-type: none"> Phenergan injection costs £6.74 for 10×1 ml ampoules containing 25 mg/ml promethazine hydrochloride (MIMS, January 2014).

Key points

Intramuscular promethazine hydrochloride ([Phenergan injection](#)) is licensed:

- for the symptomatic treatment of allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions
- for sedation and treatment of insomnia in adults
- as an adjunct to preoperative sedation in surgery and obstetrics
- as a paediatric sedative.

Intramuscular promethazine hydrochloride is sometimes used off-label for the rapid tranquillisation of people with mental health conditions who have agitation or aggression. Specialists involved in the production of this evidence summary have advised that, in practice, it is generally given in combination with an intramuscular antipsychotic such as haloperidol for this indication, rather than being used alone.

NICE issued a clinical guideline on [Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments](#) (NICE clinical guideline 25) in 2005. NICE does not recommend the routine use of intramuscular haloperidol in combination with intramuscular promethazine for rapid tranquillisation in psychiatric practice in the UK. Although the combination has been shown to be effective and relatively safe elsewhere, the Guideline Development Group concluded that there is insufficient evidence of its safety in UK clinical practice. Intramuscular haloperidol in combination with intramuscular promethazine may be considered as an alternative to intravenous administration of benzodiazepines or haloperidol only in very exceptional circumstances, which should be specified and recorded, and under the guidance of a senior psychiatrist.

This evidence summary is based on a Cochrane systematic review ([Huf et al. 2009](#)) of intramuscular haloperidol in combination with intramuscular promethazine that was published after the NICE guideline was developed. Two RCTs that were assessed during the development of the [NICE guideline on violence](#) are included in the evidence summary because they form part of the Cochrane review. Two small additional RCTs ([Baldaçara et al. 2011](#) and [Mantovani et al. 2013](#)) looking at haloperidol plus promethazine were also identified but are only briefly discussed because they add little to the evidence provided by the Cochrane review. No published studies were identified that assess promethazine alone or in combination with other antipsychotics for rapid tranquillisation.

The Cochrane review ([Huf et al. 2009](#)) included 4 RCTs (all part of the TREC [Rapid Tranquillisation Clinical Trial] collaboration) investigating intramuscular haloperidol (up to 10 mg) in combination with intramuscular promethazine (up to 50 mg) for treating agitation or aggression thought to be caused by psychosis in a total of 1117 people attending psychiatric emergency rooms. The primary outcome was the proportion of people who were tranquil or asleep after administration. The results of the studies are reported separately because of heterogeneity.

Two of the trials compared haloperidol plus promethazine with an intramuscular benzodiazepine. [TREC Rio-I](#) (n=301) found that, compared with the combination, the likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with intramuscular midazolam (up to 15 mg) (67% compared with 89% respectively; [risk ratio](#) [RR] 2.90, 95% [confidence interval](#) [CI] 1.75 to 4.80; [number needed to treat](#) [NNT 5], 95% CI 2 to 12). There was no significant difference between the groups at 2 hours.

Conversely, [TREC Vellore-I](#) (n=200) found that the likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with haloperidol plus promethazine compared with intramuscular lorazepam (up to 4 mg) (95% compared with 81% respectively; RR 0.26, 95% CI 0.10 to 0.68; NNT 8, 95% CI 6 to 17). The combination was still superior to lorazepam at 2 hours but there was no significant difference between the groups at 4 hours.

The difference between the results of TREC Rio-I and TREC Vellore-I does not appear to be solely due to the different benzodiazepines used. Despite the 2 studies having similar designs, the proportions of people receiving haloperidol plus promethazine who were tranquil or asleep by 30 minutes differ substantially between the TREC Rio-I and TREC Vellore-I (67% compared with 95% respectively). Possible reasons for this are discussed in the [evidence strengths and limitations](#) section of this evidence summary.

The [NICE full guideline on violence](#) assessed the TREC Rio-I and TREC Vellore-I trials and considered that the results were not relevant to UK clinical practice because the primary objective of the studies was sleep, whereas in the UK the primary objective is to calm the person to enable other psychosocial techniques to be used.

The other 2 trials included in the Cochrane review compared haloperidol plus promethazine with an intramuscular antipsychotic. [TREC Rio-II](#) (n=316) found that the likelihood of being tranquil or asleep at 20 minutes was higher with haloperidol plus promethazine compared with intramuscular haloperidol alone (up to 10 mg) (70% compared with 54% respectively; RR 0.65, 95% CI 0.49 to 0.87; NNT 7, 95% CI 5 to 17). There was no significant difference between the groups at 40 minutes or 1 hour, but at 2 hours more people were likely to be tranquil or asleep with the combination than with haloperidol alone.

[TREC Vellore-II](#) (n=300) found no statistically significant difference between haloperidol plus promethazine and intramuscular olanzapine (up to 10 mg) in the likelihood of being tranquil or asleep at 15 minutes, 30 minutes, 2 hours or 4 hours. However, significantly more people in the haloperidol plus promethazine group were tranquil or asleep by 1 hour compared with the olanzapine group (99% compared with 94% respectively; RR 0.11, 95% CI 0.01 to 0.87; NNT 19, 95% CI 17 to 129).

Promethazine ([Phenergan injection](#)) is contraindicated in people with central nervous system depression and those who have taken monoamine oxidase inhibitors within the past 14 days. Cautions include respiratory conditions, coronary artery disease, epilepsy and hepatic and renal insufficiency. Adverse effects include drowsiness, dizziness, restlessness, headaches, nightmares, tiredness, disorientation and anticholinergic effects.

Promethazine enhances the effects of anticholinergic agents, tricyclic antidepressants, sedatives and hypnotics, and alcohol. When it is used in combination with an antipsychotic for rapid tranquillisation there may be additional risks. For example, the adverse effects of intramuscular [haloperidol](#) include extrapyramidal and cardiovascular adverse effects. The NICE clinical guideline on [violence](#) advises that rapid tranquillisation can cause excessive sedation and loss of consciousness, loss of airway, and respiratory and cardiovascular collapse. NICE recommends that vital signs should be monitored after rapid tranquillisation, and blood pressure, pulse, temperature, respiration and hydration should be recorded regularly, at intervals agreed by a multidisciplinary team, until the person becomes active again.

According to the Cochrane review ([Huf et al. 2009](#)), serious adverse events were seen in 2 out of 301 people in TREC Rio-I, 1 out of 200 people in TREC Vellore-I and 4 out of 300 people in TREC

Vellore-II. TREC Rio-II was stopped early because of the difference in serious adverse events between the groups. Statistically significantly more people experienced serious adverse events with haloperidol alone compared with haloperidol plus promethazine (11 out of 145 people compared with 1 out of 153 people respectively; RR 0.09, 95% CI 0.01 to 0.66; NNH 15, 95% CI 14 to 40). Acute dystonia was experienced by 10 people receiving haloperidol alone, compared with none receiving the combination. The authors of the Cochrane review suggest that combining haloperidol with promethazine might protect against the adverse effects of haloperidol alone. However, this suggestion is not supported by the results of the 2 additional RCTs ([Baldaçara et al. 2011](#) and [Mantovani et al. 2013](#)). See the [safety](#) section of this evidence summary for more information.

All of the studies were undertaken in Brazil and India and may not be applicable to UK clinical practice. In addition, some of the doses of medication used in the TREC trials were higher than those used in the UK. For example, [Maudsley Prescribing Guidelines](#) recommend that lorazepam 1–2 mg is used but all participants in TREC Vellore-I received 4 mg. Similarly, a 5 mg dose of haloperidol is recommended in Maudsley but 10 mg was widely used in the TREC studies. The results of the studies relate to intramuscular haloperidol plus intramuscular promethazine in combination and cannot be extrapolated to apply to promethazine alone or in combination with other antipsychotics.

Overall, the Cochrane review provides limited evidence that haloperidol plus promethazine is effective for the rapid tranquillisation of people with agitation or aggression associated with mental illness. However, it is difficult to draw any firm conclusions because the results are heterogeneous. Also, safety analyses in the Cochrane review and 2 small RCTs do not provide conclusive evidence that the combination of promethazine with haloperidol is safer than other intramuscular treatments, or that it reduces the adverse effects of antipsychotics when used for rapid tranquillisation.

The NICE clinical guideline on [violence](#) advises that it is preferable to use lorazepam alone for rapid tranquillisation when behavioural disturbance occurs in a non-psychotic context. It recommends that lorazepam in combination with an antipsychotic should be considered when behavioural disturbance occurs in the context of psychosis. Intramuscular haloperidol in combination with intramuscular promethazine is 1 of a few options that may be considered only in very exceptional circumstances, which should be specified and recorded, and under the guidance of a senior psychiatrist. This NICE guideline is currently being updated ([Violence and aggression \[update\]](#)), with publication expected in April 2015.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Regulatory status of promethazine

Intramuscular promethazine hydrochloride (Phenergan injection) is licensed:

- for the symptomatic treatment of allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions
- for sedation and treatment of insomnia in adults
- as an adjunct to preoperative sedation in surgery and obstetrics
- as a paediatric sedative.

Intramuscular promethazine hydrochloride is sometimes used off-label for the rapid tranquillisation of people with mental health conditions who have agitation or aggression. Specialists involved in the production of this evidence summary have advised that, in practice, it is generally given in combination with an intramuscular antipsychotic such as haloperidol for this indication, rather than being used alone.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using promethazine outside its authorised indications.

Evidence statements

- The Cochrane review ([Huf et al. 2009](#)) included 4 randomised controlled trials (RCTs) (all part of the TREC [Rapid Tranquillisation Clinical Trial] collaboration) investigating intramuscular haloperidol (up to 10 mg) in combination with intramuscular promethazine (up to 50 mg) for treating agitation or aggression thought to be caused by psychosis in a total of 1117 people attending psychiatric emergency rooms.
- Two of the trials compared haloperidol plus promethazine with an intramuscular benzodiazepine. [TREC Rio-I](#) (n=301) found that, compared with the combination, the likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with midazolam (up to 15 mg) (67% compared with 89% respectively; [risk ratio](#) [RR] 2.90, 95% [confidence interval](#) [CI] 1.75 to 4.80; [number needed to treat](#) [NNT] 5, 95% CI 2 to 12). Conversely, [TREC Vellore-I](#) (n=200) found that the likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with haloperidol plus promethazine compared with lorazepam (up to 4 mg) (95% compared with 81% respectively; RR 0.26, 95% CI 0.10 to 0.68; NNT 8, 95% CI 6 to 17).
- The other 2 trials included in the Cochrane review compared haloperidol plus promethazine with an intramuscular antipsychotic. [TREC Rio-II](#) (n=316) found that the likelihood of being tranquil or asleep at 20 minutes was higher with haloperidol plus promethazine compared with haloperidol alone (up to 10 mg) (70% compared with 54% respectively; RR 0.65, 95% CI 0.49 to 0.87; NNT 7, 95% CI 5 to 17).
- [TREC Vellore-II](#) (n=300) found no statistically significant difference between haloperidol plus promethazine and intramuscular olanzapine (up to 10 mg) in the likelihood of being tranquil or asleep at 15 minutes or 30 minutes.
- Promethazine ([Phenergan injection](#)) is contraindicated in people with central nervous system depression and those who have taken monoamine oxidase inhibitors within the past 14 days. Cautions include respiratory conditions, coronary artery disease, epilepsy and hepatic and renal insufficiency. Adverse effects include drowsiness, dizziness, restlessness, headaches, nightmares, tiredness, disorientation and anticholinergic effects.
- Promethazine enhances the effects of anticholinergic agents, tricyclic antidepressants, sedatives and hypnotics, and alcohol. When it is used in combination with an antipsychotic for rapid tranquillisation there may be additional risks. For example, the adverse effects of intramuscular [haloperidol](#) include extrapyramidal and cardiovascular adverse effects. The NICE clinical guideline on [violence](#) advises that rapid tranquillisation can cause excessive sedation and loss of consciousness, loss of airway, and respiratory and cardiovascular collapse.

NICE recommends that vital signs should be monitored after rapid tranquillisation, and blood pressure, pulse, temperature, respiration and hydration should be recorded regularly, at intervals agreed by a multidisciplinary team, until the person becomes active again.

- According to the Cochrane review ([Huf et al. 2009](#)), serious adverse events were seen in 2 out of 301 people in TREC Rio-I, 1 out of 200 people in TREC Vellore-I and 4 out of 300 people in TREC Vellore-II. TREC Rio-II was stopped early because of the difference in serious adverse events between the groups. Statistically significantly more people experienced serious adverse events with haloperidol alone compared with haloperidol plus promethazine (11 out of 145 people compared with 1 out of 153 people respectively; RR 0.09, 95% CI 0.01 to 0.66; NNH 15, 95% CI 14 to 40). Acute dystonia was experienced by 10 people receiving haloperidol alone, compared with none receiving the combination.
- [Baldaçara et al. \(2011\)](#) compared 5 intramuscular interventions for treating agitation and aggression in 150 people with psychosis or bipolar disorder: haloperidol 5 mg plus promethazine 50 mg; haloperidol 5 mg plus midazolam 15 mg; haloperidol 5 mg alone; olanzapine 10 mg; and ziprasidone 20 mg. Excessive sedation was the most common adverse effect (70% of all adverse effects) and was significantly highest in the haloperidol plus midazolam group ($p < 0.001$). Extrapyramidal adverse effects were experienced by 5 people receiving haloperidol plus promethazine, 5 people receiving haloperidol only, and 3 people receiving haloperidol plus midazolam.
- [Mantovani et al. \(2013\)](#) compared 4 low-dose intramuscular interventions for treating psychomotor agitation in 100 people. The 4 intervention arms were haloperidol 2.5 mg plus promethazine 25 mg; haloperidol 2.5 mg plus midazolam 7.5 mg; olanzapine 10 mg; and ziprasidone 10 mg. Compared with the haloperidol plus midazolam group, statistically significantly more people in the haloperidol plus promethazine group experienced extrapyramidal adverse effects ($p < 0.05$); there were no significant differences between haloperidol plus midazolam and the other treatments.
- All of the studies were undertaken in Brazil or India and may not be applicable to UK clinical practice. In addition, the doses of some drugs used in the TREC trials were higher than those generally recommended in the UK; the doses of most drugs used in [Mantovani et al. \(2013\)](#) were lower. The results of the studies relate to intramuscular haloperidol plus intramuscular promethazine in combination and cannot be extrapolated to apply to promethazine alone or in combination with other antipsychotics.
- Overall, the Cochrane review provides limited evidence that haloperidol plus promethazine is effective for the rapid tranquillisation of people with agitation or aggression associated with mental illness. However, it is difficult to draw any firm conclusions because the results are

heterogeneous. Also, safety analyses in the Cochrane review and 2 small RCTs do not provide conclusive evidence that the combination of promethazine with haloperidol is safer than other intramuscular treatments, or that it reduces the adverse effects of antipsychotics when used for rapid tranquillisation.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

One Cochrane systematic review was identified ([Huf et al. 2009](#)), which included 4 RCTs investigating the effect of intramuscular haloperidol in combination with intramuscular promethazine for treating agitation or aggression thought to be caused by psychotic illness in people in psychiatric emergency room settings. All 4 RCTs were part of the TREC (Rapid Tranquillisation Clinical Trial) collaboration. The findings of this review are presented in table 1.

Two small RCTs in psychiatric emergency room settings were also identified that assessed intramuscular haloperidol plus promethazine. They add little to the evidence provided by the Cochrane review but are briefly discussed in this evidence summary, primarily in the safety sections.

The first of the small studies ([Baldaçara et al. 2011](#)) compared 5 intramuscular interventions for treating agitation and aggression in 150 people with psychosis or bipolar disorder: haloperidol 5 mg plus promethazine 50 mg; haloperidol 5 mg plus midazolam 15 mg; haloperidol 5 mg alone; olanzapine 10 mg; and ziprasidone 20 mg. All were given intramuscularly. At 1 hour, all the treatments statistically significantly reduced aggression ($p < 0.001$) and agitation ($p < 0.001$), and increased sedation ($p = 0.016$).

The second small study ([Mantovani et al. 2013](#)) compared 4 low-dose intramuscular interventions for treating psychomotor agitation in 100 people. The 4 intervention arms were haloperidol 2.5 mg plus promethazine 25 mg; haloperidol 2.5 mg plus midazolam 7.5 mg; olanzapine 10 mg; and ziprasidone 10 mg. All treatments statistically significantly reduced agitation between 30 minutes and 90 minutes ($p < 0.001$).

Table 1 Summary of the trials included in the [Huf et al. \(2009\)](#) Cochrane systematic review

Trial 1: TREC Rio-I			
	Haloperidol (up to 10 mg IM) plus promethazine (up to 50 mg IM)	Midazolam (up to 15 mg IM)	Analysis
Randomised	n=150	n=151	
Efficacy	n=150	n=151	
Primary outcome: tranquil or asleep by 30 minutes ^a	101/150 67%	134/151 89%	Significantly more people were tranquil or asleep by 30 minutes with midazolam RR 2.90, 95% CI 1.75 to 4.80 NNT 5, 95% CI 2 to 12
Selected secondary outcomes:			
Tranquil or asleep by 2 hours	138/150 92%	144/151 95%	No significant difference between groups
Not asleep by 30 minutes ^a	107/150 71%	58/151 38%	Significantly more people were awake at 30 minutes with haloperidol plus promethazine RR 1.86, 95% CI 1.48 to 2.33 NNT 3, 95% CI 2 to 5

Other outcomes with no significant differences between the groups			<ul style="list-style-type: none"> • The proportion refusing oral medication within 24 hours • The proportion needing to see a doctor within 24 hours • The proportion with another episode of aggression within 24 hours • The proportion requiring restraint or seclusion by 2 hours • The proportion requiring additional tranquillising medication by 2 hours • The proportion not discharged from hospital at 15 days • Study drop-out rates at 2 hours, 24 hours and 2 weeks
Safety	n=150	n=151	
People reporting serious adverse events	1 person who had epilepsy had a seizure 15 minutes after administration and recovered with benzodiazepine treatment	Respiratory rate fell in 1 person who used alcohol and possibly cocaine, but he/she recovered with flumazenil treatment	No significant difference between the groups
Trial 2: <u>TREC Vellore-I</u>			
	Haloperidol (up to 10 mg IM) plus promethazine (up to 50 mg IM)	Lorazepam (up to 4 mg IM)	Analysis
Randomised	n=100	n=100	

Efficacy	n=100	n=100	
Primary outcome: tranquil or asleep by 30 minutes	95/100 95%	81/100 81%	Significantly more people were tranquil or asleep by 30 minutes with haloperidol plus promethazine RR 0.26, 95% CI 0.10 to 0.68 NNT 8, 95% CI 6 to 17
Selected secondary outcomes:			
Tranquil or asleep by 2 hours	97/100 97%	88/100 88%	Significantly more people were tranquil or asleep by 2 hours with haloperidol plus promethazine RR 0.25, 95% CI 0.07 to 0.86 NNT 12, 95% CI 9 to 60
Tranquil or asleep by 4 hours	4/100 96%	4/100 96%	No significant difference between the groups
Not asleep by 30 minutes	31/100 31%	78/100 78%	Significantly more people were awake at 30 minutes with lorazepam RR 0.40, 95% CI 0.29 to 0.54 NNT 3, 95% CI 2 to 3
Mean CGI score at 30 minutes	1.89 (SD 0.7)	2.49 (SD 1.1)	Significantly more people improved with haloperidol plus promethazine Mean difference -0.60, 95%CI -0.86 to -0.34 The difference was still statistically significant at 1 hour, but not at 2 hours and 4 hours

Other outcomes with no significant differences between the groups			<ul style="list-style-type: none"> • The proportion requiring restraint or seclusion by 30 minutes, 1 hour, 2 hours and 4 hours • The proportion requiring additional tranquillising medication by 30 minutes, 1 hour, 2 hours and 4 hours • The proportion needing to see a doctor within 4 hours • The proportion not discharged from hospital at 4 hours • The proportion refusing oral medication within 2 weeks • Study drop-out rates at 4 hours and 2 weeks
Safety	n=100	n=100	
People reporting serious adverse events	None	1 person with a history of asthma complained of moderate worsening of respiratory difficulty after administration	<p>No significant difference between the groups</p> <p>No changes in extrapyramidal symptom scores were seen in any participants</p>
Trial 3: <u>TREC Rio-II</u>			
	Haloperidol (up to 10 mg IM) plus promethazine (up to 50 mg IM)	Haloperidol alone (up to 10 mg IM)	Analysis
Randomised	n=160	n=156	

Efficacy	n=160	n=156	3 people from the combination treatment group and 2 people from the haloperidol alone group were randomised but left the study before they received treatment; analysis was by ITT with no improvement assumed in people who had left
Primary outcome: tranquil or asleep by 20 minutes	112/160 70%	84/156 54%	Significantly more people were tranquil or asleep by 20 minutes with haloperidol plus promethazine RR 0.65, 95% CI 0.49 to 0.87 NNT 7, 95% CI 5 to 17
Selected secondary outcomes:			
Tranquil or asleep by 2 hours	143/160 89%	126/156 81%	Significantly more people were tranquil or asleep by 2 hours with haloperidol plus promethazine RR 0.55, 95% CI 0.32 to 0.96 NNT 12, 95% CI 8 to 132 There was no significant difference between the groups at 40 minutes or 1 hour
Not asleep by 20 minutes	132/160 83%	145/156 93%	Significantly more people were awake at 20 minutes with haloperidol alone RR 0.89, 95% CI 0.82 to 0.96 NNT 10, 95% CI 7 to 28
Doctor called to see person within 2 hours	30/153 20%	43/145 30%	Significantly more people receiving haloperidol alone needed to see a doctor RR 0.66, 95% CI 0.44 to 0.99 NNT 10, 95% CI 6 to 337

<p>Other outcomes with no significant differences between the groups</p>			<ul style="list-style-type: none"> • The proportion refusing oral medication within 24 hours • The proportion with another episode of aggression within 24 hours • The proportion requiring restraint or seclusion within 2 hours • The proportion requiring additional tranquillising medication within 2 hours • The proportion not discharged from hospital at 2 weeks • Study drop-out rates before treatment and at 24 hours
<p>Safety</p>	<p>153</p>	<p>145</p>	<p>Adverse effects were reported as not available for 5 non-completers, which would leave 311 people in the safety population (157 in the combination treatment group and 154 in the haloperidol alone group). However, adverse effects are only reported for 298 people; it is unclear why</p>
<p>People reporting serious adverse events</p>	<p>1/153 0.7%</p>	<p>11/145 8%</p>	<p>Significantly more people experienced serious adverse events with haloperidol alone</p> <p>RR 0.09, 95% CI 0.01 to 0.66</p> <p>NNH 15, 95% CI 14 to 40</p> <p>1 person in each group had a seizure</p> <p>This trial was stopped early because of the difference in serious adverse events between the groups</p>

People reporting dystonia	None	10/145 7%	Significantly more people experienced dystonia with haloperidol alone RR 0.05, 95% CI 0.00 to 0.76 NNH 16, 95% CI 15 to 62
Trial 4: TREC Vellore-II			
	Haloperidol (up to 10 mg IM) plus promethazine (up to 50 mg IM)	Olanzapine (up to 10 mg IM)	Analysis
Randomised	n=150	n=150	
Efficacy	n=150	n=150	
Primary outcome: tranquil or asleep by 15 minutes	136/150 91%	131/150 87%	No significant difference between the groups
Selected secondary outcomes:			
Tranquil or asleep at 1 hour	149/150 99%	141/150 94%	Significantly more people were tranquil or asleep by 1 hour with haloperidol plus promethazine RR 0.11, 95% CI 0.01 to 0.87 NNT 19, 95% CI 17 to 129 There was no significant difference between the groups at 30 minutes, 2 hours or 4 hours

Not asleep at 15 minutes	64/150 43%	85/150 57%	Significantly more people were awake at 15 minutes with olanzapine RR 0.75, 95% CI 0.60 to 0.95 NNT 8, 95% CI 5 to 36 The difference between the groups remained significant at 30 minutes, 1 hour, 2 hours and 4 hours
Mean CGI score at 15 minutes	1.83 (SD 1.01)	2.11 (SD 1.03)	Significantly more people improved with haloperidol plus promethazine Mean difference -0.28, 95% CI -0.51 to -0.05 The difference was still statistically significant at 30 minutes, 1 hour, 2 hours and 4 hours
Additional tranquillising medication required with 4 hours	31/150 21%	65/150 43%	Significantly more people receiving olanzapine needed additional tranquillising medication RR 0.48, 95% CI 0.33 to 0.69 NNT 5, 95% CI 4 to 8
Doctor called to see person within 4 hours	23/150 15%	49/150 33%	Significantly more people receiving olanzapine needed to see a doctor RR 0.47, 95% CI 0.30 to 0.73 NNT 6, 95% CI 5 to 12

Other outcomes with no significant differences between the groups			<ul style="list-style-type: none"> • The proportion requiring restraint or seclusion by 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours • The proportion refusing additional oral medication within 24 hours • The proportion needing further observations after 4 hours • The proportion not discharged from hospital within 4 hours, or admitted to hospital within 4 hours • The proportion taking oral medication at 2 weeks • Study drop-out rates at any time point
Safety	n=150	n=150	
People reporting serious adverse events	1 person had dehydration	2 people had akathisia and 1 had nausea	<p>No significant difference between the groups</p> <p>No changes in extrapyramidal symptom scores were seen in any participants</p>
<p>Abbreviations: CGI, Clinical Global Impression, a scale measuring severity of illness and clinical improvement; <u>CI, confidence interval</u>; IM, intramuscular; <u>ITT, intention to treat</u>; n, number of participants; <u>NNH, number needed to harm</u>; <u>NNT, number needed to treat</u>; <u>RR, relative risk</u>; SD, standard deviation.</p> <p>^a The primary outcome used in TREC Rio-I was tranquil or asleep by 20 minutes but these results are reported as tranquil or asleep by 30 minutes in the Cochrane review because the reviewers selected 30 minutes as the primary outcome. Similarly, the proportion of people not asleep was assessed at 20 minutes, not 30 minutes.</p>			

Safety

The summary of product characteristics for promethazine ([Phenergan injection](#)) states that it is contraindicated in people with central nervous system depression, known hypersensitivity, or those who have taken monoamine oxidase inhibitors within the past 14 days. Cautions include

respiratory conditions, coronary artery disease, epilepsy and hepatic and renal insufficiency. Adverse effects include drowsiness, dizziness, restlessness, headaches, nightmares, tiredness, disorientation and anticholinergic effects.

Promethazine enhances the effects of anticholinergic agents, tricyclic antidepressants, sedatives and hypnotics, and alcohol. When promethazine is used in combination with an antipsychotic for rapid tranquillisation there may be additional risks. For example, the adverse effects of intramuscular [haloperidol](#) include extrapyramidal and cardiovascular adverse effects. The NICE clinical guideline on [violence](#) advises that rapid tranquillisation can cause excessive sedation and loss of consciousness, loss of airway, and respiratory and cardiovascular collapse. NICE recommends that vital signs should be monitored after rapid tranquillisation, and blood pressure, pulse, temperature, respiration and hydration should be recorded regularly, at intervals agreed by a multidisciplinary team, until the person becomes active again.

See table 1 for a summary of adverse events seen in the Cochrane review.

In [Baldaçara et al. \(2011\)](#), there was no statistically significant difference in the incidence of adverse effects between the 5 groups ($p < 0.001$). Excessive sedation was the most common adverse effect (70% of all adverse effects) and was significantly highest in the haloperidol plus midazolam group ($p < 0.001$). Extrapyramidal adverse effects were experienced by 5 people receiving haloperidol plus promethazine, 5 people receiving haloperidol only, and 3 people receiving haloperidol plus midazolam.

In [Mantovani et al. \(2013\)](#), compared with the haloperidol plus midazolam group, statistically significantly more people in the haloperidol plus promethazine group experienced extrapyramidal adverse effects ($p < 0.05$); there were no significant differences between haloperidol plus midazolam and the other treatments.

Cost effectiveness and cost

[Phenergan injection](#) costs £6.74 for 10×1 ml ampoules containing 25 mg/ml promethazine hydrochloride ([MIMS](#), January 2014).

Relevance to NICE guidance programmes

NICE issued a clinical guideline on [Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments](#) (NICE clinical guideline 25) in 2005.

NICE does not recommend the routine use of intramuscular haloperidol in combination with intramuscular promethazine for rapid tranquillisation in psychiatric practice in the UK. Although the combination has been shown to be effective and relatively safe elsewhere, the Guideline Development Group concluded that there is insufficient evidence of its safety in UK clinical practice. Intramuscular haloperidol in combination with intramuscular promethazine may be considered as an alternative to intravenous administration of benzodiazepines or haloperidol only in very exceptional circumstances, which should be specified and recorded, and under the guidance of a senior psychiatrist.

This evidence summary is primarily based on a Cochrane systematic review ([Huf et al. 2009](#)) of intramuscular haloperidol in combination with intramuscular promethazine that was published after the NICE guideline was developed. Two RCTs ([TREC Rio-I](#) and [TREC Vellore-I](#)) that were assessed by NICE are included in the evidence summary because they form part of the Cochrane review. No published studies were identified assessing promethazine alone or in combination with other antipsychotics for rapid tranquillisation.

The NICE clinical guideline on violence is currently being updated ([Violence and aggression \[update\]](#)), with publication expected in April 2015. The [final scope](#) for this guideline states that it will review the effectiveness, acceptability and safety of available drugs and their dosages for rapid tranquillisation. The scope states that recommendations for pharmacological interventions will normally fall within licensed indications, and only exceptionally, if clearly supported by evidence, will use outside of a licensed indication be recommended.

Other NICE guidelines covering the use of rapid tranquillisation include:

- [Bipolar disorder](#) (NICE clinical guideline 38)
- [Schizophrenia \(update\)](#) (NICE clinical guideline 82)
- [Service user experience in adult mental health](#) (NICE clinical guideline 136).

Intervention and alternatives

Promethazine hydrochloride is a long-acting antihistamine with antiemetic, anticholinergic and sedative properties. It is available as oral and injectable formulations. Promethazine ampoules ([Phenergan](#), Sanofi) contain 25 mg/ml promethazine hydrochloride for intramuscular or intravenous injection and are licensed:

- for symptomatic treatment of allergic conditions of the upper respiratory tract and skin including allergic rhinitis, urticaria and anaphylactic reactions
- for sedation and treatment of insomnia in adults
- as an adjunct in preoperative sedation in surgery and obstetrics
- as a paediatric sedative.

Intramuscular promethazine hydrochloride is sometimes used off-label for the rapid tranquillisation of people with mental health conditions who have agitation or aggression. Specialists involved in the production of this evidence summary have advised that, in practice, it is generally given in combination with an intramuscular antipsychotic such as haloperidol for this indication, rather than being used alone.

Condition

Disturbed or violent behaviour by a person in an inpatient psychiatric setting poses a serious risk to the individual, other service users and staff. In 1998 to 1999, it is reported that an NHS Executive survey found that there were approximately 65,000 violent incidents against staff across the NHS ([NICE full guideline on violence](#)).

The [NICE full guideline on violence](#) defines rapid tranquillisation as the use of medication to calm or lightly sedate the person and reduce the risk to self and others. The aim is to control severe mental and behavioural disturbance (including aggression associated with schizophrenia, mania and other psychiatric conditions) to allow a thorough psychiatric evaluation to take place, while allowing comprehension and response to spoken messages throughout. Rapid tranquillisation usually involves administering medication over a brief period of 30 to 60 minutes. In the UK, excessive sedation or sleep is not considered a desirable outcome; a state of calm is preferred, with the person remaining conscious if possible.

NICE clinical guideline on [violence](#) advises that rapid tranquillisation, physical intervention and seclusion are not primary treatment techniques and should only be considered if de-escalation and other strategies have failed to calm the person. When determining which interventions to use, it is advised that clinical need, safety of the individual and others, and, where possible, advance directives should be taken into account. The intervention selected should be a reasonable and proportionate response to the risk posed by the person.

Alternative treatment options

Benzodiazepines are often used for rapid tranquillisation; however, they can cause respiratory depression at high doses or in combination with alcohol or some other illegal substances. Lorazepam has a short half-life, which limits the risk of excessive sedation. If benzodiazepines are contraindicated or have previously been ineffective, antipsychotics are commonly considered; however, they can cause adverse extrapyramidal and cardiovascular adverse effects. Using a combination of a benzodiazepine and an antipsychotic can allow a lower dose of antipsychotic to be used (see the [NICE full guideline on violence](#)).

The NICE clinical guideline on [violence](#) advises that oral medication should be offered for rapid tranquillisation whenever possible. If oral treatment is refused, is not indicated by previous clinical response, is not appropriate to the level of risk posed by the situation, or is ineffective, parenteral treatment may be considered. The intramuscular route is preferred to the intravenous route from a safety point of view.

When behavioural disturbance occurs in a non-psychotic context, NICE recommends that it is preferable to use oral lorazepam alone for rapid tranquillisation. Intramuscular lorazepam may be used if necessary. When behavioural disturbance occurs in the context of psychosis, an oral antipsychotic should be considered in combination with oral lorazepam to achieve early onset of calming or sedation or use of a lower dose of antipsychotic. If parenteral therapy is considered necessary in a person with psychosis, NICE recommends a combination of an intramuscular antipsychotic and an intramuscular benzodiazepine (haloperidol and lorazepam). Intramuscular olanzapine may also be considered for moderate disturbance in people with psychosis.

When the NICE guideline was developed there was evidence that intramuscular haloperidol in combination with intramuscular promethazine is effective for rapid tranquillisation by inducing sleep. However, the Guideline Development Group considered that the evidence was not relevant to UK clinical practice because the primary objective of the studies was sleep and, in the UK, the primary objective is to calm the person to enable other psychosocial techniques to be used (see the [NICE full guideline on violence](#)). There is also insufficient evidence that the safety of intramuscular midazolam alone has been sufficiently demonstrated in the UK, although it has been shown to be effective and relatively safe elsewhere. The Guideline Development Group was therefore unable to recommend either intramuscular haloperidol plus intramuscular promethazine or intramuscular midazolam alone for routine psychiatric practice in the UK.

Intramuscular haloperidol in combination with intramuscular promethazine may be considered as an alternative to intravenous administration of benzodiazepines or haloperidol only in very

exceptional circumstances, which should be specified and recorded, and under the guidance of a senior psychiatrist.

In general, all drugs used for rapid tranquillisation carry risks of excessive sedation and loss of consciousness, loss of airway, and respiratory and cardiovascular collapse. The different classes of medications and individual drugs within these classes have specific risks that need to be considered.

The NICE clinical guideline on [violence](#) recommends that vital signs should be monitored after rapid tranquillisation, and blood pressure, pulse, temperature, respiration and hydration should be recorded regularly, at intervals agreed by a multidisciplinary team, until the person becomes active again.

Evidence review: efficacy

One Cochrane [systematic review](#) was identified ([Huf et al. 2009](#)). It included 4 [randomised controlled trials](#) (RCTs) investigating intramuscular haloperidol in combination with intramuscular promethazine for treating agitation or aggression thought to be caused by psychotic illness in people attending psychiatric emergency rooms.

Two small RCTs in psychiatric emergency room settings were also identified that assessed intramuscular haloperidol plus promethazine. They add little to the evidence provided by the Cochrane review but are briefly discussed in this evidence summary, primarily in the safety sections. [Baldaçara et al. \(2011\)](#) compared 5 pharmacological interventions for treating agitation or aggression in people with psychosis or bipolar disorder. [Mantovani et al. \(2013\)](#) compared low doses of 4 pharmacological interventions for treating psychomotor agitation of any cause.

No published studies were identified that assess promethazine alone or in combination with other antipsychotics for rapid tranquillisation.

Cochrane systematic review

The Cochrane systematic review ([Huf et al. 2009](#)) examined whether intramuscular haloperidol in combination with intramuscular promethazine is effective for treating agitation or aggression thought to be caused by psychotic illness. It included RCTs published before February 2008 that compared haloperidol plus promethazine with:

- intramuscular haloperidol or another antipsychotic alone

- an intramuscular benzodiazepine alone
- an intramuscular anticonvulsive alone
- intramuscular haloperidol plus a benzodiazepine
- placebo or no intervention.

The primary outcomes were the proportions of people who were not tranquil or asleep 30 minutes after administration; who had another episode of aggression within 24 hours; and who had serious adverse events within 24 hours.

Four RCTs, including a total of 1117 people, were included in the Cochrane review. All 4 trials were part of the TREC (Rapid Tranquillisation Clinical Trial) collaboration. Two of the trials ([TREC Rio-I](#) and [TREC Rio-II](#)) were conducted in Rio de Janeiro, Brazil; the other 2 ([TREC Vellore-I](#) and [TREC Vellore-II](#)) were conducted in Vellore, India.

The TREC Rio trials were undertaken in specialist psychiatric emergency rooms in large hospitals in the inner city; the TREC Vellore trials were undertaken in the psychiatric emergency rooms in a large general hospital serving the city and the surrounding area. All the centres had limited funding and a rapid turnover of people.

The trials included all people who were being considered for rapid tranquillisation in the psychiatric emergency rooms. In the Rio trials, over two-thirds of participants had schizophrenia and almost 20% had mania; in the Vellore trials only around 16% of participants had schizophrenia and almost 50% had mania. Participants in the Rio trials were slightly older (mean age 38 years) than in the Vellore trials (mean age 31 years). Most participants in the trials were described to be severely agitated or worse.

All 4 RCTs included an intramuscular haloperidol (up to 10 mg) plus intramuscular promethazine (up to 50 mg) arm. The trials compared this combination with:

- TREC Rio-I (n=301): intramuscular midazolam (up to 15 mg)
- TREC Rio-II (n=316): intramuscular haloperidol alone (up to 10 mg)
- TREC Vellore-I (n=200): intramuscular lorazepam (up to 4 mg)
- TREC Vellore-II (n=300): intramuscular olanzapine (up to 10 mg).

All treatments were administered as single doses.

Haloperidol plus promethazine compared with benzodiazepines

TREC Rio-I and TREC Vellore-I (total n=501) compared intramuscular haloperidol plus intramuscular promethazine with an intramuscular benzodiazepine (midazolam and lorazepam respectively). The primary outcome in TREC Rio-I was tranquil or asleep by 20 minutes but the results are reported as tranquil or asleep by 30 minutes in the Cochrane review because the reviewers selected 30 minutes as the primary outcome. The primary outcome of TREC Vellore-I was the proportion of people tranquil or asleep by 4 hours. Meta-analysis of these 2 studies could not be undertaken because of heterogeneity.

In TREC Rio-I, 67% of people receiving haloperidol plus promethazine were tranquil or asleep by 30 minutes (reported in the trial as 20 minutes) compared with 89% receiving midazolam. The likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with midazolam (risk ratio [RR] 2.90, 95% confidence interval [CI] 1.75 to 4.80, number needed to treat [NNT] 5, 95% CI 2 to 12). Conversely, in TREC Vellore-I, the likelihood of being tranquil or asleep by 30 minutes was statistically significantly higher with haloperidol plus promethazine compared with lorazepam (RR 0.26, 95% CI 0.10 to 0.68; NNT 8, 95% CI 6 to 17). In this trial, 95% of people receiving haloperidol plus promethazine were tranquil or asleep by 30 minutes compared with 81% receiving lorazepam.

By 2 hours, in TREC Rio-I there was no longer a statistically significant difference in the proportion of people who were tranquil or asleep with haloperidol plus promethazine compared with midazolam. In TREC Vellore-I, the likelihood of tranquillisation or sleep at 2 hours remained statistically significantly higher with haloperidol plus promethazine, compared with lorazepam (RR 0.25, 95% CI 0.07 to 0.86; NNT 12, 95% CI 9 to 60). However, there was no statistically significant difference between the groups at 4 hours, by which time 96% of both groups were tranquil or asleep.

The NICE full guideline on violence (NICE clinical guideline 25) assessed the TREC Rio-I and TREC Vellore-I trials and considered that the results were not relevant to UK clinical practice because the primary objective of the studies was sleep, whereas in the UK the primary objective is to calm the person to enable other psychosocial techniques to be used.

In TREC Rio-I, significantly more people were asleep at 30 minutes (reported in the trial as 20 minutes) with midazolam, compared with haloperidol plus promethazine (62% compared with 29% respectively; RR 1.86, 95% CI 1.48 to 2.33; NNT 3, 95% CI 2 to 5). By contrast, significantly more people in the haloperidol plus promethazine group were asleep at 30 minutes in TREC

Vellore-I, compared with the lorazepam group (69% compared with 22% respectively; RR 0.40, 95% CI 0.29 to 0.54; NNT 3, 95% CI 2 to 3).

TREC Vellore-I reported outcomes on the Clinical Global Impressions scale (CGI; a measure of severity of illness and clinical improvement). Haloperidol plus promethazine statistically significantly improved the mean CGI score compared with lorazepam at 30 minutes (mean difference -0.60 , 95% CI -0.86 to -0.34). Significance was maintained 1 hour after administration but there was no difference between treatments after this time.

For other outcomes assessed, there was no statistically significant difference between haloperidol plus promethazine and the benzodiazepines in study drop-out rates or in the proportions of people:

- requiring restraint or seclusion
- requiring additional tranquillising medication or refusing oral medication
- needing to see a doctor
- who had another episode of aggression within 24 hours (reported for TREC Rio-I only)
- who were not discharged from hospital.

More details are available in table 1 in the [summary of the evidence](#) section.

Haloperidol plus promethazine compared with antipsychotics alone

Haloperidol plus promethazine compared with haloperidol alone

TREC Rio-II (n=316) compared intramuscular haloperidol plus intramuscular promethazine with intramuscular haloperidol alone. The primary outcome was the proportion of people who were tranquil or asleep by 20 minutes.

By 20 minutes, 70% of people receiving haloperidol plus promethazine were tranquil or asleep, compared with 54% of those receiving haloperidol alone. The difference was statistically significant (RR 0.65, 95% CI 0.49 to 0.87; NNT 7, 95% CI 5 to 17). There was no statistically significant difference between the groups at 40 minutes or 1 hour; however, at 2 hours significantly more people were tranquil or asleep with haloperidol plus promethazine than with haloperidol alone (89% compared with 81% respectively; RR 0.55, 95% CI 0.32 to 0.96; NNT 12, 95% CI 8 to 132).

Statistically significantly more people were asleep at 20 minutes with haloperidol plus promethazine compared with haloperidol alone (17% compared with 7% respectively; RR 0.89, 95% CI 0.82 to 0.96; NNT 10, 95% CI 7 to 28), but there was no significant difference in the proportions of people awake by 40 minutes, 1 hour or 2 hours.

There was a statistically significant decrease in the proportion of people needing to see a doctor within 24 hours with haloperidol plus promethazine, compared with haloperidol alone (20% compared with 30% respectively; RR 0.66, 95% CI 0.44 to 0.99; NNT 10, 95% CI 6 to 337).

There was no significant difference between haloperidol plus promethazine and haloperidol alone in study drop-out rates or the proportion of people:

- refusing oral medication within 24 hours
- with a further episode of aggression within 24 hours who had another episode of aggression within 24 hours
- requiring restraint or seclusion within 2 hours
- requiring additional tranquillising medication within 2 hours
- who were not discharged from hospital by 2 weeks.

Haloperidol plus promethazine compared with olanzapine alone

TREC Vellore-II (n=300) compared intramuscular haloperidol plus intramuscular promethazine with intramuscular olanzapine alone. The primary outcome was the proportion of people who were tranquil or asleep by 15 minutes and 2 hours.

By 15 minutes, 91% of people receiving haloperidol plus promethazine were tranquil or asleep, compared with 87% of those receiving olanzapine. There was no statistically significant difference between the groups in this outcome at 15 minutes, 30 minutes, 2 hours or 4 hours. However, significantly more people in the haloperidol plus promethazine group were tranquil or asleep by 1 hour compared with the olanzapine group (RR 0.11, 95% CI 0.01 to 0.87; NNT 19, 95% CI 17 to 129).

People receiving haloperidol plus promethazine were statistically significantly more likely to be asleep at all time points (15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours) compared with people receiving olanzapine (for example, 15 minutes: 57% compared with 43% respectively; RR 0.75, 95% CI 0.60 to 0.95; NNT 8, 95% CI 5 to 36).

The mean CGI score was statistically significantly improved with haloperidol plus promethazine compared with olanzapine at all time points (for example, 15 minutes: mean difference -0.28 , 95%CI -0.51 to -0.05).

The proportion of people who needed additional tranquillising medication within 4 hours was statistically significantly lower with haloperidol plus promethazine compared with olanzapine (21% compared with 43% respectively; RR 0.48, 95% CI 0.33 to 0.69; NNT 5, 95% CI 4 to 8). The proportion of people who needed to see a doctor within 4 hours was also statistically significantly lower with haloperidol plus promethazine compared with olanzapine (15% compared with 33%; RR 0.47, 95% CI 0.30 to 0.73; NNT 6, 95% CI 5 to 12).

There was no significant difference between the groups in study drop-out rates or the proportion of people:

- requiring restraint or seclusion at any time point
- refusing additional oral tranquillising medication within 24 hours
- needing further observations within the first 4 hours
- who were not discharged from hospital within 4 hours or admitted to hospital within 4 hours
- taking oral medication at 2 weeks.

Additional randomised controlled trials

Baldaçara et al. (2011) was a Brazilian double-blind RCT that compared 5 intramuscular interventions for treating agitation and aggression in 150 people admitted to a psychiatric emergency room with psychosis or bipolar disorder. The 5 treatments were haloperidol 5 mg plus promethazine 50 mg; haloperidol 5 mg plus midazolam 15 mg; haloperidol 5 mg alone; olanzapine 10 mg; and ziprasidone 20 mg. At 1 hour, all the treatments statistically significantly reduced aggression ($p < 0.001$) and agitation ($p < 0.001$), and increased sedation ($p = 0.016$).

Mantovani et al. (2013) was a Brazilian double-blind RCT that compared low doses of 4 intramuscular interventions for treating psychomotor agitation in 100 people who presented with acute agitation and needed medication for rapid tranquillisation. The 4 treatments were haloperidol 2.5 mg plus promethazine 25 mg; haloperidol 2.5 mg plus midazolam 7.5 mg; olanzapine 10 mg; and ziprasidone 10 mg. All the treatments statistically significantly reduced agitation between 30 minutes and 90 minutes ($p < 0.001$).

Evidence review: safety

Summary of product characteristics

The summary of product characteristics for promethazine ([Phenergan injection](#)) states that it is contraindicated in people with central nervous system depression, known hypersensitivity, or those who have taken monoamine oxidase inhibitors within the past 14 days.

Caution is advised in:

- people with asthma, bronchitis or bronchiectasis
- people with severe coronary artery disease, narrow angle glaucoma, epilepsy or hepatic and renal insufficiency
- people with bladder neck or pyloro-duodenal obstruction
- children and young people with signs and symptoms suggestive of Reye's Syndrome
- women who are pregnant.

Adverse effects of promethazine include drowsiness, dizziness, restlessness, headaches, nightmares, tiredness and disorientation. Anticholinergic effects including blurred vision, dry mouth and urinary retention can also occur.

Promethazine enhances the effects of anticholinergic agents, tricyclic antidepressants, sedatives and hypnotics, and alcohol. When promethazine is used in combination with an antipsychotic for rapid tranquillisation there may be additional risks. For example, the adverse effects of intramuscular [haloperidol](#) include extrapyramidal and cardiovascular adverse effects. The NICE clinical guideline on [violence](#) advises that rapid tranquillisation can cause excessive sedation and loss of consciousness, loss of airway, and respiratory and cardiovascular collapse. NICE recommends that vital signs should be monitored after rapid tranquillisation, and blood pressure, pulse, temperature, respiration and hydration should be recorded regularly, at intervals agreed by a multidisciplinary team, until the person becomes active again.

Adverse effects in randomised controlled trials

Cochrane review

Haloperidol plus promethazine compared with benzodiazepines

Three serious adverse events were seen in [TREC Rio-I](#) and [TREC Vellore-I](#) (total n=501). In TREC Rio-I, 1 person who had epilepsy had a seizure 15 minutes after receiving haloperidol 5 mg and promethazine 50 mg, but recovered with benzodiazepine treatment. In the midazolam group, 1 person with aggression associated with alcohol and possibly cocaine use experienced respiratory depression and became cyanosed but recovered with flumazenil treatment. In TREC Vellore-I, 1 person with a history of asthma complained of moderate respiratory difficulty after administration of lorazepam. TREC Vellore-I assessed extrapyramidal adverse effects and reported that no participants experienced a change in their symptom score after treatment.

Haloperidol plus promethazine compared with haloperidol alone

The [TREC Rio-II](#) trial (n=316; safety analysis n=298) was stopped early because of the difference in serious adverse events between the groups. Statistically significantly more people experienced serious adverse events with haloperidol alone compared with haloperidol plus promethazine (11 people compared with 1 person respectively; [relative risk \[RR\]](#) 0.09, 95% [confidence interval \[CI\]](#) 0.01 to 0.66; [number needed to harm \[NNH\]](#) 15, 95% CI 14 to 40). Acute dystonia was experienced by 10 people receiving haloperidol alone, compared with none receiving the combination (RR 0.05, 95% CI 0.00 to 0.76; NNH 16, 95% CI 15 to 62). One person in each group had a seizure after treatment.

Haloperidol plus promethazine compared with olanzapine alone

In [TREC Vellore-II](#) (n=300), 4 serious adverse events were seen. One person in the haloperidol plus promethazine group experienced dehydration. Two people in the olanzapine group experienced akathisia and 1 experienced nausea.

Additional randomised controlled trials

In [Baldaçara et al. \(2011\)](#), there was no statistically significant difference in the incidence of adverse effects between the 5 groups ($p < 0.001$). Excessive sedation was the most common adverse effect (70% of all adverse effects) and was significantly highest in the haloperidol plus midazolam group ($p < 0.001$).

Extrapyramidal adverse effects were experienced by 5 people in the haloperidol plus promethazine group, 5 people in the haloperidol only group, and 3 people in the haloperidol plus midazolam group. Hypotension was experienced by 6 people in the ziprasidone group, 5 people in the haloperidol plus midazolam group, 3 people in the haloperidol plus promethazine group, and 1 person in the olanzapine group.

In [Mantovani et al. \(2013\)](#), 24 hours after administration, at least 1 extrapyramidal adverse effect was experienced by 20 people (74.1%) receiving haloperidol plus promethazine; 14 people (56%) receiving olanzapine; 12 people (52.2%) receiving ziprasidone; and 11 people (44%) receiving haloperidol plus midazolam. Compared with the haloperidol plus midazolam group, statistically significantly more people in the haloperidol plus promethazine group experienced extrapyramidal adverse effects ($p < 0.05$); there were no significant differences between haloperidol plus midazolam and the other treatments. Extrapyramidal adverse effects were reported to be mild, with a mean score of 0.76 (range 0 to 6) out of a possible 21.

Evidence review: economic issues

Cost

[Phenergan injection](#) costs £6.74 for 10×1 ml ampoules containing 25 mg/ml promethazine hydrochloride ([MIMS](#), January 2014).

Current drug usage

[Prescription cost analysis for England](#) showed that, in 2012, 100 prescription items of promethazine injection 25 mg/ml were dispensed in the community at a cost of £1100.

It is not known whether any of the items were prescribed in combination with intramuscular haloperidol for rapid tranquillisation. However, rapid tranquillisation should only take place in psychiatric units, wards and emergency departments where there are adequate resources to monitor and support people (including resuscitation facilities), and hospital prescriptions are not included in this data.

Evidence strengths and limitations

Cochrane review

The 4 TREC randomised controlled trials (RCTs) in the Cochrane review (Huf et al. 2009) were considered to be at low risk of bias because allocation was adequately concealed and any plausible biases were thought to be unlikely to seriously affect the results. However, the TREC trials were conducted by the authors of the Cochrane review, who noted their conflict of interest. Industry funding was not provided for any of the studies.

All the included trials were blind until treatment had been allocated to prevent selection bias. Some, but not all of the assessments were blinded. Although this may have affected the objectivity of the assessments, the authors state that the trials were designed to reflect a real-life situation.

The 4 trials included 1117 participants overall, and drop-out rates were low, with outcomes assessed for 99% of people. All efficacy analyses were performed by intention-to-treat; those who left the study were assumed to have had no improvement in aggression or agitation. In TREC Rio-II, adverse effects were reported as not available for 5 non-completers, which would leave 311 people (out of the original 316 people) in the safety population. However, adverse effects are only reported for 298 people; it is unclear why.

The 4 studies had similar designs. They compared the same doses of intramuscular haloperidol plus intramuscular promethazine (although in TREC Rio-1, half of the participants received haloperidol 5 mg and in the other studies most of the participants received 10 mg); most people had psychosis or mania; and broadly similar outcomes were measured. However, the combination was compared with 4 different comparators. In addition, some of the doses of medication used in the TREC trials were higher than those used in the UK. For example, Maudsley Prescribing Guidelines recommend that lorazepam 1–2 mg is used, but all participants in TREC Vellore-I received 4 mg. Similarly, a 5 mg dose of haloperidol is recommended in Maudsley but 10 mg was widely used in the TREC studies. The NICE clinical guideline on violence does not specify doses.

The results of the Cochrane review relate to intramuscular haloperidol plus intramuscular promethazine in combination and cannot be extrapolated to apply to promethazine alone. The studies were undertaken in India and Brazil and it is unclear whether the results are applicable to the UK.

The TREC Rio-I and TREC Vellore-I trials both compared haloperidol plus promethazine with a benzodiazepine; however, there was statistically significant heterogeneity between the results,

which does not appear to be solely due to the different benzodiazepines used. For the outcome of tranquil or asleep by 30 minutes, TREC Rio-I found that midazolam was more effective than haloperidol plus promethazine, whereas TREC Vellore-I found that haloperidol plus promethazine was significantly more effective than lorazepam. Significantly more people were asleep at 30 minutes with midazolam, compared with haloperidol plus promethazine in TREC Rio-I, whereas more people were asleep with the combination treatment, compared with lorazepam in TREC Vellore-I. (Note that the [NICE full guideline on violence](#) suggests that sleep is an undesirable outcome because in the UK the primary objective is to calm the person to enable other psychosocial techniques to be used.)

The authors of the Cochrane review assessed the difference between the 2 studies. Despite the studies having similar designs, 67% of people in TREC Rio-I who were receiving haloperidol plus promethazine were tranquil or asleep by 30 minutes, compared with 95% receiving the combination in TREC Vellore-I. The open nature of the study and the differences between the populations (for example, substance misuse, age and body mass index) were considered unlikely to have affected the results. In the Rio-I trial, the primary outcome was measured at 20 minutes, which was assumed by the authors of the review to be the same outcome as for 30 minutes. This may have underestimated the effect of the treatments in that study because more and more people were becoming tranquil over time. Also, in TREC Vellore-I most participants received 10 mg of haloperidol but 52% of participants in TREC Rio-I received only 5 mg. Another factor that may account for the disparity includes the difference in the study setting. In Rio de Janeiro, the busy psychiatric emergency rooms are said to filter people directly into the psychiatric hospital wards and people are rarely discharged within hours. In Vellore, the department of psychiatry is said to be tranquil, with open spaces permitting more tolerance of aggressive behaviour, and there is often rapid discharge back to the care of the family.

In TREC Rio-II, statistically significantly more people experienced serious adverse events (primarily dystonia) with haloperidol alone compared with haloperidol plus promethazine (11 people compared with 1 person respectively). The authors suggest that combining haloperidol with promethazine might protect against the adverse effects of haloperidol alone.

Additional RCTs

[Baldaçara et al. \(2011\)](#) was a double-blind RCT undertaken in Brazil. Randomisation was by permuted blocks but it is not known whether allocation was concealed. Two authors of the study received funding from the pharmaceutical industry. The trial was small: only 30 people were included in each arm which limits the [power](#) of the study to detect differences between the groups. One of the antipsychotics used, ziprasidone, is not licensed in the UK.

[Mantovani et al. \(2013\)](#) was a double-blind RCT undertaken in Brazil; allocation was concealed. The trial received no commercial funding. Only around 25 people were included in each arm of the study. Analyses were not by [intention to treat](#). Of 112 people who were randomised to receive treatment, complete data were not available for 8 people who were subsequently not included in the analyses. The reasons for the incomplete data are not reported. The doses of haloperidol, promethazine and midazolam used in this trial (2.5 mg, 25 mg and 7.5 mg respectively) were at least half of the standard doses generally used in the other trials, and generally used in UK clinical practice.

The authors of the [Cochrane review](#) suggest that combining haloperidol with promethazine might protect against the adverse effects of haloperidol alone (primarily dystonia); however, the results of these 2 studies do not support this. Extrapyramidal adverse effects were experienced by people receiving haloperidol plus promethazine in [Baldaçara et al. \(2011\)](#) and [Mantovani et al. \(2013\)](#). In [Mantovani et al. \(2013\)](#), these adverse effects were more frequent with haloperidol plus promethazine than with other treatments.

As with the [Cochrane review](#), the results of [Baldaçara et al. \(2011\)](#) and [Mantovani et al. \(2013\)](#) relate to intramuscular haloperidol plus intramuscular promethazine in combination and cannot be extrapolated to apply to promethazine alone.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- Broad internet search: Google e.g.

a. allintitle: rapid tranquilization filetype:pdf

b. allintitle: rapid tranquillisation filetype:pdf

c. allintitle: rapid tranquillization filetype:pdf

d. allintitle: promethazine

- [Trip Database](#)

a. "(promethazine tranquilisation) from:2002 to:2013", by quality

b. (promethazine tranquilization) from:2002 to:2013, by quality

c. "(promethazine rapid sedation) from:2002 to:2013", by quality

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
<1946 to Present>

Search Strategy: 21/11/13

1 Promethazine/ (2695)

2 promethazine.ti,ab. (1865)

3 phenergan.ti,ab. (155)

4 1 or 2 or 3 (3570)

5 exp Tranquilizing Agents/ (203933)

6 (hypnotics and sedatives).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (22629)

7 "Hypnotics and Sedatives"/ (22353)

8 tranquil*.ti,ab. (5300)

9 rapid* sedat*.ti,ab. (35)

10 5 or 6 or 7 or 8 or 9 (221370)

11 4 and 10 (1244)

12 limit 11 to (english language and yr="2002 -Current") (162)

Embase (via Ovid)

Database: Embase <1996 to 2013 November 20>

Search Strategy: 21/11/13

1 Promethazine/ (5226)

2 promethazine.ti,ab. (1002)

3 phenergan.ti,ab. (37)

4 1 or 2 or 3 (5334)

5 tranquil*.ti,ab. (1851)

6 rapid* sedat*.ti,ab. (31)

7 exp tranquilizer/ (183130)

8 hypnotic sedative agent/ (5794)

9 5 or 6 or 7 or 8 (187612)

10 4 and 9 (3037)

11 limit 10 to (english language and yr="2002 -Current") (2026)

12 limit 11 to exclude medline journals (383)

13 exp review/ (1528278)

14 (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (101915)

15 ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (8175)

16 ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (20580)

17 (pooling or pooled or mantel haenszel).ti,ab,sh. (54165)

18 (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (3854)

19 or/14-18 (162008)

20 13 and 19 (64257)

21 Meta Analysis/ (73303)

22 (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (108524)

23 ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (105685)

24 (integrative research review\$ or research integration).ti,ab,sh. (78)

25 or/21-24 (180823)

26 20 or 25 (210115)

27 clinical trials, phase iv/ or clinical trials, phase iii/ or randomised controlled trials/ or multicenter studies/ (48548)

28 (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (967473)

29 27 or 28 (972791)

30 (animal\$ not human\$).sh. (1860222)

31 29 not 30 (879287)

32 (cost\$ or economic\$).tw. (463398)

33 26 or 31 or 32 (1413913)

34 12 and 33 (92)

Cochrane Central Register of Controlled Trials (CENTRAL)

Search Name: ESUOLM Promethazine 211113

Last Saved: 21/11/2013 10:39:21.388

ID Search

#1 MeSH descriptor: [Promethazine] this term only

#2 promethazine:ti,ab

#3 phenergan:ti,ab

#4 #1 or #2 or #3

#5 MeSH descriptor: [Tranquilizing Agents] explode all trees

#6 MeSH descriptor: [Hypnotics and Sedatives] this term only

#7 tranquil*:ti,ab

#8 (rapid* sedat*):ti,ab

#9 #5 or #6 or #7 or #8

#10 #4 and #9

CRD HTA, DARE and EED database

#1 Promethazine/

#2 promethazine in any field

#3 phenergan in any field

#4 #1 or #2 or #3 or #4

Grey literature and ongoing trials

- [NICE Evidence Services](#)
- [Health Canada - Clinical Trials Search](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

Manufacturer's website

[Sanofi](#)

Evidence selection

A literature search was conducted from 2002 onwards to avoid overlap with the NICE clinical guideline on [Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments](#) (NICE clinical guideline 25). We included any randomised controlled trials (RCTs) comparing promethazine with any comparator(s) for rapid tranquillisation in people with agitation or aggression and with any underlying mental health condition. We excluded outdated reviews, case series, conference abstracts, and RCTs related to other uses of promethazine.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good

clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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