East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine details	
Name, brand name	Alimemazine, syn. trimeprazine , brand name Valergan – discontinued
Manufacturer	Zentiva, Concordia Int.
Proposed indication	Sleep disorders in children and adolescents (unlicensed)
Requested by	Surrey PCN in light of price increase

SUMMARY

Clinical Effectiveness

The purpose of this paper is to evaluate the evidence for continuous use of alimemazine in therapy of sleep disorder in children and adolescents.

Alimemazine is a first-generation H1-antihistamine and phenothiazine derivative with hypnotic, antihistamine, antiemetic and week antipsychotic activity (1, 2). Alimemazine is unlicensed in the UK for insomnia and this indication is not included within the BNF for Children (3).

Clinical trial evidence for pharmacological treatments other than melatonin is relatively scarce. The efficacy of alimemazine for children with sleep problems has been investigated in four small randomised controlled trials (4).

A systematic review published in 2000 addressed treatments for settling problems and night waking in young children. Four pharmacological studies were identified. Two of the drug trials used trimeprazine (alimemazine) vs. placebo, 1 used extinction (ignoring child's crying) plus trimeprazine vs. extinction alone, and the fourth used niaprazine (an antihistamine unavailable in the UK). The authors concluded that the drugs seem to be effective in the short term but evidence of long-term effect is patchy and contradictory (5). The review included only studies of young children (aged 5 and under), RCT only (crossover or parallel design), placebo-controlled studies and studies with clearly defined measureable outcomes. Studies of children with learning difficulties were not included (6).

Two trials reported by Richman and Simonoff were of drug only versus placebo—either up to 60 mg or 90mg. Both showed a statistically significant positive effect of drugs in the short term. The clinical significance is less clear as in both trials even the children receiving treatment continued to wake at night and up to one third did not improve with drugs. The picture is less convincing concerning a longer lasting effect. The same two studies included a follow up period. In one study the sleep score dropped marginally from 12.4 at baseline to 10.1 at six months follow up. These were calculated based on sleep diaries and parenteral reports, which have shown a large degree of inconsistency. One third of the subjects had withdrawn from the study at this stage. In the second study by Simonoff with a shorter follow up period, there was a reduction in number of wakes at night from 2.8 at baseline to 1.6 at four weeks' follow up. As both studies were of a cross over design there was no matched untreated group with which to compare these rates. France et al 1991 used trimeprazine as an adjunct to an extinction programme (ignoring a child's crying) rather than as a treatment in its own right. Although trimeprazine (plus extinction) did reduce night waking during the first 10 days of the trial more than placebo (plus extinction), there was no difference between the two groups at the end of treatment and at four weeks' follow up (6).
Conclusions drawn from this systematic review should be considered tentative as trials conducted were small and the methodological quality generally poor (6). The strength of evidence recommendation is (SORT) = B, due to inconsistent findings from RCTs included in the systematic review.

Another small RCT by France et al used two different doses of trimeprazine vs placebo. No clinically significant effects of the low dose were detected, whereas the effects of the high dose were not consistently replicated across nor within participants. (7)

Tab. 1 Randomized controlled trials of drug treatment of children's sleep problems

Study	Children, No., and problems	Intervention (dose)	Intervention length	Controls	Outcomes	Results
Richman, 1985	22, aged 12-24 mo, recruited from community survey, with night waking	Trimeprazine tartrate (30-60 mg)	2 weeks	Placebo	Sleep disturbance score (number of night wakes and settling)	12.1 with placebo ; 8.6 with treatment ($P < 0.01$)
Simonoff and Stores, 1987	20, aged 12-36 mo, referred for study, with night waking	Trimeprazine (45-90 mg)	4 weeks	Placebo	Night waking (frequency and duration)	2.4 wakes per night with placebo ; 1.4 wakes per night with treatment($P < 0.001$)
France et al, 1991	30, aged 7-27 mo, referred to sleep program with sleep disturbance	Extinction plus trimeprazine (30 mg)	4 weeks	Extinction plus placebo	Night waking (frequency and duration)	Intervention group improved quicker than placebo group ($P < 0.01$); no difference shown in longer term
France et al, 1999	12, aged 6–27 mo, with sleep problems	Trimeprazine two different doses (15 & 30 mg)	2x period of 21 days (low dose), OR 10 days (high dose), followed by 7 days wash-out period (x2)	Placebo	Night waking (frequency and duration)	No clinically significant effects of the low dose, whereas the effects of the high dose were not consistently replicated across nor within patients

Adapted from
De Bruyne P, Christiaens T, Boussery K, Mehuys E, Van Winckel M. Are antihistamines effective in children? A review of the evidence. Arch Dis Child. 2017;102(1):56-60 (4).
Ramchandani P, Wiggs L, Webb V, Stores G. A systematic review of treatments for settling problems and night waking in young children. BMJ. 2000;320(7229):209-13 (6).

The consensus statement of the **British Association for Psychopharmacology** states that antihistamines may have a role in short-term symptomatic treatment of insomnia in children. This is category II evidence (evidence from small, well-designed, but not necessarily representative samples) (8).
The sedative side effects of antihistamines may speed up behavioural programmes over short periods (France et al., 1991) but seem not to work without behavioural interventions; in a placebo-controlled double-blind trial in infants aged 6–27 months the same authors found no significant effect of 15mg or 30mg trimeprazine tartrate, and concluded that it is not recommended as a pharmacological treatment for infant sleep disturbance unless as an adjunct to a behavioural therapy program (France et al., 1999). Clinically, the short-term use of an H1 blocker for transient or extreme insomnia can be helpful and is frequently employed. However, tolerance can develop quickly and some children can experience dramatic and paradoxical over-arousal (8).

Safety

Many medications, in particular those introduced before 1985 have not been optimally studied in RCTs and in their day, they received authorisation out of lack of regulation of the required specifications and they remain on the market because the pharmacovigilance systems have not detected enough ADRs requiring their withdrawal (4).
A good example of this is the case of the first-generation antihistamines such as alimemazine. There is widespread use of first-generation H1-antihistamines in children; they have been on the market for a long time and many of them have received over-the-counter status (e.g. promethazine), though these first-generation H1-antihistamines are known to have the most major side effects due to poor receptor selectivity for the H1 receptor (4).

The most important ADRs are related to anticholinergic and histamine-like properties of alimemazine. Common side effects include drowsiness, headache and dizziness (> 1/100), anticholinergic effects such as constipation, urinary retention and accommodation disturbances are less common (1/100 to 1/1000), while extrapyramidal effects such as parkinsonism, acute dystonia and tardive dyskinesia, malignant neuroleptic syndrome, blood pressure drop and tachycardia or hematopoietic effects were reported rarely (<1/1000) (9).

A more recent study in the Netherlands has echoed the above side effect concerns associated with the use of antihistamines children (10).
The negative neurocognitive effect of antihistamines was described by Van Ruitenbeek et al. (11).

Jaundice, usually transient, occurs in a very small percentage of patients. A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has the biochemical and other characteristics of obstructive jaundice and is associated with obstructions of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice (12).

Hypotension or pallor may occur in children. Cardiac arrhythmias, including atrial arrhythmia: A-V block, ventricular tachycardia and fibrillation have been reported during therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. ECG changes, usually benign, include widened QT interval, ST depression, U-waves and T-wave changes. Respiratory depression is possible in susceptible patients (12).

A mild leukopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation (12).

Acute dystonias or dyskinesias, usually transitory are commoner in children and young adults and usually occur within the first 4 days of treatment or after dosage increases (12).

At least 13 cases of lethal overdose were reported after receiving therapeutic doses of alimemazine with blood concentrations 10-50 times higher than typical maximum plasma concentration.
There have been several case reports of serious and in some cases lethal events after use of alimemazine in therapeutic doses (of 3 mg / kg) in children, including hypotension, bradycardia, respiratory depression, seizures, malignant neuroleptic syndrome and malignant hyperthermia. Some older reports suggest an association between the use of phenothiazines, primarily alimemazine and promethazine, and sudden infant death syndrome (9).
Up to date a total of 217 reactions were reported to MHRA through the Yellow Card Scheme in the UK (period from 1967 to 07/2017). These included 99 ADR reports, 73 serious ADR reports and 6 fatal ADR reports.

The safety of alimemazine prescribing was reviewed by NPSA in 2007 concerning two medicine error incidents. One of which was when alimemazine was prescribed at 3ml of 7.5mg/5ml solution and overdose was given as the only strength available was 30mg/5ml solution (Low harm).
Another medication error occurred when patient was prescribed 'as required' doses of both chlorphenamine and alimemazine, and nursing staff were unaware of antihistamine properties of alimemazine (No harm) (13).

The use of both strengths in paediatric settings raises safety concerns and measures should be taken to prevent medicines errors from occurring, e.g. by prescribing the dose in both milligrams and millilitres. Additional patient information of indication ('for insomnia') shall be considered alongside standard BNF warning label.

NHS England has called for an action to tackle the over-prescribing of psychotropic drugs to people with learning disabilities after three separate reports highlighted the need for change. Research commissioned by the health body and delivered in three reports from the Care Quality Commission, Public Health England and NHS Improving Quality has found that:

- There is a much higher rate of prescribing of medicines associated with mental illness amongst people with learning disabilities than the general population, often more than one medicine in the same class, and in the majority of cases with no clear justification;
- Medicines are often used for long periods without adequate review, and;
- There is poor communication with parents and carers, and between different healthcare providers (14).

Patient factors

Alimemazine is considered as a RED drug on the North West Surrey traffic light system for sleep disorders in children and adolescents. The red traffic light status reflects the limited use in children and adolescents. Paediatric consultants at children behavioural services sometimes trial alimemazine in those patients who do not respond to melatonin.

The available data shows a significant degree of alimemazine prescribing in primary care. A total number of 841 prescription items of alimemazine were issued across East Surrey, Guildford & Waverley, Surrey Downs and Surrey Heath CCG in current 12 months based on NHS business authority data from ePACT. In the

same time period this accounted for 307 prescription items in Crawley, Horsham & Mid Sussex (CHMS) CCG.
There is a strong incentive from children's parents and family to receive treatment close to home. Although the experience from auditing these patients in CHMS is that this is often not done in safe manner. Several cases were identified where alimemazine was used when contraindicated, namely in patients with the history of epilepsy.

Before any changes in the colour status, it will be helpful to map the extent to which alimemazine is used by paediatric specialists and if promethazine could be considered as an alternative. Shared care agreement should be considered if promethazine (or alternative first generation H1-antihistamine) is used long term in these patients to allow monitoring of treatment outcomes, dose adjustments and toxicity and ADRs monitoring.
Patients may need to have their therapy stopped or repatriated back to the initiating provider if they are unable to change to an alternative option. As the prescribing may have been on-going for many years, patient's expectations would need to be managed and any repatriation may adversely affect the patient.

Cost implications

Drug tariff

Following discontinuation of the Vallergan® brand, over the last two years the NHS list price of alimemazine has increased by more than 1500% for both tablets and liquid. The lack of market competition is reflected in alimemazine listed as category A drug in Drug Tariff with current prices of
£112.85 per pack of 28 x 10 mg tablets, £243.51 per 100 ml of 30mg/5ml oral and £179.55 per 100 ml of 7.5mg/5ml oral solution.

Cost implications to local health authority

Based on information from The NHS Business Authority (ePACT data) the annual spend on alimemazine in East Surrey, Guildford & Waverley, Surrey Downs and Surrey Heath CCGs accounted for £268,557 whilst the figure in Crawley, Horsham and Mid Sussex CCG was £115,390. This includes only prescriptions issued within Primary care. The total cost to the NHS will be much higher.

Cost of alimemazine and comparative treatments

The table below gives the overview of the costs of alimemazine, melatonin and comparative treatment in first generation H1-atihistamines - promethazine. Cost is calculated for age groups of two, six and twelve years as well as the adults. In the paediatric settings, alimemazine is prescribed at generally large doses of 2 mg/kg nocte (only licensed in children as premedication to anaesthesia). For the cost purposes, the doses were capped at 60 mg per day in line with Guys' formulary, although Simonoff et al. used doses of up to 90 mg in trial patients. Promethazine cost was calculated using maximum Children BNF doses for corresponding age groups (3).

Tab. 2 Annual treatment cost for children 2 years and over.

Age / Drug and dose	**2 years (12kg)**	**6 years (21 kg)**	**12 years (39 kg)**	**Adult**
Alimemazine	2mg / kg on	2mg / kg on	capped at 60 mg on	capped at 60 mg on
7.5 mg/5 mL	£9,648	£16,896	£24,132	£24,132
30mg/5 mL	£3,273	£5,726	£8,182	£8,182
10 mg tablet	NA	NA	£8,125	£8,125
Promethazine	15 mg on	25 mg on	50 mg on	50 mg on
5mg/5mL	£144	£240	£480	£480
25 mg tablet	NA	£ 28	£56	£56
Melatonin	capped at 10 mg on	capped at 10 mg on	capped at 10 mg on	capped at 10 mg on
2mg MR tab	NA	£ 862	£ 862	£ 862
5mg/5mL	£ 835	£ 835	£ 835	£ 835

Note: Prices are based on October 2017 Drug Tariff prices of alimemazine 7.5mg/5ml oral solution (100 ml = £ 179.55) and 30mg/5ml oral solution (100 ml= £ 243.51), alimemazine 10 mg tablets (28 = £ 112.85), promethazine 5mg/5ml oral solution SF (100 ml = £ 2.85), promethazine 25 mg tablets (56 = 4.65£), melatonin 2mg modified-release tablets (30 = £ 15.39), melatonin 5mg/5ml oral solution (200 ml = £ 49.70)
Doses are based on Children BNF and BNF maximum daily doses (3, 15).

Relevant guidance / reviews

The Clinical Knowledge Summaries (NICE) do not recommend antihistamines for the management of short-term insomnia in adolescents and adults of 16 years and over, noting insufficient evidence to support their use, and significant potential for adverse effects (16).
Children under 16 years of age are not included in this summary, although it is known that children have higher susceptibility to adverse drug effects than general adult population

The consensus statement of the **British Association for Psychopharmacology** states that antihistamines may have a role in short-term symptomatic treatment of insomnia in children. This is category II evidence (evidence from small, well-designed, but not necessarily representative samples). On the contrary, the authors made a recommendation that antihistamines have a limited role in psychiatric and primary care practice for the management of insomnia in adults. (Level D recommendation; i.e. directly based on category IV evidence or extrapolated from category I, II, or III evidence) (8).

Likely place in therapy relative to current treatments

It is anticipated that treatment of sleep disorder in children and adolescents will be initiated by specialist paediatricians or neurologists specialising in behavioural disorders. The following three scenarios should be considered by the PCN:

1. Decision is made to **black list** alimemazine to treat night waking and insomnia in children **without an alternative first generation antihistamine**:
   This would trigger a need for a specialist appointment who would either consider an alternative treatment (e.g. melatonin) or to discontinue treatment.

2. Decision is made to **black list** alimemazine to treat night waking and insomnia in children **whilst offering a first generation H1-antihistamine (e.g. promethazine) as an alternative:**
   A treatment would need to be reviewed with a view of running a switch program to patients. The appropriate way to instigate the switch program should be agreed to ensure any changes are implemented in safe manner (an incident has been reported by Derbyshire CCG whereby promazine was prescribed instead of the intended promethazine, following an alimemazine switch programme).
   There is a possibility that this change will trigger a need for a follow-up specialist appointment.
   An additional consideration will be required as to the place of promethazine on traffic light system with at least two alternative scenarios:

   2a) **blue traffic light status** for promethazine, i.e. initiated under specialist for continuation in primary care without a formal shared care agreement

   2b) **amber traffic light status** for promethazine, i.e. initiated under specialist for continuation in primary care with shared care agreement, similarly to melatonin and other insomnia treatments in children.

3. Decision is made to keep the current status quo, the alimemazine **traffic light status** will remain **red**, i.e. for initiation and continuous prescribing under specialist care only.

Recommendation to PCN

The recommendation to the PCN in regards to place of alimemazine in treatment of insomnia in children and adolescents:

To blacklist alimemazine for all new patients.
Existing patients should be allowed a 6- to 12-month grace period, where the treatment should be reviewed by specialist. The traffic light status should be changed to BLACK for all patients after this transitional period.

The lack of supporting evidence, safety concerns and increased costs do not support the use of alimemazine in any care setting.

Medicine details

Name and brand name	Alimemazine (non-proprietary), formerly Valergan brand – discontinued
Licensed indication, formulation and usual dosage	Unlicensed for insomnia in children (and adults) Alimemazine 10mg tablets Alimemazine 30mg/5ml oral solution Alimemazine 7.5mg/5ml oral solution Dosage 2 mg/ kg on, usually capped at 60 mg

Summary of mechanism of action, and relevant pharmacokinetics	Pharmacotherapeutic group: Antihistamines, Sedating Antihistamines, ATC code: R06AD01. (1, 15) Alimemazine is a first-generation H1-antihistamine in the phenothiazine chemical class (4). It possesses antipruritic and antihistaminic properties with anticholinergic and sedative side effects. Studies evaluating the antipruritic effects of trimeprazine have concluded that the antipruritic effect is due to central sedative action rather than peripheral H1-blockade (17). Oral bioavailability of alimemazine tablet is 70%. The mean time to peak plasma level is 3.5 hours for the syrup and 4.5 hours for the tablets. The mean relative bioavailability for the tablets with respect to the syrup is approximately 70%. Alimemazine undergoes extensive liver metabolism. The listed metabolites of alimemazine are N-desalkyl metabolites, which activity is unknown. The elimination half-life of the parent compound is 4.78 to 8 hours (17). The rate of metabolism and excretion of phenothiazines decreases in old age. (12)
Important drug interactions	The sedative effects of phenothiazines may be intensified (additively) by alcohol, anxiolytics & hypnotics, opiates, barbiturates and other sedatives. There may be increased antimuscarinic and sedative effects of phenothiazines with tricyclic antidepressants & MAOI's (including moclobemide). Respiratory depression may occur (12). The hypotensive effect of most antihypertensive drugs especially alpha adrenoreceptor blocking agents may be exaggerated by phenothiazines. The use of antimuscarinics will increase the risk of antimuscarinic side effects when in conjunction with antihistamines. The mild anticholinergic effect of phenothiazines may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc. (12) The action of some drugs may be opposed by phenothiazines; these include amphetamine, levodopa, clonidine, guanethidine, and adrenaline (12). Anticholinergic agents may reduce the antipsychotic effect of phenothiazines (12). Some drugs interfere with absorption of phenothiazines: antacids, anti-Parkinson, and lithium. Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol and phenobarbital have been observed but were not of clinical significance (12). High doses of phenothiazines reduce the response to hypoglycaemic agents, the dosage of which may have to be raised. Adrenaline must not be used in patients overdosed with phenothiazines (12). As with other neuroleptic phenothiazines, caution is advised with concomitant use of QT prolonging drugs or drugs that cause electrolyte imbalance(12).
Monitoring requirements	Nil
Prescribing considerations	Alimemazine is contraindicated for use in children less than 2 years of age due to the risk of marked sedation and respiratory depression (12). Patients are strongly advised not to consume alcoholic beverages or medicines containing alcohol throughout treatment. The sedative effects of phenothiazines may be intensified (additively) by alcohol (12). Exposure to sunlight should be avoided during treatment. Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of phenothiazines. Care must be taken to avoid contact of the drug with the skin. Skin rashes of various kinds may also be seen in patients treated with the drug. Patients on high dosage may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight. Ocular changes and the development of a metallic greyish-mauve colouration of exposed skin have been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years) (12). Liquid formulations: The sugar content should be considered in patients with diabetes or on low-sugar diets. This medicine contains sulphites that may cause or exacerbate anaphylactic

	reactions (12). There are further prescribing considerations for adult patients- please refer to the latest edition of the BNF.
Other considerations	Prescribe the dose in both milligrams and millilitres to prevent medication errors as two strengths are available.

Potential patient group (if appropriate to include)	
Brief description of disease	Insomnia is usually described as difficulty in falling asleep and/or staying asleep. (5) Although non-drug treatments, such as behavioural therapy can be extremely effective in some forms of paediatric insomnia, clinical experience and studies with children with neuropsychiatric disorders indicate that these patients have lower response rates to behavioural therapy (5).
Potential patient numbers per 100,000	Problems of settling to sleep and night waking are affecting about 20% of children aged 1-3 years and about 10% of children aged 4.5 years. Such problems are frequently persistent and are associated with behavioural difficulties such as autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD) (5, 6). The prevalence of sleep disturbance in children with learning disability is in the range of 58–86% (18).
Outcomes required	Long-term reduction of frequency and duration of night wakes and settling time. Outcomes to be measured using standardised sleep questionnaires and diaries (see link to templates below): Melatonin Sleep Questionnaire and Diary - May 2014 Melatonin - Sleep chart - Jan 2012

Summary of current treatment pathway

Pharmacological treatment options of sleep disorders in children and adolescents include melatonin and alimemazine.
Melatonin is recommended for prescribing as 2nd line where non-pharmacological strategies have failed and underlying physical causes are managed. Treatment should be initiated by or under the supervision of a specialist and transferred to GP for prescribing after one months (general children population) or three months or when patient's dose is stable (children and adolescents with underlying ADHD).

Melatonin for sleep disorders and children - Amber Star information sheet - May 2014
NWS CCG - Melatonin (Circadin) for sleep disorder in children with ADHD

Not all patients respond to melatonin and the specialists in the Children Behavioural Service at ASPH sometimes trial alimemazine in these patients (3rd line after melatonin and non-pharmacological strategies).
NWSCCG: Alimemazine for Sleep disorders in children and adolescents

Evidence review

Ramchandani, et al., 2000. A systematic review of treatments for settling problems and night waking in young children

Search protocol: Trials from Medline (1966 to September 1998), Embase (1980 to June 1998), PsycLIT journals
(1974 to September 1998), Biological Abstracts (1985 to June 1998), Cinahl (1982 to September 1998), Sigle (1980 to June 1998), and the Cochrane database (including the Cochrane Controlled Trials Register (issue 2, 1998) (6).

Inclusion criteria: Children aged 5 and under, settling problem (refusing or taking a long time to settle at night or tantrums at bedtime) or night waking (waking frequently or waking for long periods, or both); RCTs (cross over or parallel design); with placebo, waiting list, or another intervention as control; not specifically studies of children with behavioural problems, and studies with outcome measures that included number of night

wakes, time to settle, or number of nights in which these problems occurred (6).

Results: Four pharmacological studies identified, three of those on alimemazine (the fourth used niaprazine – an antihistamine unavailable in the UK). Two of the drug trials used alimemazine vs. placebo, 1 used extinction (ignoring child's crying) plus alimemazine vs. extinction alone (6).

Trials: Two trials were of drug only versus placebo—either up to 60 mg or 90 mg. Both showed a statistically significant positive effect of drugs in the short term. The clinical significance is less clear as in both trials even the children receiving treatment continued to wake at night, and up to one third did not improve with drugs. The picture is less convincing concerning a longer lasting effect. The same two studies14 18 included a follow
up period. In one study14 the sleep score dropped marginally from 12.4 at baseline to 10.1 at six months' follow up. One third of the subjects had, however, withdrawn from the study at this stage. In the second study, with a shorter follow up period, there was a reduction in number of wakes at night from 2.8 at baseline to 1.6 at four weeks' follow up. As both studies were of a cross over design there was no matched untreated group with which to compare these rates (6).
The remaining drug trial requires separate consideration. France et al used trimeprazine as an adjunct to an extinction programme (ignoring a child's crying) rather than as a treatment in its own right. Although trimeprazine (plus extinction) did reduce night waking during the first 10 days of the trial more than placebo (plus extinction), there was no difference between the two groups at the end of treatment and at four weeks' follow up (6).

Safety: Authors didn't upraise safety and adverse effect profile to a greater extent, although they identified daytime drowsiness as an important issue.

Discussion: Conclusions should be considered tentative as most trials conducted thus far have been small and the methodological quality generally poor. There seems to be evidence that drugs are effective in the short term treatment of night waking in young children (particularly trimeprazine from 30-90 mg nightly). There is, however, only patchy and contradictory evidence of a long term effect (6).

De Bruyne et al, 2017. Are antihistamines effective in children? A review of the evidence.

Trials: The efficacy of alimemazine for children with sleep problems has been investigated in four small randomised controlled trials. These trials found conflicting results with some reporting short term improvement while on alimemazine(4).

Safety: Case reports described significant morbidity in children of 4 years and younger after alimemazine use and intoxication. All case reports were published more than 10 years ago (4).

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Alimemazine is non-formulary in Crawley, Horsham & Mid Sussex, Brighton & Hove, Coastal West and East Sussex CCG. Further afield, the traffic light position for alimemazine was recently reviewed in the following other localities: • Manchester- added to 'Do Not Prescribe' list • Derbyshire - blacklisted as not cost effective and not supported by high quality clinical evidence. • Nottinghamshire - extended as second line to promethazine for paediatric sedation (previously only for pruritus in dermatology settings) • SW London & St. George's- for disturbed behaviour in children & adolescents according to rapid tranquillisation protocol • Buckinghamshire - children sedation undergoing MRI or CT scan classified as RED and on recommendation of paediatric / haematology specialist with continuation in primary care (AMBER) • Hampshire- premedication, dermatology use and in children with severe behavioural insomnia.
Recommendations from national / regional decision making groups	The Clinical Knowledge Summaries (NICE) do not recommend antihistamines for the management of short-term insomnia in adolescents and adults of 16 years and over, noting insufficient evidence to support their use, and significant potential for adverse effects (16). The consensus statement of the **British Association for Psychopharmacology**

	states that antihistamines may have a role in short-term symptomatic treatment of insomnia in children. This is category II evidence (evidence from small, well-designed, but not necessarily representative samples). On the contrary, the authors made a recommendation that antihistamines have a limited role in psychiatric and primary care practice for the management of insomnia in adults. (Level D recommendation; i.e. directly based on category IV evidence or extrapolated from category I, II, or III evidence) (8). The **European Sleep Research Society**'s guideline for the diagnosis and treatment of insomnia does not recommend antihistamines for insomnia treatment in adults (strong to weak recommendations, low- to very-low-quality evidence) (19).
Stakeholder views	Two responses from consultants based within Sussex Community Trust Child and Adolescent Mental Health Services (CAMHS) and St. Peter's Hospital agreed on the behavioural interventions and good sleep hygiene (for instance Sleep Scotland Programme) as a first choice in management of children with insomnia. However, the level of alimemazine prescribing differs significantly between the two consultants. Dr Mura at St. Peter's hospital has never used alimemazine to treat insomnia in children, whereas Dr Atkinson at Sussex Community Trust used it successfully in children with neurodevelopmental disorders (such as autism), who did not respond to melatonin. Dr Atkinson also stressed the negative impact of insomnia in children with neurodevelopmental problems on the stress burden of the parents and pointed out that the use of alimemazine in a limited group of children can avoid family breakdown and the need for child residential placement. The Clinical Commissioners expressed their concerns about poor methodological quality of studies (e.g. the impact of sleep score on patient outcomes), and requested a clarification of the lengths of intervention periods to be able to decide on proposed traffic light status. A transitional period was suggested in case of a change to BLACK traffic light status to minimise any negative impact on existing patients. Also additional safety evidence was included in this review.
CCG priorities	The medicine expenditure in NHS hospitals is increasing at a rate of 15% per annum as more complex and specialised medicines enter the market. The need to manage these medicines in the context of financial constraints is critical as identified in Carter review in 2016. Alimemazine is an obsolete first generation H1-antihistamine, where the price has increased exponentially in recent years. Significant number of prescribing items is in primary care with several CCGs now recognising its potential financial impact and considering deprescribing initiatives or switch programmes.

Health economic considerations

Cost per year per patient

The annual treatment costs below are based on October 2017 Drug Tariff.

Age / Drug and dose	2 years (12kg)	6 years (21 kg)	12 years (39 kg)	Adult
Alimemazine	2mg / kg on	2mg / kg on	capped at 60 mg on	capped at 60 mg on
7.5 mg/5 mL	£9,648	£16,896	£24,132	£24,132
30mg/5 mL	£3,273	£5,726	£8,182	£8,182
10 mg tablet	NA	NA	£8,125	£8,125

Alternative treatments cost per patient per year

The calculations below are based on October 2017 Drug Tariff and maximum daily doses in BNF and Children BNF for insomnia (3, 15)

Age / Drug and dose	2 years (12kg)	6 years (21 kg)	12 years (39 kg)	Adult
Promethazine	15 mg on	25 mg on	50 mg on	50 mg on
5mg/5mL	£144	£240	£480	£480
25 mg tablet	NA	£ 28	£56	£56

	Melatonin	capped at 10 mg on	capped at 10 mg on	capped at 10 mg on	capped at 10 mg on
	2mg MR tab	NA	£ 862	£ 862	£ 862
	5mg/5MmL	£ 835	£ 835	£ 835	£ 835
Other financial considerations	Nil				
Health economic data	Nil				

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