Medicines Adverse Reactions Committee

Meeting date	12/09/2019	Agenda item	3.2.3
Title	**Dextromethorphan – Benefit-risk review**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name + Sponsor**
Dextromethorphan	See Table 1
Dextromethorphan + Guaifenesin	See Table 2
Dextromethorphan + Phenylephrine	See Table 3
Dextromethorphan + Phenylephrine + Brompheniramine	See Table 4
Dextromethorphan + Phenylephrine + Paracetamol	See Table 5
Dextromethorphan + Phenylephrine + Paracetamol + Chlorphenamine	See Table 6
Dextromethorphan + Paracetamol + Doxylamine	See Table 7

PHARMAC funding	None.
Previous MARC meetings	Meeting 132: 13 Dec 2007 The safety and efficacy of cough and cold medicines for use in children Meeting 138: 11 Jun 2009 The safety and efficacy of cough and cold medicines for use in children Meeting 143: 23 Sep 2010 Consideration of antitussive-expectorant and antitussive-mucolytic combination cough and cold medicines (s36)
International action	Updates to prescribing and consumer information in Europe regarding warnings on dependence, serotonin syndrome, risk of serious adverse events in children; and more about overdose, including symptoms, signs and management.
Prescriber Update	Watching briefs - Update on cough and cold products (May 2008) Medicines interaction - SSRIs and dextromethorphan *(*May 2009*)* Cough and cold medicines – further contraindication recommended (Nov 2009) Cough and cold medicines update and reminder (Jun 2010) Cough and cold medicines – an update (Mar 2011) Reminder: cough and cold medicines in children (Jun 2013) Reminder: using cough and cold medicines in children is inappropriate (Jun 2016)
Classification	Pharmacist-only medicine
Usage data	See section 3.3 (company reports)
Advice sought	**The Committee is asked to advise:** • Whether the balance of benefits and risk for the use of dextromethorphan for the symptomatic treatment of unproductive cough is favourable. • Any regulatory action is required to improve the balance of benefits and risks.

Dextromethorphan-containing products, with status 'Consent given' – as at 19 June 2019

(Source: Medsafe Product/Application search https://www.medsafe.govt.nz/regulatory/dbsearch.asp)

Table 1: Dextromethorphan-only products

Product name	Sponsor	Approval date
Benadryl Dry Forte Oral solution, 3 mg/mL	Johnson & Johnson (New Zealand) Limited	14/03/2002
Bisolvon Dry Oral solution, 2 mg/mL	Sanofi-aventis New Zealand limited	28/04/2016
Bisolvon Dry Pastilles Pastille, 10.5 mg	Sanofi-aventis New Zealand limited	10/12/2015
Robitussin Dry Cough Forte Oral solution, 30 mg/10mL	Pfizer New Zealand Limited	14/10/1999
Robitussin Dry Cough Liquid Capsules Liquid filled capsule, 15 mg	Pfizer New Zealand Limited	1/12/2016
Strepsils Dry Cough Lozenge, 5 mg	Reckitt Benckiser (New Zealand) Limited	31/12/1969
Vicks Cough Lozenges Honey Flavour for Dry Cough Lozenge, 7.34 mg	CARSL Consulting (on behalf of Procter & Gamble)	4/10/2007
Vicks Cough Syrup Honey Flavour for Dry Cough Syrup, 1.333 mg/mL	CARSL Consulting (on behalf of Procter & Gamble)	19/07/2007
Vicks Formula 44 for Dry Coughs Syrup, 0.133% w/v	CARSL Consulting (on behalf of Procter & Gamble)	10/08/2000

Table 2: Dextromethorphan + Guaifenesin products

Product name	Sponsor	Approval date
Robitussin Cough & Chest Congestion Oral solution	Pfizer New Zealand Limited	9/04/1998

Table 3: Dextromethorphan + Phenylephrine products

Product	Sponsor	Approval date
Benadryl PE Dry Cough & Nasal Congestion Syrup	Johnson & Johnson (New Zealand) Limited	16/12/2009

Table 4: Dextromethorphan + Phenylephrine + Brompheniramine products

Product name	Sponsor	Approval date
Congested Cold & Cough Oral solution, Pharmacy Health	PSM Healthcare Ltd trading as API Consumer Brands	2/07/2015
Dimetapp Cough & Cold Elixir	Pfizer New Zealand Limited	15/08/1996
Dimetapp Cough & Cold Colour Free Elixir	Pfizer New Zealand Limited	18/07/2002

Table 5: Dextromethorphan + Phenylephrine + Paracetamol products

Product name	Sponsor	Approval date
Dimetapp Multi Symptom Cough Cold & Flu Liquid filled capsule	Pfizer New Zealand Limited	19/07/2012
Dimetapp Multi Symptom Cough Cold & Flu Liquid filled capsule	Pfizer New Zealand Limited	19/07/2012

Table 6: Dextromethorphan + Phenylephrine + Paracetamol + Chlorphenamine products

Product name	Sponsor	Approval date
Codral All-In-One Cough, Cold & Flu Day & Night Combination capsule	Johnson & Johnson (New Zealand) Limited	22/05/2014
Codral Cold & Flu + Cough Day & Night Combination capsule	Johnson & Johnson (New Zealand) Limited	8/01/2009
Dimetapp Cough Cold & Flu Decongestant Day & Night Liquid filled capsule	Pfizer New Zealand Limited	24/05/2012
Dimetapp Cough Cold & Flu Night Relief Liquid filled capsule	Pfizer New Zealand Limited	24/05/2012

Table 7: Dextromethorphan + Paracetamol + Doxylamine products

Product name	Sponsor	Approval date
Dimetapp Cough Cold & Flu Daytime/Nightime Capsule	Pfizer New Zealand Limited	23/07/2009

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1 PURPOSE

The purpose of this paper is to present a benefit-risk review of dextromethorphan (DXM).

DXM is contraindicated in children aged under 6 years. Although this paper is not specifically looking at children, they are included because DXM is still used in children aged 6 years and older.

2 BACKGROUND

2.1 Reclassification to a restricted medicine

At the 61st Medicines Classification Committee (MCC) meeting on 2 November 2018, Medsafe presented a submission proposing the reclassification of cough medicines containing the active ingredients DXM, opium tincture, squill oxymel and pholcodine from general sale and pharmacy-only medicines to restricted medicines [1].

This recommendation was based on national and international reports of misuse/abuse or a potential for abuse of these products [1]. A high dose of DXM can cause euphoric, stimulant, and dissociative effects and may even be fatal. The effect is highly dependent of the capability of the individual to metabolise the medicine. Chronic DXM abuse may also lead to bromide toxicity (due to the hydrobromide salt) – and is marked by fatigue, ataxia, headache and memory loss [2].

Medsafe was alerted to concerns within the community about the abuse of DXM containing cough medicines, especially by adolescents and young adults [1]. Concern was raised over the easy availability of DXM medicines which could be bought at a pharmacy or supermarket without healthcare professional supervision.

The MCC paper discussed the risk of DXM abuse being the first step to abuse of stronger substances [1]. Another concern was that DXM cough and cold products frequently also contain for example acetaminophen, and there are also interaction risks.

Both the Centre for Adverse Reactions Monitoring (CARM) and the National Poisons Centre indicated in the paper that they would not usually receive reports of abuse/misuse of medicines and that it is very hard to find a useful measure of the true extent of abuse/misuse through the current systems in New Zealand [1].

At the meeting, the MCC recommended that DXM should be reclassified from a general sale and pharmacy-only medicine to a restricted medicine [3]. The MCC also suggested that Medsafe should review the risk-benefit profile and efficacy of DXM.

The DXM re-classification notice was published in the *New Zealand Gazette* on 25 February 2019:

> *Restricted Medicines*
>
> Dextromethorphan; in liquid form when in packs containing not more than 600 milligrams and with a recommended daily dose of not more than 120 milligrams; in medicines for the treatment of symptoms of cough and cold in adults and children aged 6 years and over

2.2 Previous MARC reviews

DXM, in the context of cough and cold treatments, has been reviewed previously by the MARC.

2.2.1 132nd meeting December 2007

In December 2007, the Medicines Adverse Reactions Committee (MARC) first reviewed the benefits and risks of over the counter (OTC) cough and cold medicines in children [4]. The Committee noted that in children aged less than 2 years there was very limited evidence for efficacy, an absence of evidence-based dosage advice and evidence of significant toxicity in overdose for the use of OTC cough and cold medicines. The MARC concluded that the risk-benefit profile for the use of cough and cold medicines in children under 2

years was currently unfavourable and recommended that they be contraindicated in this age group. The sponsors for all cough and cold medicines committed to ensuring that all products would carry the warning not to use in children under 2 years by 1 May 2009.

2.2.2 138th meeting June 2009

In May 2009 Medsafe undertook a further review of the available data supporting the safety and efficacy of OTC cough and cold products in children – focusing on use in children aged >2 years [5]. After a preliminary review of the data Medsafe determined that in addition to a review of the data by the full MARC, further expert advice was required. An independent review group "The Cough and Cold Review Group" consisting of relevant stakeholders including current members of the MARC, and representatives from Plunket, the community, general practice, nursing, paediatrics, pharmacy and the pharmaceutical industry was convened for this purpose.

The Cough and Cold Review group met on two occasions in July and August 2009 [6]. At the first meeting the Group considered the efficacy and safety of cough and cold medicines in children. At the second meeting the Group finalised their recommendations, considered risk management options, and advised on implementation and communication. The Group made the following recommendations to Medsafe:

- All medicines indicated for the treatment of the symptoms of the common cold and containing guaifenesin, ipecacuahna, DXM, pholcodine, oral phenylephrine, pseudoephedrine, brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, preomethazine or triprolidine should be contraindicated in children <6 years of age.
- All medicines indicated for the treatment of the symptoms of the common cold containing only bromhexine or topical nasal decongestants (oxymetazoline, xylometazoline and intra-nasal phenylephrine) should remain contraindicated in children <2 years of age.
- The Group recommended that the risk-benefit profile of cough and cold medicines in children be re-evaluated by the Medicines Adverse Reactions Committee when the results of the studies currently underway in the United States become available (expected in 2011).

In addition to the above recommendations, the group recommended that the sponsors of cough and cold medicines containing apparently illogical combinations of ingredients should be asked for justification to support the risk-benefit balance for these combinations.

Comment
Medsafe notes that these studies were never provided, therefore no changes have been made to contraindications in children aged under 6 years.

2.2.3 143rd meeting September 2010

In September 2009, Medsafe issued a section 36 notice for cough and cold medicines containing the combination of an antitussive plus an expectorant or an antitussive plus a mucolytic agent [7]. There were only two products marketed in New Zealand at that time, guaifenesin and DXM hydrobromide (Robitussin Cough and Chest Congestion) and bromhexine hydrochloride and pholcodine (Duro-Tuss Cough Liquid Expectorant TT50-6169). Medsafe considered that the responses provided by the sponsors were inadequate and the matter was referred to the MARC in September 2010.

After considering the available evidence for the safety and efficacy of these combination products, the majority of the Committee considered the risk-benefit balance to be unfavourable and recommended that consent be revoked for these products. However, the MARC considered that this recommendation should only apply to the combinations specifically reviewed (ie, combinations of bromhexine and pholcodine and guaiphenesin and DXM). The MARC considered that in the future any applications to Medsafe seeking registration of an antitussive-mucolytic or antitussive-expectorant combination containing other combinations of ingredients must include adequate clinical data for evaluation. The Minister's Delegate declined to accept the recommendation.

2.3 Cough

Cough is an important protective reflex and a universal symptom in health, but when persistent, it is the most common reason why patients seek medical attention [8].

Cough is associated with significantly impaired health-related quality of life [8]. Sleep disturbance, nausea, chest pains, and lethargy occur frequently, and patients with chronic cough often experience social embarrassment, urinary incontinence, and low mood.

People often self-prescribe non-prescription over-the-counter (OTC) cough medicines for themselves or their children, and many health professionals in primary care settings recommend them to their patients as a first-line treatment [9]. A national telephone survey of medication use in the US indicated that in a given week, 10% of children are given an OTC cough preparation by their carers [9].

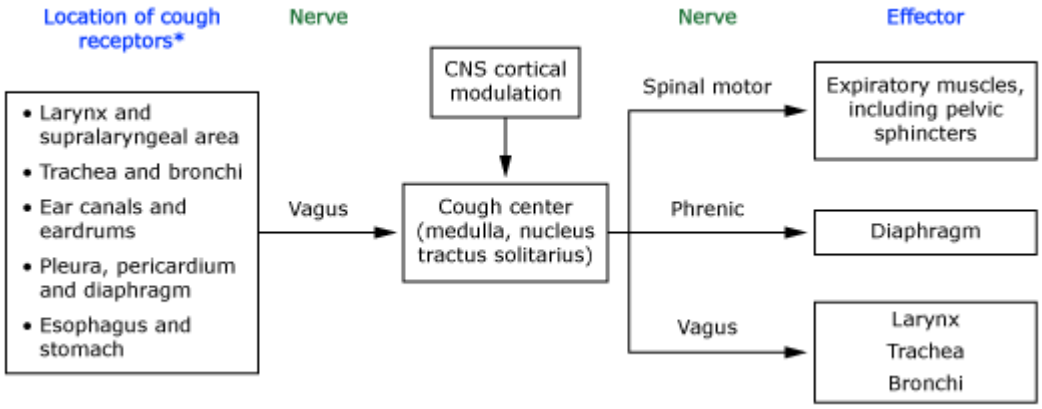
2.3.1 Cough reflex

Each cough occurs through the stimulation of a complex reflex arc (Figure 1) [10]. This is initiated by the irritation of cough receptors that exist not only in the epithelium of the upper and lower respiratory tracts, but also in the pericardium, oesophagus, diaphragm, and stomach. Chemical receptors sensitive to acid, cold, heat, capsaicin-like compounds, and other chemical irritants trigger the cough reflex via activation of ion channels of the transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin type 1 (TRPA1) classes. Mechanical cough receptors can be stimulated by triggers such as touch or displacement. Laryngeal and tracheobronchial receptors respond to both mechanical and chemical stimuli.

Impulses from stimulated cough receptors traverse an afferent pathway via the vagus nerve to a "cough centre" in the medulla, which itself may be under some control by higher cortical centres [10]. Sex-related differences in cough reflex sensitivity explain the observation that women are more likely than men to develop chronic cough. The cough centre generates an efferent signal that travels down the vagus, phrenic, and spinal motor nerves to expiratory musculature to produce the cough.

During vigorous coughing, intrathoracic pressures may reach 300 mm Hg and expiratory velocities approach 500 miles per hour [10]. While these pressures and velocities are responsible for the beneficial effects of cough on mucus clearance, they are also responsible for many of the complications of cough, including exhaustion, self-consciousness, insomnia, headache, dizziness, musculoskeletal pain, hoarseness, excessive perspiration, urinary incontinence, cough-induced fractures, and concern that "something is wrong".

Figure 1: Simplified schematic diagram of the cough reflex



* Cough receptors include rapid acting receptors (RAR), slow acting receptors (SAR), C fibres, and other cough receptors. Some receptors are mechanosensitive and others are chemosensitive. Impulses from these receptors are all carried by the vagus nerve.

Source: Silvestri R and Weinberger S. 2019. Evaluation of subacute and chronic cough in adults. In: *UpToDate* June 2019. URL: https://www.uptodate.com/contents/evaluation-of-subacute-and-chronic-cough-in-adults (accessed 30 July 2019).

2.3.2 Cough in adults

Cough is one of the most common symptoms for which outpatient care is sought [10]. Cough can be classified based on its duration: acute, subacute or chronic.

- Acute cough exists for less than 3 weeks and is most commonly due to an acute respiratory tract infection. Other causes include acute exacerbation of underlying chronic pulmonary disease, pneumonia and pulmonary embolism.
- Subacute cough lasts for 3 to 8 weeks and is usually due to infection or the common cold and lingers long after the other acute symptoms have resolved.
- Chronic cough lasts longer than 8 weeks and common causes include upper airway cough syndrome (previously known as postnasal drip syndrome but revised to include all upper airway abnormalities causing cough), asthma, and gastroesophageal reflux. Other causes of chronic cough include respiratory tract infection, ACE inhibitors, chronic bronchitis, bronchiectasis, lung cancer, and non-asthmatic eosinophilic bronchitis.

2.3.3 Cough in children

Children are not small adults and the causes of cough in children may be different to the causes in adults [11].

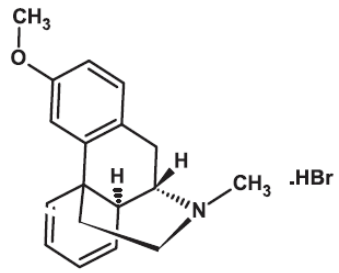
The most common cause of cough in children is viral infection producing "normal cough", but all children with persistent cough, ie, a cough lasting more than 4–8 weeks or "chronic cough", must be carefully evaluated in order to rule out specific causes that may include the entire paediatric pulmonology spectrum [12]. Exposure to tobacco smoke and other environmental contaminants, or smoking by the children and adolescents themselves, are common causes of cough or the failure of cough to resolve at all ages. The treatment of cough should be based on the aetiology.

2.4 Dextromethorphan (DXM)

Dextromethorphan hydrobromide was first reported in 1953 as a treatment of cough without the undesirable side effects of codeine, ie, drowsiness, nausea, dependency, and constipation, and has since become the active ingredient in many OTC medicines [8].

DXM is a cough suppressant used for the relief of non-productive cough. It is a methyl ether of dextrorotatory (D) isomer of levorphanol, a codeine analogue [13]. DXM is used clinically in the form of salt, DXM hydrobromide (Figure 2). Physically, it is a white crystal or crystalline powder, sparingly soluble in water and freely soluble in alcohol.

Figure 2: Dextromethorphan hydrobromide structure



Source: Dicpinigaitis PV, Morice AH, Birring SS, et al. 2014. Antitussive drugs – past, present and future. *Pharmacological Reviews* 66: 468–512.

2.4.1 Pharmacodynamics

DXM has a central action on the cough centre in the medulla. It is also an antagonist of N-methyl-D-aspartate (NMDA) receptors and a σ-receptor agonist [14]. Although structurally related to morphine, DXM has no classical analgesic properties and little sedative activity.

As a cough suppressant, DXM hydrobromide is reported to act within half an hour of an oral dose and to exert an effect for up to 6 hours [14]. It is given orally in doses of 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24 hours. At appropriate adult doses (ie, 30 mg orally every 4 hours for 7 days) the therapeutic blood levels of DXM range from 0.002 to 0.207 mg/L [13]. DXM is readily absorbed into the bloodstream and crosses the blood–brain barrier with measurable cerebral spinal fluid/plasma ratio of 32.8 to 80%.

2.4.2 Pharmacokinetics

DXM is rapidly absorbed from the gastrointestinal tract; its peak serum level is reached at approximately 2 to 2.5 hours after oral administration [13]. It is metabolised in the liver and excreted in the urine as unchanged DXM and demethylated metabolites including dextrorphan, which has some cough suppressant activity [14].

DXM undergoes a first-pass metabolism via hepatic portal vein and is O-demethylated to produce the active metabolite; it is further N-demethylated, and partially conjugated with glucuronic acid and sulfate ions [13]. Cytochrome P450 in the 2D6 isoenzyme is responsible for the inactivation of DXM. Poor metabolisers or those receiving medications inhibiting CYP2D6 experience accumulation of the active drug. Examples of drug interactions resulting in an increase of DXM levels include interactions with monoamine oxidase inhibitors (MAO-Is), fluoxetine, paroxetine, and haloperidol (see also the interactions section described in the Bisolvon data sheet below).

Phenotyping has found that poor metabolisers of DXM vary from approximately 1% to 10% in different ethnic groupings based on genetic polymorphism with respect to debrisoquine oxidation [15]. The mean prevalence of poor metabolisers is approximately 7.4% in white populations of Europe. It varies from 1% to 3.2% across different areas of the Indian subcontinent. Rates of poor metabolisers of debrisoquine include: Swiss 10%, British white persons 8.9%, Nigerians 8%, Swedes 6.8%, Ghanaians 6.3%, French 3.9%, Iraqi Arabs 3.5%, Egyptian Arabs 1.4%, Saudi Arabians 1%, and Chinese 1%.

DXM is eliminated renally unchanged or as a demethylated metabolite [13]. The plasma elimination half-life of DXM is 1.2 to 3.9 hours. However, the rate of metabolism varies between individuals according to phenotype (extensive v poor metabolisers), with half-life being as long as 45 hours in patients who are poor metabolisers [16].

Comments
Poor metabolisers are at risk of DXM overdose, and it is unknown before treatment if a patient is a poor metaboliser. This is especially important in children where there is a smaller gap between a safe dose and an overdose.

2.5 Product prescribing and labelling information

2.5.1 New Zealand data sheets

There are currently only two DXM-containing products with data sheets published on the Medsafe website: Bisolvon Dry Oral Liquid and Bisolvon Dry Pastilles.

2.5.1.1 Bisolvon Dry Oral Liquid and Pastilles – Sanofi-aventis [16, 17].

- Oral liquid: DXM hydrobromide 10 mg/5 mL.
- Pastille: DXM hydrobromide monohydrate 10.5 mg (equivalent to DXM hydrobromide anhydrous 10 mg).

Indications and dose (data sheet sections 4.1 and 4.2)

Bisolvon Dry is used for the symptomatic treatment of dry, irritant, unproductive coughs.

Oral liquid

- Adults and children aged ≥12 years: 5–15 mL, every 4–6 hours when necessary. Maximum daily dose is 60 mL (120 mg DXM hydrobromide). Do not exceed 4 doses in a 24-hour period.

- Children aged 6–11 years: 2.5–7.5 mL, every 4–6 hours when necessary. Maximum daily dose is 30 mL (60 mg of DXM hydrobromide). Do not exceed 4 doses in a 24-hour period.

Pastilles

- Adults and children aged 12 years and older: 1–3 pastilles (10–30 mg DXM hydrobromide) every 4-6 hours when necessary. Maximum daily dose is 12 pastilles (120 mg DXM hydrobromide)
- Children aged 6–11 years: 1 pastille (10 mg DXM hydrobromide) every 4-6 hours when necessary.

Contraindications (section 4.3)

- hypersensitivity to DXM or to any of the inactive ingredients in the formulation
- concomitant treatment or treatment within the previous 14 days with monoamine oxidase (MAO) – inhibitors
- bronchial asthma
- chronic obstructive pulmonary disease
- pneumonia
- respiratory insufficiency
- respiratory depression
- breastfeeding.

Special warnings and precautions (section 4.4)

DXM should not be used for chronic persistent cough accompanying a disease state, or for cough associated with excessive secretions.

In patients with neurological illness associated with a markedly reduced cough reflex (such as stroke, Parkinson's disease and dementia) antitussive treatment should be administered with particular caution and only after careful benefit-risk assessment.

DXM should not be given to patients with or at risk of developing respiratory failure, e.g. asthma, chronic obstructive airways disease, and pneumonia. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. DXM should be used with caution in patients receiving serotonergic drugs (other than MAO – inhibitors) such as selective serotonin re-uptake inhibitors (SSRI) e.g. fluoxetine, paroxetine or tricyclic anti-depressives.

DXM is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor CYP2D6 metabolisers. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of DXM. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors.

Due to potential histamine release DXM should be avoided in cases of mastocytosis.

Paediatric use: Use in children aged 6–11 years only on the advice of a doctor, pharmacist or nurse practitioner.

Interactions (section 4.5)

DXM possesses weak serotonergic properties. Thereby DXM may increase the risk of serotonin toxicity (serotonin syndrome) particularly if taken with other serotonergic agents, such as MAO-inhibitors or SSRIs. Especially pre-treatment or concomitant treatment with drugs that impair metabolism of serotonin, such as antidepressants of the MAO inhibitor type, may result in the development of a serotonin syndrome with characteristic symptoms like neuromuscular hyperactivity (e.g. tremor, clonus, myoclonus, hyperreflexia, and pyramidal rigidity), autonomic hyperactivity (e.g. diaphoresis, fever, tachycardia, tachypnea, mydriasis) and altered mental status (e.g. agitation, excitement, confusion).

DXM should not be used in patients taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days. The use of DXM with, or within two weeks of taking MAOIs, may increase the risk of serious side effects such as hypertensive crisis, hyperpyrexia and convulsions.

DXM when used with SSRI's (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine) may result in a "serotonin syndrome" with changes in mental status (e.g agitation, excitement, confusion), hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor.

DXM is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the DXM concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of DXM (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of DXM have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of DXM. If concomitant use of CYP2D6 inhibitors and DXM is necessary, the patient should be monitored, and the DXM dose may need to be reduced. The above cited effects may occur if any of these medicines have been administered recently, even if they are no longer being taken.

Concomitant use of DXM and other CNS depressants (e.g. alcohol, narcotic analgesics and tranquillizers) may increase the CNS depressant effects of these drugs.

If DXM is used in combination with secretolytics in patients with pre-existing chest disease such as cystic fibrosis and bronchiectasis who are affected by mucus hypersecretion reduced cough reflex can lead to serious accumulation of mucus.

Undesirable effects (section 4.8)

Side effects with usual doses are uncommon but may include mild drowsiness, fatigue, dystonias, dizziness and gastrointestinal disturbances (nausea or vomiting, stomach discomfort, or constipation).

Side effects that may occur with high doses (overdosage) include excitation, confusion, psychosis, nervousness, irritability, restlessness, "serotonin syndrome", severe nausea and vomiting, and respiratory depression.

Drug tolerance: DXM has minor addictive potential. Following prolonged use (i.e. exceeding the recommended treatment period) patients may develop tolerance as well as mental and physical dependence. Patients with a tendency towards abuse or dependence should only be given Bisolvon Dry for short periods and under strict medical supervision.

Cases of DXM abuse and dependency have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or use of psychoactive substances.

Very common: ≥1/10; Common: ≥1/100<1/10; Uncommon: ≥1/1,000<1/100; Rare: ≥1/10,000<1/1,000; Very rare: <1/10,000; Not known: cannot be estimated from the data available

Psychiatric disorders:

Common: confusion

Very rare: drug dependence

Frequency not known: hallucinations

Nervous system disorders:

Very common: somnolence, dizziness

Frequency not known: vertigo, slurred speech and nystagmus, dystonia especially in children.

Skin and subcutaneous tissue disorders:

Frequency not known: skin reactions such as rash with pruritis

Immune system disorders:

Frequency not known: hypersensitivity, urticaria, fixed drug eruption, anaphylactic reaction, angioedema, bronchospasm

Gastro-intestinal disorders:

Common: gastrointestinal disorders (nausea, vomiting, constipation)

General disorders and administration site conditions:

Common: fatigue

Overdose (section 4.9)

The mainstay of treatment is supportive and symptomatic care. If necessary close intensive care monitoring with symptom-related treatment should be initiated. Naloxone can be used as an antagonist.

Symptoms: In case of overdose known side effects may occur with higher frequency or severity: nausea, vomiting and gastrointestinal disorders, dizziness, fatigue and somnolence and hallucinations. Likewise, restlessness and excitability may develop into agitation with increasing overdose. In addition, symptoms such as impaired concentration and consciousness up to coma as a sign of severe intoxication, changes in mood such as dysphoria and euphoria, psychotic disorders like disorientation and delusions up to confusional or paranoid states, increased muscle tone, ataxia, dysarthria, nystagmus and vision disturbance as well as respiratory depression, changes in blood pressure and tachycardia may occur.

DXM may increase the risk of serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents.

Comment
With the up-scheduling of DXM to a restricted classification, data sheets are now required for these products. Medsafe expects sponsors to supply data sheets for their DXM-containing products by 25 February 2020 (ie, one year after the classification change).

2.5.2 Label Statements Database

The Label Statements Database (https://medsafe.govt.nz/regulatory/labelling.asp) lists the warning and advisory statements that are required on medicine and related product labels under regulations 13(1)(i) and 14(1)(f) of the Medicines Regulations 1984. There is a requirement to include warning statements on cough and cold medicines, including those containing DXM (Table 8).

Table 8: Label Statements Database entry for Antitussives

Medicine/Group/Class	Conditions	Statements or requirements	Required by

Antitussives Includes: Dextromethorphan Pholcodine	In cough and cold medicines	• Do not use in children under 6 years old. • Consult a healthcare professional before using in children aged six years and over. • Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional.	1/08/2011

2.6 International regulatory action

Table 9: Summary of regulatory action taken worldwide for cough and cold medicines, including dextromethorphan

Date	Organisation	Warning/Advice	Regulatory Action
United States			
Jan 2006	American College of Chest Physicians	Question use of cough medicines in children	None taken. In the USA most OTC cough and cold medicines are marketed under the authority of a monograph. Amendment of the monograph can take many years to implement. Most companies in the US have voluntarily amended product labels to state 'do not use in children under 4 years of age' or words to that effect
March 2007	Citizen's Petition submitted to FDA	Concerned regarding safety and efficacy of non-prescription cough and cold medicines in children under 6 years	
Aug 2007	FDA Advisory	Do not use cough and cold products in children under 2 years unless given specific directions to do so by a healthcare provider	
Jan 2008	FDA Advisory	Cough and cold medicines not be used to treat infants and children less than 2 years because serious and potentially life-threatening side effects can occur from such use	
Sep 2010	FDA Drug Safety and Risk Management Advisory Committee	Review of evidence regarding abuse in teenagers	Voted against placing restrictions on DXM, as they concluded that the potential risk of abuse among teenagers did not warrant restricting DXM under the Controlled Substances Act
Jan 2018	FDA Safety Communication	Cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated. For those children in whom cough treatment is necessary, alternative medicines are available. These include over-the-counter (OTC) products such as DXM, as well as prescription benzonatate products	Concern over risks and benefits of prescription cough and cold medicines containing codeine or hydrocodone – limit use to those aged ≥18 years
May 2018	Colorado state	Concerns over abuse	Prohibit sales to minors (16th state to do so, others include: California, New York, Arizona, Louisiana, Virginia, Tennessee, Kentucky, Washington, New Jersey
Canada			
Oct 2007	Health Canada Advisory	Do not use in children under 2 years	Voluntary recall of products by sponsors

Dec 2008	Health Canada Advisory	Use contraindicated in children under 6 years	Products required to be re-labelled by Autumn 2009
United Kingdom			
March 2008	MHRA	Recommended that cough and cold preparations should not be used in children under 2 years of age	Relabelled by Oct 2008. Products labelled for use in under 2s removed from general sale.
Feb 2009	MHRA	Recommended that cough and cold medicines should not be used in children under 6 years and restricted the sale of products for 6–12-year-olds to pharmacy only	No product recall, packaging expected to be updated for Autumn/ Winter 2009
Australia			
April 2008	TGA	Contraindicated the use of cough and cold medicines in children under 2 years.	Implemented by June 2009. Recall of non-compliant stock not required
August 2012	TGA	Recommended that cough and cold medicines should not be used in children under 6 years. Recommended that children aged 6-11 should only be given medicines to treat cough and cold symptoms on the advice of a doctor, pharmacist or nurse practitioner.	No change to classification (pharmacy only) but updates made to Required Advisory Statements for Medicines Labelling (RASML)
Sweden			
2000		Concern over misuse	Withdrawn from the market – although still able to buy over the internet
2018		Increase in products purchased over the internet; some deaths in young people	Classified as a narcotic
Europe			
2016	EMA/PRAC	Warnings for drug abuse in adolescents and young adults; information about drug metabolism and genetic differences	Prescribing information changes
2017	France, Switzerland, Czech Republic	Concern over abuse	Reclassified to prescription-only
June 2019	EMA/PRAC	Warnings for serotonin syndrome, paediatric use and overdose	Prescribing information changes (see section 3.2.2)

2.7 Position statements/Guidelines

2.7.1 NZ/Australia

Thoracic Society of Australia and New Zealand: Cough in children: definitions and clinical evaluation [18]

- Children should be managed according to child-specific guidelines, which differ from adult guidelines.
- Treatment of cough in children should be based on aetiology, and there is little evidence for using medications for symptomatic relief of cough.

- If medications are used, it is imperative that the children are routinely followed up, and medications ceased if there is no effect on the cough within an expected timeframe.

Figure 4 shows the Thoracic Society's key statements on general management of acute and chronic cough in children, along with the levels of evidence (E1-4).

Figure 3: Key statements on general management of cough in children

Key clinical issues of cough studies

A detailed clinical history is of key importance when evaluating a child with cough (E4).

While parental reporting of wet or dry cough has good reliability, parental reporting of nocturnal cough has poor reliability when compared with objective measures (E3).

As reporting of cough is prone to large placebo and time-period effects, observational studies (non-randomised controlled trials) on interventions for cough are of very limited value (E3).

Key recommendations for acute cough in children

Although most children with acute cough are likely to have an acute upper respiratory tract infection, all should be evaluated for the possibility of a more serious problem (E4):

- Is a characteristic recognisable cough present (eg, paroxysmal)?
- Are there symptoms or signs of a lower respiratory disease (tachypnoea, dyspnoea, wheeze or other chest auscultation abnormalities; eg, crackles, asymmetric breath sounds)?
- Is the child otherwise unwell (looks toxic, rigors, dehydrated, or vomiting)?
- Has the child aspirated (acute history of choking)?

Both over-the-counter (OTC) and prescription medications are generally ineffective for the symptomatic relief of acute cough and should be rarely used (E1). There are no (non-OTC) medications that have a registered indication in Australia for the relief of cough. Serious adverse events and accidental poisoning have been reported with use of OTC medications for cough (E3).

Key recommendations for chronic cough in children

Children with chronic cough should (E4):

- be carefully evaluated, especially for symptoms and signs of an underlying respiratory or systemic disease (noting "specific cough pointers", Box 2);
- have spirometry (if school age) and chest radiography performed; and
- be re-evaluated, as minimal airway secretions may be present in dry cough and hence wet cough may initially be perceived as dry cough.

The three most common causes of chronic cough in adults (gastro-oesphogeal reflux disease, asthma and postnasal drip) are relatively uncommon causes of chronic cough in children. Empirical treatment for these conditions is largely unsuitable in children (E3).

OTC or prescription medications are ineffective for chronic cough and should be rarely used for the symptomatic treatment of cough (E4).

Treatment for chronic cough should be based on aetiology. If medication trials are undertaken, a response should not be assumed to be due to the medication tried. This is especially true for asthma medications, where a diagnosis of asthma should not be made based on a single episode of cough (which "responds" to asthma medications) in the absence of other symptoms of asthma (E3).

An isolated chronic cough in children is unlikely to be asthma without other specific pointers to this disease. Asthma medication, especially high doses of inhaled corticosteroids, can have adverse effects.
If treatment is trialled, the child should be reviewed within 2–4 weeks. If there is no improvement, the treatment should be stopped rather then escalated (E2).

Common management approaches

A history of environmental exposures, particularly tobacco smoke exposure, should be sought and intervention initiated if appropriate (E3).

Exploration of parental concerns and expectations is beneficial, and specific education is more beneficial than nonspecific education (E3).

Psychological overlays/intervention should be considered when nonspecific cough is present (E4). ◆

Key: E1 = systematic review of all relevant randomised controlled trials; E2 = well-designed RCTs; E3 = well-designed cohort or case-control studies; E4 = consensus opinion of authors.

Best Practice Advisory Centre (bpac NZ): Do cough and cold preparations work in children? [19]

The Best Practice Advisory Centre of New Zealand (bpac NZ) states that coughs and colds are self-limiting and do not require pharmacological interventions, which only relieve the symptoms [19]. Children with coughs and colds should be allowed to rest, be made comfortable and be given plenty of fluids. Simple analgesics such as paracetamol may be considered for symptomatic treatment of associated pain or fever, and saline drops or spray may be used for nasal congestion. Honey (straight or added to a drink) may be trialled in children aged over one year, for the purpose of providing comfort.

2.7.2 USA

American College of Chest Physicians: Diagnosis and Management of Cough Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines [20]

- Antitussives are not recommended for patients with acute cough caused by the common cold/upper respiratory infection. They may be considered for post-infectious cough in adults if other measures fail, and for short-term symptomatic relief of cough due to chronic bronchitis.
- Antitussives should not be used in children. Children should be managed according to the studies and guidelines for children.

The recommendations scale is as follows: A, strong; B, moderate; C, weak; D, negative; I, inconclusive (no recommendation possible); E/A, strong recommendation based on expert opinion only; E/B, moderate recommendation based on expert opinion only; E/C, weak recommendation based on expert opinion only; and E/D, negative recommendation based on expert opinion only.

The section and relevant recommendation number(s) are copied below.

Cough and the common cold

Rec 1. Patients with acute cough (as well as post-nasal drip and throat clearing) associated with the common cold can be treated with a first-generation antihistamine/decongestant preparation (brompheniramine and sustained-release pseudoephedrine). Naproxen can also be administered to help decrease cough in this setting. Level of evidence, fair; benefit, substantial; grade of recommendation, A

Chronic Cough Due to Chronic Bronchitis

Rec 19. In patients with chronic bronchitis, central cough suppressants such as codeine and DXM are recommended for short-term symptomatic relief of coughing. Level of evidence, fair; benefit, intermediate; grade of evidence, B

Postinfectious Cough

Rec 4. For adult patients with postinfectious cough, not due to bacterial sinusitis or early on in a *Bordetella pertussis* infection, while the optimal treatment is not known:

> Rec 4e. Central acting antitussive agents such as codeine and DXM should be considered when other measures fail. Level of evidence, expert opinion; net benefit, intermediate; grade of evidence, E/B

Cough Suppressant and Pharmacologic Protussive Therapy

Rec 5. In patients with chronic bronchitis, central cough suppressants, such as codeine and DXM, are recommended for the short-term symptomatic relief of coughing. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

Rec 6. In patients with cough due to upper respiratory infection, central cough suppressants have limited efficacy for symptomatic relief and are not recommended for this use. Level of evidence, good; benefit, none; grade of recommendation, D

Rec 10. In patients with acute cough due to the common cold, over the counter combination cold medications, with the exception of an older antihistamine-decongestant, are not recommended until randomized controlled trials prove they are effective cough suppressants. Level of evidence, fair; benefit, none; grade of recommendation, D

Guidelines for Evaluating Cough in Pediatrics

Rec 9. In children with cough, cough suppressants and other over-the-counter cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality. Level of evidence, good; benefit, none; grade of recommendation, D

Rec 10. In children with nonspecific cough, parental expectations should be determined, and the specific concerns of the parents should be sought and addressed. Level of evidence, low; benefit, intermediate; grade of recommendation, E/B

Rec 11. In all children with cough, exacerbating factors such as exposure to tobacco smoke should be determined and interventional options for the cessation of exposure advised or initiated. Level of evidence, low; benefit, substantial; grade of recommendation, B

Rec 12. Children should be managed according to the studies and guidelines for children (when available), because etiologic factors and treatments in children are sometimes different from those in adults. Level of evidence, low; benefit, substantial; grade of recommendation, B

Rec 13. In children ≤ 14 years of age with chronic cough, when pediatric-specific cough recommendations are unavailable, adult recommendations should be used with caution. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

Comments
These position statements and guidelines state that antitussives should not be used in children. The source of the cough must be identified first, and children should be treated according to child-specific guidelines.
Centrally-acting antitussives are only recommended for short-term symptomatic treatment of adult patients with chronic bronchitis, or where other treatments fail in adults with post-infectious cough.

3 BENEFIT–RISK REVIEW

3.1 Efficacy

Most of the efficacy studies for DXM treatment of cough were conducted before 2000. Many of these studies also included a safety component. The three studies below (two systematic reviews and one summary of literature) described below cover much of the existing literature for the use of DXM in acute and chronic cough.

3.1.1 Smith et al (2014) [9]

This Cochrane review assessed the effects of oral OTC cough preparations for acute cough in children and adults in community settings. The included studies were randomised controlled trials (RCTs) comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in community settings. All cough outcomes were considered (such as frequency, severity, improvement in symptoms and different ways of measuring including sound pressure levels, cough counts, patient questionnaires, etc). Secondary outcomes of interest were significant adverse effects.

The authors considered that pooling of the results was inappropriate due to the small numbers of trials in each category, the limited quantitative data available and the marked differences between trials in terms of participants, interventions and outcome measurement. Where available, the effect of individual treatments was summarised as outlined in the original studies using mean differences in scores for continuous data, or simple presentations of means in each group or comparison of proportions for dichotomous data.

The first Cochrane review on this topic was in 2001, with updates in 2004, 2007, 2010, 2010 and this update in 2014. In total, 2389 potential titles have been identified for screening since the first review in 2001 and 29 RCTs were identified as eligible for inclusion in this 2014 review.

The 29 RCTs (19 in adults, 10 in children) involved 4835 people (3799 adults and 1036 children). All studies were placebo-controlled RCTs. However, assessment of the risk of bias of the included studies was limited by poor reporting, particularly for the earlier studies.

Of the 29 RCTs:

- three trials in adults compared DXM with placebo Lee (2000) [21]; Parvez 1996 [22]; Pavesi 2001 [23]).
- four trials in children compared DXM with placebo in children (Taylor 1993 [24], Korppi 1991 [25]; Paul 2004 [26]; Bhattacharya 2012 [27]).
- three studies in adults compared DXM combinations with placebo (Thackray 1978 [28]; Tukiainen 1986 [29]; Mizoguchi 2007 [30]). The authors noted that these studies were very heterogeneous and used very different drug preparations and dose frequency, limiting their comparability
- two trials in children compared DXM combinations with placebo (Reece 1966 [31]; Korppi 1991 [25]).

These DXM RCTs are summarised in Table 10. The companies that cited these RCTs in their reports (section 3.3) are also listed in the table.

Table 10: Summary of dextromethorphan RCTs included in Cochrane review of OTC cough and cold medicines for acute cough [9]

Study [Ref. no] [redacted]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Cochrane reviewer comments
Studies in adults								
Lee 2000 [21] [redacted]	43 adults Mean age 23 years (range 18–60) 70% women UK	URTI	DXM 30mg Placebo	Single dose	Cough frequency recordings, cough sound pressure levels, questionnaire on cough severity (scale from 0-3)	Decline in cough frequency (from 50 to 19 per 10-minute period in the active treatment arm compared with 42 to 20.5 in the placebo arm, P=0.38 at 180 minutes follow-up). Mean subjective cough scores showed a decline from 2.0 to 1.0 in the active treatment group compared to a decline from 2.0 to 1.5 in the placebo group (mean difference in decline in cough scores 0.5 at 180 minutes, P=0.08).	Not reported	Only retrospective power calculation reported
Parvez 1996 [22] [redacted]	451 adults in 3 studies Mean age 30 years 65% men Mainly non-smokers India	URTI	DXM 30mg Placebo	Single dose	Cough acoustic signals captured via microphone over 180 minutes. Differences in mean changes between cough counts	Differences in mean change between cough counts varied from 19 to 36 percent ($p<0.05$) in the three studies	Not reported	Many multiple comparisons with no corrections and high probability of Type I error Trial supported by pharmaceutical industry
Pavesi 2001 [23] [redacted]	710 adults in 5 different studies Mean age 30 years 50% women 90% non-	Uncomplicated URTI	DXM 30mg Placebo	Single dose	3-hour continuous cough reporting, measuring cough bouts, cough components, cough effort, cough	Average treatment difference was 12% to 17% in favour of DXM for cough bouts (P=0.004), cough components (P=0.003) and cough effort		Funded and conducted by pharmaceutical company Results poorly reported

Study [Ref. no] (Cited by)[a]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Cochrane reviewer comments
	smokers South Africa and India				intensity and cough latency	(P=0.001), with an increase in cough latency (P=0.002)		
Thackray 1978 [28]	70 adults Mean age 34 years, range 18-60 61% women UK	Common cold	Vicks Medinite syrup (DXM 15mg, ephedrine 600mg, doxylamine 7.5mg, paracetamol 600mg per dose)	Single dose at bedtime for 2 days	Questionnaire, 6-point rating scale. Cross-over design	57.6% of participants in the active treatment group rated the formulation as "good" or better in relieving cough compared to 32.2% in the placebo group (P< 0.01).	7 participants in the active treatment group reported giddiness/drowsiness compared to 4 participants in the placebo group	Main investigator was medical director of the company supplying the drug for the study. Cross-over after 1 day, no washout period
Tukiainen 1986 [29] [redacted]	108 adults Mean age 38 years 55% women 48% smokers Finland	Cough associated with URTI	DXM 30mg DXM 30mg + salbutamol 2mg Placebo	3 times daily for 4 days	Patient diary and symptom score from 0 to 3	Spontaneous improvement of cough in all groups, no statistically significant differences in cough scores between active treatments and placebo for both cough frequency and severity during the day DXM/ salbutamol was superior to placebo or DXM alone in relieving cough at night (mean symptom score 0.19 versus 0.67 and 0.44, respectively on day four, P< 0.01)	DXM/salbutamol combination led to more tremor than placebo (no figures given, P value < 0.05), and no serious adverse effects were reported	No power calculation reported Trial supported by pharmaceutical company
Mizoguchi 2007 [30]	485 patients 18-65 years USA	URTI with cough, for >1 day and <5 days	Test syrup containing DXM 15mg, doxycycline 7.5mg, ephedrine 8mg, paracetamol 600mg	Single nocturnal dose	Cough outcomes: mean cough score on day 1 and 2. % improved with cough 3 hours following active treatment	Significant improvement in mean cough score the morning after treatment and the following day (mean cough score 2.5 versus 2.08 on day two,	19 adverse events in 14 patients, no difference between treatment and control Reported in <1% of participants, none reported as serious	Interim power calculation carried out during study by independent external statistician

Study [Ref. no] (Cited by)[a]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Cochrane reviewer comments
						MD 0.42, P<0.0001). Improvements in the proportion reporting improvement in cough three hours after taking the medication (intervention 57% and control 43%).		Trial supported by pharmaceutical company
Studies in children								
Taylor 1993 [24] [redacted]	57 children Mean age 4.7 years (18 months-12 years) 53% boys USA	Night cough due to URTI	DXM 15mg/5ml + guaifenesin 100mg/5ml Codeine 10mg/5 mg ml + guaifenesin 100mg/5ml Placebo	Single dose at bedtime for 3 nights	Parent questionnaire, cough score from 0 to 4	Neither DXM (cough score reduction of 2.1, P=0.41) nor codeine (cough score reduction of 2.2, P=0.70) was more effective than placebo (cough score reduction of 2.2) on day 3	Drowsiness, diarrhoea and hyperactivity: placebo 7/13 (54%), DXM 6/19 (32%) codeine 5/17 (29%) (p=0.8)	Post-hoc power calculation demonstrates that study powered to detect a difference of 0.9 in cough score – equivalent to a natural resolution of cough at day 3. Authors argue that smaller reductions in cough are unlikely to be clinically important.
Korppi 1991 [25] [redacted]	78 children Mean age 3.8 years 53% boys Finland	Respiratory infection	DXM (<7 years: 1.5mg/5ml; ≥7 years: 10 ml) DXM 1.5 mg/ml + salbutamol 0.2mg/ml (<7 years – 5 ml; ≥7 years: 10 ml) Placebo	3 times daily	Daily symptom score recorded by parents, including cough frequency and severity (scale 0-3)	No difference between groups (Mean difference in cough symptoms on day 3 P=0.04)	Low incidence, no differences between groups	Small study with no power calculation reported.
Paul 2004 [26] [redacted]	100 children 2–18 years USA	Cough due to URTI	DXM: dose based on age (2-5 years: 7.5mg; 6-11 years: 15mg; 12-18 years: 30mg)	Single nocturnal dose	Cough frequency score on a 7-point scale Sleep disturbance in children and their	DXM was no more effective than diphenhydramine or placebo in reducing cough frequency or	Adverse effects: 13/33 in DXM arm 9/33 in diphenhydramine 9/33 in placebo	

Study [Ref. no] (Cited by)[a]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Cochrane reviewer comments
			Diphenhydramine 1.25mg/kg Placebo		parents Composite 5-item score	impact on child or parental sleep (composite symptom score intervention 10.06, control 10.85, mean difference 0.79).		
Bhattacharya 2012 [27] [redacted]	120 children Mean age 5 years (1-12 years)	Cough due to URTI	DXM 5mg Promethazine 0.5mg/kg Placebo	DXM 6-8 hourly for 3 days Promethazine 8-hourly for 3 days Placebo for 3 days	Cough frequency score; child's sleep score; parental sleep score; post-tussive vomiting score; composite score of the above and adverse effects	No difference from placebo treatment. No significant difference in composite symptom scores on day 3 (intervention 4.6, control 5.0, mean difference 0.4).	Adverse events: 34% in DXM group, 32% promethazine group, 5% in placebo group. Drowsiness, irritability, abdominal pain, nausea	
Reece 1966 [31]	43 children Mean age 3.6 years (2 months–12 years) 58% boys USA	Cough due to URTI	Triaminicol syrup (DXM, guaifenesin, pseudoephedrine) Dorcol paediatric cough syrup [DXM, guaifenesin, pseudoephedrine]	Unclear	Parent assessment of treatment response	69% children in both active treatment groups showed a satisfactory response compared to 57% placebo group; not significant (P=0.5)	Not reported	Power calculation not reported Medication sponsored by medical director of lab who also performed the analysis

[redacted]

b. Full study not retrieved.

Summary and applicability of evidence

There was no convincing evidence either for or against effectiveness of OTC medicines in acute cough.

The number of trials in each group of drugs was small, there was poor overall quality of the studies and studies showed conflicting evidence. The authors stated that the results of this systematic review have to be interpreted with caution as the number of trials in each group was small.

There were marked differences between the studies even within groups of drugs with similar mode of action, making it difficult to compare trials directly. There is variation between countries in relation to medications available OTC, making international comparisons more difficult.

Inclusion and exclusion criteria for participants varied, and active drugs were administered in different total daily doses. The duration of drug therapy varied from a single-dose treatment to an 18-day course. For example, six studies testing antitussives, either alone or in combination with other agents, used short-term cough relief after a single dose as an outcome (including the DXM studies: Lee, Mizoguchi, Parvez, Paul, Parvesi), whereas more relevant outcomes for patients would be the effect after one day, three days or a week.

Outcomes were assessed and measured in many different ways, which included questionnaires, cough severity scores, acoustic signals, tape recordings, daily diaries and assessment by a physician. Most studies failed to provide quantitative data on cough as the main outcome of interest, which made it very difficult to assess whether positive study results were clinically relevant.

Four studies carried out multiple comparisons (including Parvez and Pavesi), thereby increasing the probability of a type I error. The authors also noted that this review also highlights a need for an outcome measure for acute cough that is clinically relevant, valid, reliable and easy to use in RCTs.

Comment

This review shows limited evidence supporting the use of DXM for acute cough in adults. There is no evidence of benefit in children. As noted by the authors, there are many limitations to the review, including but not limited to: poor quality of trials overall, small numbers of participants in included trials and differences in interventions and outcome measures. Acute cough also tends to be self-limiting and there is likely to be an improvement in symptoms over time, regardless of the treatment used. Even in those studies which do demonstrate a statistically significant benefit, the benefit is found to be small.

The UK's National Institute for Health and Care Excellence (NICE) recently published an antimicrobial prescribing guideline for cough, which contained an evidence review of antitussives for self-care [32]. The Smith et al systematic review was included in NICE's evidence review. NICE's overall risk of bias/quality assessment of the Smith et al review was generally positive, but they commented that participant numbers and event rates in intervention and control groups were inadequately reported. It was also unclear whether the authors attempted to access missing data. Of the DXM RCTs included in the Smith et al review, NICE assessed these as being of very low or low quality.

3.1.2 Yancy et al (2013) [33]

This paper was a systematic review of symptomatic therapies for chronic cough. Meta-analysis with random-effects models was used to summarise effects of treatments.

Methods

The authors identified 49 studies (3,067 patients), comprising 68 therapeutic comparisons. Studies eligible for inclusion were English language, prospective, comparative (vs placebo or active therapy) assessments of pharmacologic and nonpharmacologic therapies aimed at treating the symptom of cough in patients with unexplained or refractory chronic cough (persisting 4 weeks if aged ≥14 years or 8 weeks if aged <14 years or as stated by study authors). Articles were excluded if (1) the therapy was directed at an underlying aetiology, (2) cough resulted from invasive respiratory tract instrumentation, (3) the only outcomes assessed were induced sputum or bronchoprovocation challenge, (4) the therapy was not commercially available globally or

had been withdrawn from the US market or rejected by the US Food and Drug Administration, or (5) the study was a case-control design.

The authors used meta-analysis for comparisons where at least three studies reported the same outcome. They considered measures of cough severity, regardless of the scale used, to be similar enough to combine estimating effect sizes as standardized mean differences (SMDs). Cough frequency data were analysed with the use of the rate ratio (RR) as an effect size measure. They performed a mixed treatment meta-analysis to incorporate data from placebo comparisons and head-to-head comparisons. For treatments that could not be included in the mixed-treatment meta-analysis, they calculated effect sizes from data reported in the studies (raw data, means and variances, or test statistics) to present results in comparable terms.

Summary of the included dextromethorphan studies

Seven of the included studies involved DXM and all were in adult populations. These DXM studies are summarised in Table 11. Note that the Yancy paper presented limited information about the included studies. Medsafe was able to retrieve some of these studies and added additional information to the table. The companies that cited these studies in their reports are also noted in the table.

Table 11: Summary of dextromethorphan studies included in the Yancy et al meta-analysis

Study [Ref. no.] (Cited by)[a]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Yancy comments
Cass and Frederick 1953[b] [34] [redacted]	69 adults USA	Persistent cough (cause not recorded)	DXM Codeine Placebo		Cough severity Adverse events		Drowsiness	Quality: fair
Cass 1954 [35] [redacted]	69 adults Hospital patients USA	Persistent cough (cause not recorded)	DXM 6, 12 or 18 mg tablets Codeine 15 mg tablet Placebo tablet	3 times per day for 7 days for each treatment	Cough severity (scale 0-4) Adverse events	6 mg DXM significantly more effective than placebo, and significantly less effective than 12 or 18 mg of DXM or 15 mg codeine. No difference between 12 and 18 mg DXM or between 15 mg codeine and 12 or 18 mg DXM.	Codeine had more side effects than DXM at any dose (drowsiness, nausea, vomiting, constipation) No difference between placebo and DXM.	Quality: poor
Cass and Frederick 1956[b] [36] [redacted]	63	Persistent cough (cause not recorded)	DXM DXM Codeine Placebo		Cough severity			Quality: fair
Matthys 1983 [37] [redacted]	16 adults Mean age 55.9 years (25-74 years) 69% male 56% current or former smokers	Chronic cough (secondary to pulmonary TB, bronchial cancer or obstructive lung disease)	Double-blind crossover: DXM 20 mg capsule Codeine 20 mg capsule Placebo capsule	2 doses on 3 consecutive nights	Cough severity Cough frequency/resolution Patient preference	No significant difference between cough frequency and cough severity index (freq x intensity) for antitussives but both significantly more effective than placebo ($p<0.0001$) DXM lowered cough intensity more than codeine ($p<0.0008$), majority of patients preferred it ($p<0.001$)		Quality: fair

Study [Ref. no.] (Cited by)[a]	Population	Indication	Treatment	Frequency & Duration	Outcome measure	Efficacy	Adverse Effects	Yancy comments
Ruhle 1984 [38] [redacted]	24 adults Mean age 53.0 years (range 30–75 years) 75% males	Chronic cough (due to COPD, asthma, chronic bronchitis, TB)	Double-blind cross-over design (each patient received 2 of the 3 treatments): DXM 30 mg/10 ml Glaucine 30 mg/10 ml Placebo	Single dose	Cough severity – patient + nurse questionnare Cough frequency/resolution (contact throat microphone) Adverse events	No difference between treatments or placebo for cough severity. Mean cough counts lower for active treatments vs placebo but only glaucine significant ($p<0.05$).	11/24 patients reported side effects: 2 after placebo, 1 after glaucine and 8 after DXM	Quality: fair
Del Donno 1994[b] [39] [redacted]	124 adults	Dry or slightly productive cough (due to COPD, unexplained cough, acute or unspecified bronchitis, other respiratory disease)	Randomised single-blind: DXM 30 mg Moguisteine 200 mg	3 doses over 2 days	Percentage reduction in audio-tape recorded coughs compared with baseline Patient assessment (visual analogue scale; VAS) cough frequency and cough troublesomeness at night Adverse events	No differences between treatments – 30% reduction in coughs, reduction in VAS scores	3/61 patients on moguisteine 4/63 DXM	Quality: good
Ramsay 2008 [40] [redacted]	42 current smokers Mean age 38.5 years (23-61 years) 48% male	Smoking-related chronic cough (no secondary disease)	Randomised double-blind crossover: DXM base 22mg/0.8 ml pre-gastrically (equivalent to 30 mg DXM) Placebo	2 doses 4 hours apart at clinical trials unit, then 3 times per day for 5 days at home	Daily diary record Leicester quality of life questionnaire Cough frequency (manual counter) Cough reflex sensitivity via citric acid challenge	Compared to placebo, DXM significantly diminished cough reflex sensitivity at 1- and 2-hours post-dose, $p<0.05$. No difference compared to placebo for cough severity, sleep disturbance, or cough-specific quality of life. Evidence of a marked 'placebo' effect.		Quality: good

[redacted]

b. Full study not retrieved.

Results

Compared with dextromethorphan, codeine was less effective in one study (Matthys), comparable in another (Cass and Frederick 1956) and more effective in two studies – but these latter studies compared standard-dose codeine to low-dose dextromethorphan (Cass and Frederick 1953, Cass 1954). Neither of the other antitussives (glaucine and moguisteine) were superior to dextromethorphan in head-to-head comparisons (Ruhle, Del Donno)

Six studies compared dextromethorphan with placebo (Cass and Frederick 1953, Cass 1954, Cass and Frederick 1956, Matthys, Ruhle, Ramsay). Four of these showed that dextromethorphan was effective at reducing cough severity, frequency, or both (Cass and Frederick 1953, Cass 1954, Cass and Frederick 1953, Matthys). In the Ramsay study, dextromethorphan was more effective than placebo in response to tussigenic challenge but not for cough severity, sleep disturbance, or cough-specific quality of life. The one study reporting negative results (Ruhle) examined a single dose of dextromethorphan versus placebo.

In two studies, nausea, constipation and drowsiness were more frequent with codeine than with dextromethorphan (Cass and Frederick 1953, Cass 1954).

Meta-analysis (all treatments)

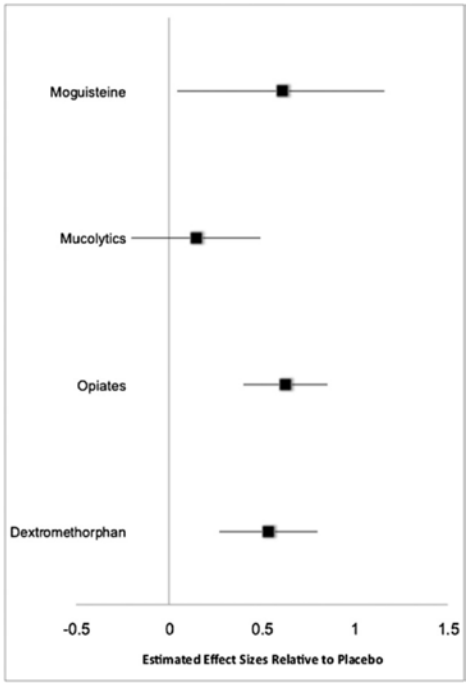
Data from 13 studies were analysed in a mixed-treatment meta-analysis for cough severity. Because studies used various measures of severity, all results were converted to effect sizes (SMDs). Effect size values of 0.20, 0.50 and 0.80 represent small, medium and large effects, respectively.

Relative to placebo, the following treatments showed a beneficial effect on cough severity (Figure 5):

- DXM (SMD, 0.37; 95% CI 0.19-0.56; P=0.0008)
- Opioids (SMD, 0.55, 95% CI 0.38-0.72, p<0.0001)
- Moguisteine (SMD, 0.46, 95% CI 0.01-0.92, p=0.0475).

The studies included in the analysis showed evidence of heterogeneity (p=0.0152). The evidence was insufficient to determine relative benefit among these therapies.

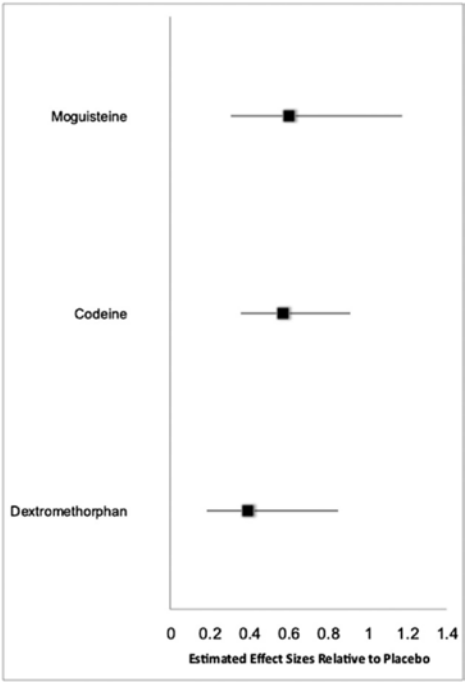
Figure 4: Meta-analysis of data on cough severity (standardised mean differences)



Seven studies were included in the meta-analysis for cough frequency (Figure 6). Relative to placebo, DXM (RR, 0.40; 95% CI 0.18-0.85, p=0.0248) and codeine (RR, 0.57; 95% CI 0.36-0.91, p=0.0260) showed a beneficial

effect on cough frequency. The effect of moguisteine was not significant (RR, 0.60; 95% CI, 0.31-1.17; p=0.1117). The studies showed significant heterogeneity (p=0.0231). The estimates were too imprecise to determine whether codeine or DXM is superior to the other.

Figure 5: Meta-analysis of data on cough frequency (rate ratios)



Discussion and conclusion

In studies that included an active or placebo comparison, there was evidence of relative efficacy for the reduction of frequency and severity of chronic cough only for codeine and DXM. Because of the small number of head-to-head comparisons and inconsistency and imprecision of results, however, the authors were unable to draw conclusions about the comparative effectiveness of these two agents. Tolerability concerns were found only for opioids.

Applicability is reduced due to the age of the evidence – publication dates ranged from 1953 to 2012, with 76% of studies being published before 2000.

The authors noted that the findings are limited by: (1) few studies explicitly exploring the target population (patients with unexplained or refractory chronic cough) or subpopulations (eg, children); (2) variable definitions of chronic cough; (3) diverse aetiologies that might respond differently to different therapies; (4) incomplete reporting of patient characteristics, study design, or outcomes; (5) small sample sizes and short durations of follow-up; (6) lack of gold standard outcomes to assess efficacy and tolerability; (7) inconsistent reporting of comparative statistical analyses; and (8) a limited number of direct comparisons between active treatments.

The authors stated there is a need for further studies in patients with unexplained or refractory cough as well as for more systematic study designs, assessment of patient-centred outcomes, and reporting.

Comment

As noted by the authors, there are serious limitations to the meta-analysis findings. There was evidence of heterogeneity in the studies, particularly for cough frequency.

The study characteristics table in the Yancy paper provided very little information about the interventions, assessments and efficacy measures (Medsafe added details to Table 11, where possible). Risk of bias in the studies was not described by the authors.

3.1.3 Dicpinigaitis (2014) [8]

This paper was a review of current understanding of the pathogenesis of cough and the hypertussive state characterising a number of diseases as well as reviewing the evidence for the different classes of antitussive drug currently in clinical use. The authors were experts in pharmacology, basic science and clinical aspects of cough.

Relevant to this risk-benefit review is the summary of DXM-related studies. Note that the review presented limited information about the included studies. Medsafe was able to retrieve some of these studies and added additional information, where possible.

Reduction in cough reflex sensitivity

Six studies reported the efficacy of DXM (30 mg) on cough induced by inhalation of aerosols of citric acid by healthy adult subjects. In all studies except one (Empey et al), oral administration of DXM was associated with a significant reduction in cough challenge when compared with placebo.

- Empey et al (1979) [41] studied 18 healthy volunteers to compare the antitussive effect of codeine (20 mg), DXM (30 mg), and noscapine (30 mg). Only codeine 20 mg had antitussive activity.
- Packman and Ciccone (1983) [42] reported a double-blind, three-period crossover study in 30 healthy volunteers of 30 mg of DXM and 7.5 mg of doxylamine with DXM and a placebo. Both treatments were significantly superior to placebo in reduction of overall cough frequency ($P < 0.0001$) for up to 8 hours post-treatment.
- Karttunen et al (1987) [43] reported the antitussive effects of DXM (30 mg) plus salbutamol (2 mg), DXM (30 mg) alone, or placebo in 19 healthy non-smoking subjects in a double-blind crossover study. Significant increases in cough threshold were shown after DXM and the DXM-salbutamol combination.
- Grattan et al. 1995) [44] investigated the effects of inhaled DXM with a single oral dose of DXM (30 mg) in 20 healthy subjects. Although oral DXM delivered significant ($P < 0.002$) reductions in induced cough frequency, it is noteworthy that the inhaled DXM (1, 3, and 30 mg) did not demonstrate an antitussive effect. Thus, a peripheral activity of DXM seems unlikely.
- Hull et al (2002) [45] investigated a series of doses of DXM in a novel "pre-gastric" formulation designed to promote transepithelial absorption in the oral cavity and oesophagus and thus provide a more rapid onset of activity. DXM (50 mg p.o.), 22 mg of DXM free base (equivalent to 30 mg of DXM HBr) delivered pre-gastrically, codeine (60 mg p.o.), DXM (50 mg) plus codeine (60 mg p.o.), or placebo were compared. All doses of DXM delivered significant reductions in induced cough frequency from baseline, and when dosed pregastrically, DXM reduced cough frequency compared with placebo at 15 minutes post-administration.
- Ramsay et al (2008) [40] reported a placebo-controlled randomised, double-blind crossover study in 42 subjects with smoking-related cough. A single dose of DXM was administered pre-gastrically as 22 mg free base and was associated with a significant ($P < 0.05$) reduction in cough reflex sensitivity. For the subjective measures of cough (patient record at home), there was a significant placebo effect.

The authors noted that the negative Empey study was the smallest and concluded it is likely to have insufficient power to produce a reliable negative result. Of the remaining five positive studies, DXM effectively diminished cough reflex sensitivity as revealed by citric acid challenge in humans. The authors questioned whether this activity translates into clinical efficacy in pathologic cough.

Efficacy against acute cough in adults

The authors described three clinical studies and one meta-analysis.

- Tukiainen et al (1986) [29] studied DXM (30 mg), DXM (30 mg), and salbutamol (2 mg) or placebo (3 times daily for 4 days) in 108 patients with cough associated with acute respiratory tract infection. Reported cough severity was reduced significantly in all groups, with DXM having no greater effect than placebo.

- Jawad et al (2000) [46]– a study of 42 patients comparing a single dose of DXM (30mg) with placebo. Objective methods were used to record count cough frequency and failed to show significant effects (except in cough pressure levels).
- Parvez et al (1996) [22] measured the effect of a single dose of DXM (30mg) on the objectively assessed cough frequency in a study of 451 patients. Cough counts were significantly reduced compared with placebo ($P < 0.05$).
- Pavesi et al (2001) [23] performed a meta-analysis of six randomised, double-blind placebo-controlled studies (funded by Procter & Gamble) with a single dose DXM (30 mg) in URTI, which demonstrated an average treatment difference of 12–17% in favour of DXM for cough bouts (P=0.004), cough components (P=0.003) and cough effort (P=0.001), with an increase in cough latency (P=0.002).

Efficacy against other forms of cough in adults

The review authors noted that placebo-controlled DXM studies are rare in other forms of cough, and therefore therapeutic efficacy is impossible to judge. The authors also noted that there are a number of small studies comparing efficacy of DXM with other antitussive agents, but methodological considerations make interpretation difficult.

- Ralph (1954) [47] compared three different doses of DXM for its ability to suppress chronic cough attributable to a range of conditions, tuberculosis, acute and chronic bronchitis, bronchiectasis, asthma, lung abscess, and bronchogenic carcinoma in 144 patients. A 15-mg dose of DXM was observed to be significantly better than 4 mg by patient report, although this was not a placebo-controlled study.
- Cass et al. (1954) [35] reported cough suppressant activity of DXM compared with codeine in 69 patients with persistent cough. DXM (6 mg) was significantly more effective than placebo, but significantly less effective than 12 mg of DXM. The review authors noted that given what is now known about the pharmacodynamics of DXM, the results of this Cass study (claimed efficacy at 10-15 mg) seem unlikely.
- Matthys el al (1983) [37] studied 16 patients with chronic, stable cough due to pulmonary tuberculosis, bronchial carcinoma, or obstructive lung disease. DXM (20 mg), 20 mg of codeine phosphate, or placebo was compared (double-blind, crossover trial, 2 doses on 3 consecutive nights), and cough was measured by means of a pressure transducer attached over the trachea. Both drugs were significantly more effective than placebo ($P < 0.0001$).
- A further study by Matthys et al. (1983) evaluated the antitussive effect of several drugs [noscapine (30 mg), DXM (20 mg), dihydrocodeine (30 mg), or codeine (20, 30, and 60 mg) administered twice daily] in patients with chronic stable cough due to bronchial carcinoma, pulmonary tuberculosis, or COPD. Patients received active antitussive drugs or placebo in a double-blind, randomised crossover design. Cough frequency and intensity were recorded for 8 hours. Noscapine, DXM, dihydrocodeine, and codeine (60 mg) all significantly reduced the cough frequency compared with placebo and produced a greater reduction of cough intensity than placebo, codeine (20 mg), or codeine (30 mg).
- Ruhle et al (1984) [38] objectively compared a single dose of glaucine (30mg), with DXM (30 mg) and placebo. In 24 patients affected by chronic cough, cough count frequency after DXM and glaucine was lower than after placebo, although only glaucine caused a significant reduction in cough frequency.
- Aylward et al. (1984) [48] – a comparison of plasma kinetics and antitussive effects in eight patients with cough associated with "simple bronchitis". Cough counts were statistically significantly different ($P < 0.05$) from placebo for both codeine (30 mg)- and DXM (60 mg)-treated patients.
- Del Donno et al. (1994) [39] compared moguisteine (3 doses of 200 mg, over 2 days) to DXM (3 doses of 30 mg, over 2 days) and found both drugs to be equally effective.
- Catena and Daffonchio (1997) [49] – a double-blind, randomised clinical trial comparing levodropropizine syrup (60 mg three times a day for 5 days) with DXM syrup (15 mg three times a day for 5 days) in 209 adult patients with moderate non-productive cough. Both levodropropizine and DXM reduced cough intensity.
- Equinozzi and Robuschi (2006) [50] compared DXM and pholcodine (taken 3 times daily for 3 days) in 129 patients with acute, frequent, non-productive cough. There was an equal reduction in the metrics of cough observed.

Efficacy in children

The review authors stated that the data on the efficacy of DXM in paediatric populations are limited. They concluded that in each case, the study sample size was too small to have detected efficacy differences compared with placebo. Four published studies examined the antitussive effect of DXM on acute cough in children with acute URTI, although none showed any significant antitussive effects.

- Korppi (1991) [25] studied 78 children with respiratory infection associated cough, randomly assigned to receive DXM, DXM-salbutamol or placebo for three days (dose dependent upon age). All groups reported some or marked relief by the medication; the differences between the groups were not statistically significant.
- Paul et al (2004) [26] – parents of 100 children with upper respiratory infections were questioned to assess the frequency, severity, and bothersome nature of their child's nocturnal cough and whether parents have improved sleep quality when their child received medications (a single age-dependent dose of DXM or diphenhydramine) compared to placebo. Neither medication produced a superior benefit when compared with placebo for any of the outcomes studied.
- Paul (2004) [51] – this study was to determine if a dose-response relationship existed among a group of children (n=33) administered a single nocturnal dose of DXM for cough due to an URTI. Subjective parental assessments of cough and sleep were obtained. No significant differences were found for any of the outcome measures when comparing the effects of different doses of DXM, but there was somewhat more symptomatic relief for patients receiving medium-dose DXM (0.45 to <0.60 mg/kg per dose) or high-dose (HD) DXM (0.60-0.94 mg/kg per dose) compared with low-dose DXM (0.35 to <0.45 mg/kg per dose).
- Yoder et al (2006) [52] – this study sought to investigate the efficacy of DXM, diphenhydramine (DPH), and placebo (PL) for symptoms attributed to URTI as determined by children, and to evaluate the concordance of perception of nocturnal symptoms between children and parents. A total of 37 children age 6 to 18 years of age were randomised in a double-masked fashion to receive a single bedtime dose of DXM, DPH, or PL. Children found no significant difference in the effect of DXM, DPH, or PL for any study outcome, and responses by parents and children were significantly correlated.

Two studies were cited that assessed the value of treating children with honey for nocturnal cough – where DXM was used as a positive control.

- Paul et al. (2007) [53] compared honey and DXM (age-dependent dosage) to no treatment in 35 children per treatment arm and were unable to show a statistically significant effect of DXM or honey on subjective reports of cough severity or sleep quality.
- Shadkam et al. (2010) [54] – a study of 139 children aged 24–60 months receiving a single dose of 2.5 mL of DXM (7.5 mg), diphenhydramine (6.25 mg) or honey, or a control arm with "supportive treatment" (saline drops, water vapor, and acetaminophen). DXM and diphenhydramine demonstrated an improvement in subjective parameters of cough compared with "supportive treatment," but these did not reach statistical significance.

Summary

The authors concluded that while many of the DXM studies have shown reduced cough sensitivity, few have demonstrated clinically significant effects, particularly in acute URTI where many trials do not meet modern standards of design. In addition, the reviewed studies did not support the use of DXM in children.

The authors stated, "perhaps surprising for drugs used to treat such a common symptom, there is a paucity of well-controlled clinical studies documenting evidence for the use of many of the drug classes in use today, particularly those available over the counter."

Comment

This is not a systematic review of the literature. It is unclear how studies were included or excluded for discussion in this paper. It was not possible to retrieve all the studies described in this paper. Also, some studies were not available online, abstracts were not available and/or were other languages.

The limitations of many of these studies are described in the systematic reviews above but include: small study sizes and being underpowered to show an effect, diverse aetiologies, differences in measurement techniques and analysis.

3.2 Safety

3.2.1 Case reports

3.2.1.1 New Zealand

Up to 30 June 2019, there were 84 spontaneous reports (159 reactions) to CARM where a product containing DXM was a suspect agent (Annex 1; note the DXM-containing products are listed by brand name rather than active ingredient). The first report was in September 1979 and the most recent was March 2019.

- There were 58 reports in females, 23 in males and sex was not recorded in 3 reports.
- Age was recorded in 64 of the 84 reports and ranged from 20 months to 84 years. There were 8 reports in children aged under 18 years (Table 12) and 56 reports in adults aged 18 years and older.
- Eleven reports were considered serious, all of these were in adults. Of the serious reports, 1 patient died, 2 had not yet recovered and 8 had recovered.
- Of the 159 reported reactions, the most frequently reported were: rash (10 reports), angioedema (7), vomiting (7), diarrhoea (6), nausea (6) and urticaria (6).
- There were 3 reports of serotonin syndrome (73025, 75084, 119378). In 2 of these reports, other cough and cold medications were co-administered.
- There were 3 reports of drug abuse (85114, 87928, 127973). The patients were aged 34, 22 and 15 years, respectively.
- There was one report of overdose effect (74296) in a male patient. Age and ethnicity were unknown.

Comment

One of the major difficulties with spontaneous reporting systems is under reporting. A figure often quoted for the reporting rate is 10% of the actual number of adverse reactions that are experienced. It is expected that the proportion of adverse drug reactions that are reported for over-the-counter medicines is even lower. In addition, many of the adverse reactions to cough and cold medicines are similar to symptoms of colds and may not be perceived as being caused by the medicine. Young children may not always be able to communicate to carers that they are experiencing a possible adverse drug reaction.

Table 12: Reports received by CARM (up to 30 June 2019) for dextromethorphan-containing products in children aged under 18 years

Report No	Date	Age	Sex	Medicine(s)	[redacted]	[redacted]	[redacted]	Reported reactions	[redacted]	[redacted]
18171	11/1988	16	Female [redacted]	Codral Cough* Pseudoephedrine				Rash erythematous		
32292	10/1996	20m	Female [redacted]	Day & Night Cold & Flu*				Dystonia		
94483	03/2011	11	Female [redacted]	Dimetapp DM Colour Free Cough & Cold*				Abdominal pain Vomiting		
95244	05/2011	3	Female [redacted]	Robitussin Cough +Chest Congestion*				Fever Diarrhoea		
98352	11/2011	4	Male [redacted]	Dimetapp DM Colour Free Cough & Cold*				Anger Hyperkinesia Batch difference		
100323	03/2012	11	Male [redacted]	Robitussin DM*				Oedema peripheral		
127973	04/2018	15	Female [redacted]	Robitussin Dry Cough Forte* Alcohol (ethyl)*				Drug abuse Depersonalisation Tachycardia Hypokalaemia Medication error		
132233	03/2019	17	Female [redacted]	Codral NOS* Ibuprofen* Jadelle				Lip swelling non-specific		

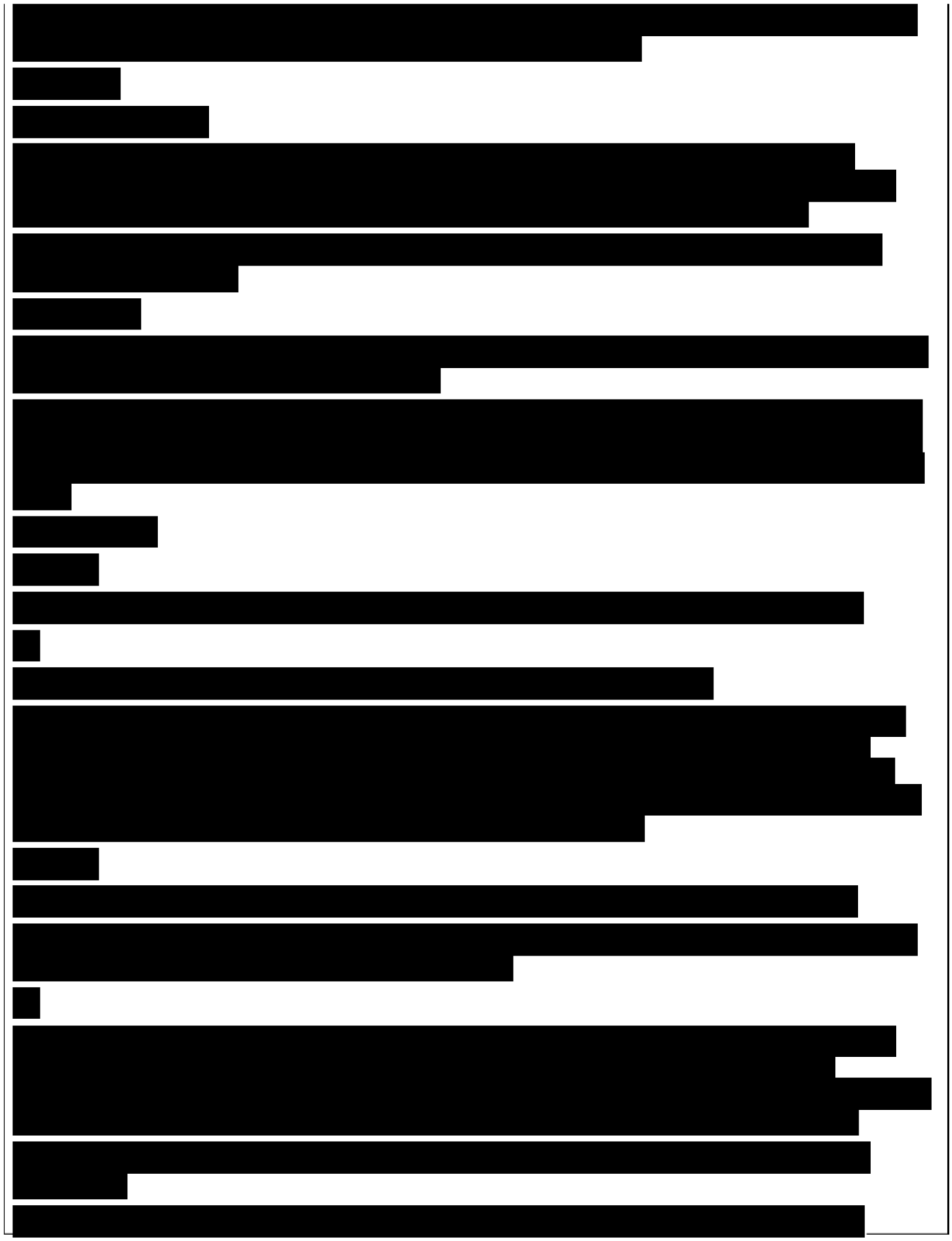
* Suspect medicine(s)

NOTE: Product formulations have changed over time. Formulations as stated in the case reports and/or the Medsafe Product Application search are as follows.

- Codral Cough = dextromethorphan + pseudoephedrine
- [redacted]
- Day & Night Cold & Flu = dextromethorphan + chlorphenamine + paracetamol +pseudoephedrine
- Dimetapp DM Colour Free Cough & Cold = dextromethorphan + brompheniramine + phenylephrine
- Robitussin Cough +Chest Congestion = dextromethorphan + guaifenesin
- Robitussin DM = dextromethorphan + guaifenesin
- Robitussin Dry Cough Forte = dextromethorphan

[redacted]

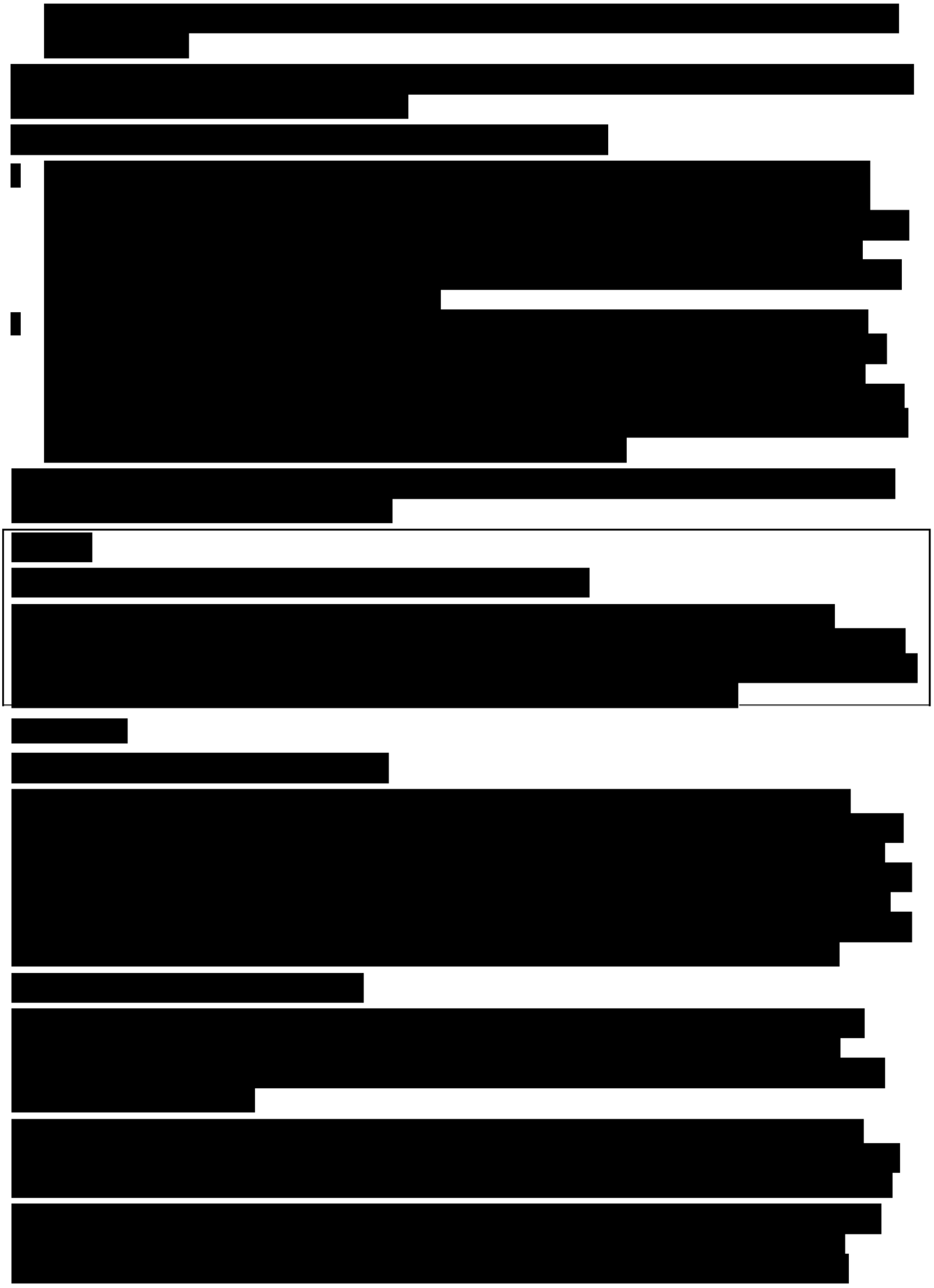
[redacted]

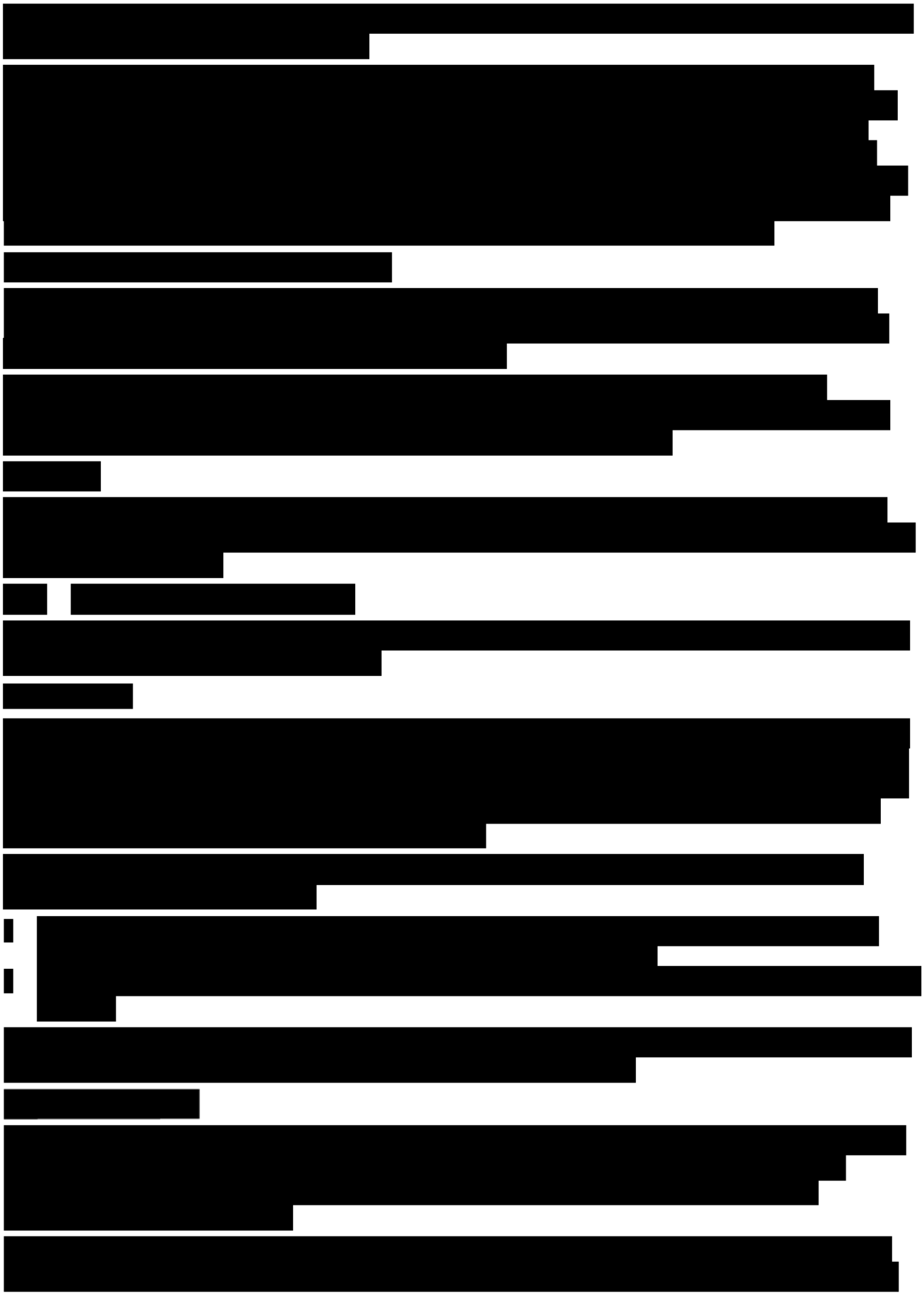


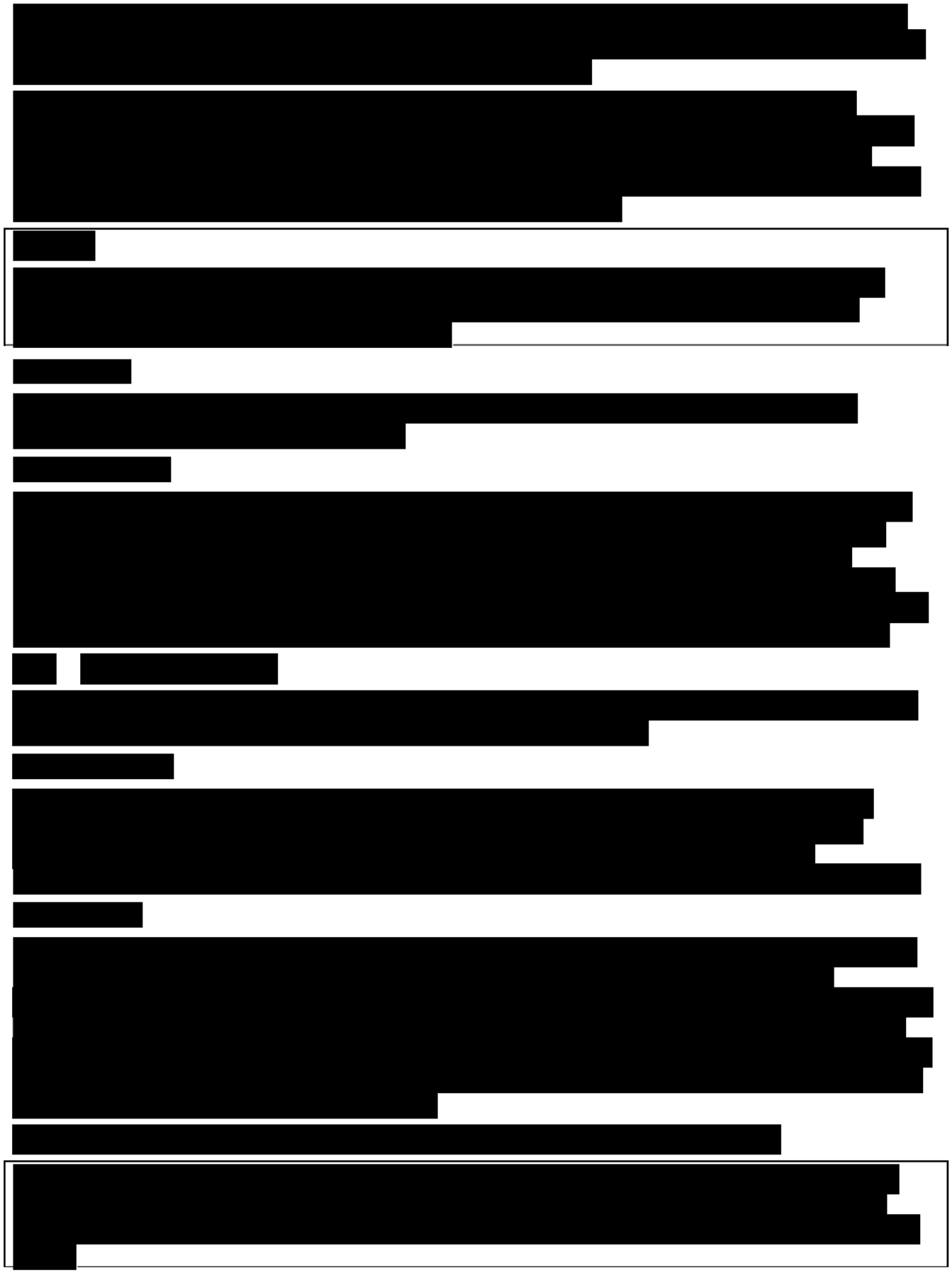
[redacted]

3.3 Company reports

[redacted]







[redacted]

[redacted]

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4 DISCUSSION AND CONCLUSIONS

Dextromethorphan (DXM) is a cough suppressant used for the relief of non-productive cough.

DXM, in the context of cough and cold medicines, has previously been reviewed by the Medicines Adverse Reaction Committee (2007, 2009 and 2010). The Committee, in line with international advisory groups and regulators, made recommendations for contraindicating the use of DXM in children aged under 6, and limiting its use in children aged 6-11 years.

There is a large body of literature for dextromethorphan but most of it was published before 2000. Of the published efficacy studies, many of them have serious design flaws making comparisons between studies difficult. There is limited evidence supporting the use of DXM in adults. Even in those studies which do demonstrate a statistically significant benefit in adults, the benefit is found to be small. There is no evidence of benefit in children. Therefore, the benefit profile since DXM was last reviewed remains unchanged.

DXM has been used as a cough suppressant for more than 50 years. It is approved in many countries worldwide, and millions of doses have been sold. The number of adverse events reported relative to doses sold is low, although the risk of underreporting is considerable. Common adverse events (as listed in the Bisolvon New Zealand data sheet) are confusion, somnolence, dizziness, gastrointestinal disorders and fatigue.

At supra-therapeutic doses, DXM can cause euphoric, stimulant, and dissociative effects. There are case reports of DXM drug abuse, overdose and death. The effect is highly dependent of the capability of the individual to metabolise the medicine.

To reduce the potential for abuse, misuse and overdose, some international regulators have reclassified DXM from an OTC medicine to a prescription medicine or prohibited its sale to minors. DXM was reclassified in New Zealand in February 2019 from a general sale and pharmacy-only medicine to a restricted medicine.

Reclassification of DXM to a restricted medicine also means that consumers (patients, parents, caregivers) can discuss appropriate treatment with a pharmacist, and pharmacists have a better opportunity to identify patients who should be referred to a doctor. Data sheets are also now required for DXM-containing products. Medsafe expects companies to submit data sheets by February 2020.

The Pharmacovigilance Risk Assessment Committee (PRA recently reviewed Periodic Safety Update Reports for DXM-containing products marketed Europe. The PRAC concluded that the benefit/risk ratio of DXM-containing products remains unchanged in the current indication, but new safety data warrants changes to the prescribing information. The PRAC recommended the addition of warnings in section 4.4 of the Summary of Product Characteristics (SmPC) on serotonin syndrome, drug dependence and use in children. The PRAC also considered that information on the symptoms and management of overdose should be included in section 4.9 of the SmPC.

5 ADVICE SOUGHT

The Committee is asked to advise:

- whether the balance of benefits and risk for the use of dextromethorphan for the symptomatic treatment of unproductive cough is favourable
- any regulatory action is required to improve the balance of benefits and risks.

6 ANNEXES

1. CARM case report data [Confidential]
2. PRAC PSUR assessment report – Dextromethorphan [Confidential]
3. CARSL Consulting – Procter & Gamble Products [Confidential]
4. Johnson and Johnson – Clinical overview [Confidential]
5. Pfizer – Dextromethorphan efficacy and safety information [Confidential]
6. Pfizer – New Zealand case reports of abuse [Confidential]
7. Sanofi-aventis – Response to agency request [Confidential]
8. Reckitt Benckiser – Vigilance summary statement [Confidential]

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