

# Proposal for reclassification of cough medicines containing dextromethorphan, opium tincture, squill oxymel and pholcodine to restricted medicines

## Purpose

Medsafe has recently been alerted to instances of abuse of cough medicines containing dextromethorphan. Concern was raised over the easy availability of opioid (and opioid-like) cough medicines which can be bought at a pharmacy or supermarket without healthcare professional supervision.

Dextromethorphan is a substance that does not belong to the opioid family but has a chemical structure closely resembling the opioids. Dextromethorphan has a history of abuse in New Zealand and other countries.

There are also other cough medicines available as pharmacy medicines which have been noted as at least having a potential for abuse, for example cough medicines containing pholcodine and Gees linctus which contains anhydrous morphine. Pholcodine and anhydrous morphine are both opioids.

Medsafe therefore requests that Medicines Classification Committee (MCC) considers reclassification of dextromethorphan, opium tincture, squill oxymel and pholcodine containing products to Pharmacist-Only (restricted) medicines. Medsafe considers that a reclassification to restricted medicine balances a need for better supervision whilst maintaining access for those who benefit from using these medicines.

## Background

### Dextromethorphan and misuse (1)

Dextromethorphan (DXM) is the D- isomer of the codeine synthetic analogue, levorphanol. DXM also structurally resembles ketamine and phenycycline which are dissociative agents, meaning that they can be used to incite a type of general anesthesia characterized by analgesia and amnesia with minimal effect on respiratory function. DXM is an opioid, but because of its stereochemistry, DXM and its metabolites do not bind to the mu and delta opioid receptors, thus avoiding classic opioid toxicity.

In regular daily dosing, DXM is a cough suppressant, affecting the signals in the brain that trigger the cough reflex by its active metabolite, dextrorphan.

In overdose, the active metabolite of DXM expresses a unique combination of euphoric, stimulant, and dissociative effects in older children and adolescents that is similar to ketamine and phenycycline (PCP) and can be classified as a dissociative agent. Dissociative effects include hallucinations, distorted perceptions of sight and sound as well as feelings of detachment from the environment and self. DXM also inhibits adrenergic neurotransmitter reuptake in the peripheral and central nervous system resulting in tachycardia, hypertension, and diaphoresis.

DXM toxicity occurs in a dose dependent fashion. The effects typically begin 30 to 60 minutes post-ingestion and persist for up to six hours. The different stages of effect are often referred to as "plateaus" by users, and are listed below along with the approximate range of doses associated with them:

- Mild stimulation (first "plateau"): adult dose: 100 to 200 mg
- Euphoria and hallucinations (second "plateau"): adult dose: 200 to 400 mg
- Dissociative "out of body" state (third "plateau"): adult dose: 300 to 600 mg
- Complete dissociation with unresponsiveness (fourth "plateau"): adult dose: >600 mg

The typical strength of a cough tablet is 10-15 mg. The effects of DXM is highly dependent on the individual ability to metabolise DXM.

DXM has a long history of abuse, especially among teenagers and young people. Initially DXM was introduced as a tablet but when problems with misuse occurred, pharmaceutical companies introduced liquid formulations designed to reduce abuse by creating an unpleasant taste if ingested in large amounts.

DXM may encourage initiation and progression of substance abuse in teenagers. Some younger adolescents consider DXM to be a harmless and legal high. Because it is easily available and produces an intense effect, DXM may entice young users to experience broader and illicit substance abuse experiences.

DXM cough and cold products frequently also contain acetaminophen, antihistamines, or pseudoephedrine that has significant toxic potential. In addition, DXM may produce a life-threatening serotonin syndrome when used in combination with monoamine oxidase inhibitors or other serotonergic agents, such as antidepressants.

Dextromethorphan is available in Australia, UK, US, Canada and many other countries. It is not available in Sweden and Norway. The medicine is available on prescription in Denmark.

#### Gees linctus (opium tincture and squill oxymel) and misuse

Gees linctus contains 1.369% w/w ( $=1.608\%w/v$ ) Opium tincture, which equals 0.0165% w/v of the active substance anhydrous morphine. The oral solution also contains SFM Oxymel Squill 1.67% w/v. Gees Linctus is indicated for relief from the wet, productive and irritating cough.

The anhydrous morphine reduces the desire to cough, and squill helps to remove phlegm. The content of anhydrous morphine in one bottle of Gees linctus (200 ml) is about 33 mg (0.16 mg/ml). The mixture also contains alcohol (20%) which may be an important reason why it would be misused. Basically, 1 teaspoon of this cough medicine has as much alcohol as about 2 teaspoons of wine.

New Zealand has a history of misuse of Gees linctus. A report released from the Ministry of Health in 2010 (2) points out that people tend to develop and maintain their opioid dependence by using OTC products, such as Gees Linctus. Gees linctus has been reported to induce a "lovely euphoria and dreaminess", if a person is prepared to drink enough volume. On the other hand, a published study from Scotland in 2016 showed that the trend was that more people abused codeine containing medicines and less abused Gees linctus, see also section "Scientific information" (3).

Anhydrous morphine is highly addictive. As a result, tolerance and physical and psychological dependence can develop rather quickly. Like all opium drugs, anhydrous morphine has the ability to deliver a euphoric high, especially the first time it is used. Achieving the same euphoria is difficult in

subsequent uses and therefore an individual will often try to increase the dose to achieve the same high. Such an approach puts the person's life at risk as the medication is increasingly potent in higher volumes (4).

### Pholcodine and misuse

Pholcodine is an opioid cough suppressant. The mechanism of action is by suppressing coughs. Pholcodine also has a mild sedative effect, but little or no analgesic effects. Pholcodine is found in cough lozenges or oral solutions, typically with the strength 1 mg/ml.

Even if pholcodine has been used as an antitussive for a long time, few studies of clinical efficacy or comparisons with other antitussives regarding efficacy and general toxicity have been presented. However, there seems to be a consensus that the addictive potential of pholcodine is low (5-7).

In Findlay's publication (6), the theory that pholcodine is not metabolised to morphine in man is presented as a fact which may contribute to its more favourable toxicity profile, low addiction dependence liability and also would be a reason for the lack of analgesic effect. In addition, pholcodine is metabolised and eliminated much more slowly than codeine.

The main point of interest regarding pholcodine recently has been if there is a link between severe allergic reactions and previous pholcodine exposure, see section "Recent international regulatory actions".

## Previous discussions by MCC

Dextromethorphan has been discussed at the 21<sup>st</sup>, 27<sup>th</sup>, 29<sup>th</sup>, 30<sup>th</sup>, 37<sup>th</sup>, 43<sup>rd</sup> and 44<sup>th</sup> meetings with the MCC:

### 21<sup>st</sup> meeting 22 March 1999:

A submission requested that the pure active substance be reclassified from pharmacy-only to prescription medicine. It comprised evidence of abuse of the active substance provided by the Police, Customs and Mental Health Section of the Ministry of Health. Police and Customs had been seizing large quantities of dextromethorphan, particularly in the South Island. The recommendations were that DXM should be classified as a:

- General Sale medicine when in liquid form containing 0.25% or less and when in solid dose form containing 15 milligrams or less per dose form
- Pharmacy-Only medicine when in liquid form containing more than 0.25% and not more than 0.3% and when in solid dose form containing more than 15 milligrams and not more than 30 milligrams per dose form
- Prescription medicine except when fulfilling the above criteria for sale as general sale or pharmacy-only medicines.

### 27<sup>th</sup> meeting 23 May 2002

A recommendation by the Drugs and Poisons Scheduling Committee (NDPSC) in Australia, to change the pharmacy-only entry to DXM in packs containing 600 mg or less of dextromethorphan

- in divided preparations containing 30 mg or less of dextromethorphan per dosage unit, with a recommended dose not exceeding 30 mg of dextromethorphan; or

- in undivided preparations containing 0.3 per cent or less of dextromethorphan, with a recommended dose not exceeding 30 mg of dextromethorphan

was rejected on the grounds that there was no evidence of abuse of general sale products in New Zealand.

#### 29<sup>th</sup> meeting 22 May 2003

The NDPSC opted not to adopt the MCC recommendation on dextromethorphan and to review the classification in two years' time: No products available in Australia at general sale and a maximum pack size limit of 600 milligrams for all OTC products. New Zealand classification to remain unchanged.

#### 30<sup>th</sup> meeting 26 November 2003

Recommendation: over-the counter packs of dextromethorphan should be limited to packs containing 600 milligrams or less and with recommended daily doses of not more than 120 milligrams.

The above recommendation was supported by a letter from Pfizer requesting reclassification from prescription medicine to pharmacy-only medicine for sustained release liquid preparations containing 0.6% or less with a recommended dose not exceeding 60 milligrams.

The Committee agreed that the imposition of upper dose limits and limits on pack size provided a safer option than the current scheduling and that the proposed word change should be incorporated into the pharmacy-only entry in the schedule. Members agreed that the pack size limits and dose limits should also be applied to the general sale entries. This could be done immediately if the change would not affect any products already on the market but would require consultation if it would result in a change of classification for any currently marketed product.

#### 37<sup>th</sup> meeting 17 May 2007

In May 2002 the Committee had declined a recommendation from the NDPSC to harmonise with the Australian scheduling. There was no provision for unscheduled dextromethorphan products in Australia. However, the MCC could see no safety grounds at the time to justify reclassifying those dextromethorphan products in New Zealand which were general sale medicines. Although the MCC declined to harmonise, there was no recommendation made at the time for the NDPSC to harmonise on the less restrictive classification.

It was noted that there were approximately 20 general sale current products registered on the New Zealand database which contained dextromethorphan.

No further information had come to hand to cause the Committee to revise its earlier recommendation for lower-dose dextromethorphan products to remain general sale medicines. Members agreed that a formal recommendation should be made to the NDPSC to harmonise on the less restrictive New Zealand classification on the grounds of harmonisation at the less restrictive level.

### 43<sup>rd</sup> meeting 13 April 2010

As part of the briefing provided to the Minister of Health, to allow him to make a decision about the recommendations of the Committee, Medsafe suggested alternate advice with respect to several of the recommendations about the appropriate classification of cough and cold medicines.

Medsafe did not agree that there was sufficient evidence of harm or abuse to warrant consideration of the reclassification of dextromethorphan, for the treatment of the symptoms of cough and cold in adults and children over 12 years of age, at the next meeting. While dextromethorphan is a weak opioid that can be subject to abuse, there is limited evidence that dextromethorphan abuse in New Zealand is a significant problem (Medsafe is only aware of two reports of abuse in recent years). Medsafe therefore recommended that the Minister of Health reject this recommendation. Medsafe proposes to monitor dextromethorphan and revisit the issue if the number of reports of abuse increases significantly.

### 44<sup>th</sup> meeting 2 November 2010

While the discussion at this meeting regarded ipecacuanha, dextromethorphan was referred to:

At its 59<sup>th</sup> meeting in June 2010, the Australian National Drugs and Poisons Schedule Committee agreed, amongst others, that the use of certain substances (including dextromethorphan, ipecacuanha and phenylephrine) in preparations for treating cough and cold be rescheduled to prescription medicine for use in children less than two years of age, restricted medicine for use in children aged from two to six years of age and pharmacy-only medicine for use in children and adults above six years of age.

## Current Classification

### Dextromethorphan

Medicines including DXM are either classified as Pharmacy-Only medicines or for General Sale. There are also products classified as restricted, but none of these are available. Capsules, lozenges as well as oral solutions are possible to buy in supermarkets.

The conditions as stated in the Schedule 1 of the Medicines Regulations 1984 for Pharmacy-Only are:

“In liquid form containing more than 0.25% or in solid dose form containing more than 15 milligrams per dose 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 the symptoms of cough and cold in children aged 6-12 years”

The conditions as Stated in the Classification database for Pharmacy-Only are:

“In liquid form containing 0.25% or less or in solid dose form containing 15 milligrams or less per dose form when in packs containing not more than 600 milligrams and with a recommended daily dose of not more than 120 milligrams;  
**except** in medicines for the treatment of the symptoms of cough and cold in children aged 6-12 years”

Of the DXM products classified as General Sale, one Dimetapp capsule contains dextromethorphan hydrobromide monohydrate 10 mg, paracetamol 300 mg and phenylephrine hydrochloride 5 mg.

The other products available for General Sale only contains dextromethorphan in the form of hydrobromide monohydrate 5-15 mg in lozenges/capsules and 1-1.333 mg/ml in syrup. Note that 10 mg dextromethorphan hydrobromide monohydrate = 7.3 mg dextromethorphan.

Of the DXM products classified as Pharmacy-Only, the content of dextromethorphan hydrobromide monohydrate in capsules, tablets and lozenges varies between 10 and 15 mg, and in oral solution it varies between 2 and 3 mg/ml. Some tablets also contain 500 mg paracetamol.

In the UK, dextromethorphan cough medicines can be bought from pharmacies. Dextromethorphan cough medicines can be bought in the pharmacy or in the supermarket in the US. In some states, DXM is prohibited for sale to minors. Dextromethorphan is available without prescription in Canada. In Australia the classification is Schedule 2 (Pharmacy only) when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan, and otherwise it is a prescription only medicine.

### Gees linctus

All Gees linctus products are classified as Pharmacy-Only medicines. The conditions for Opium in the Schedule 1 of the Medicines Regulations 1984 are:

“In medicines for oral use containing not more than 0.2% of morphine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means, or in a yield that would constitute a risk to health, when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine”

The condition for Squill is:

“In medicines containing more than 1%”

A similar product is available in pharmacies in the UK. Gees linctus is not available in The US, Canada or Australia.

### Pholcodine

Products containing pholcodine are classified as Pharmacy-Only with the following condition:

“In medicines for oral use containing not more than 15 milligrams of pholcodine per solid dosage unit or per dose of liquid with a maximum daily dose not exceeding 100 milligrams of pholcodine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means, or in a yield that would constitute a risk to health, when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine”

The Expert Committee on Drugs liable to produce Addiction of the World Health Organization have classified  $\beta$ -4-morpholinylethylmorphine in group II of the 1931 Convention. This treaty established two groups of drugs. Group I was subject to stricter regulations than Group II. Pholcodine is a class B substance in the UK but can be purchased in UK pharmacies. It is not approved in Canada. In the United States, pholcodine is not prescribed as it is classified as a Schedule I drug, the most highly controlled drug category, which includes the likes of heroin, LSD and ecstasy.

## Relevant products

The table below shows dextromethorphan hydrobromide monohydrate containing medicines currently available in New Zealand:

Product name	Active ingredients	Sponsor	Approval date
Benadryl Dry Forte oral solution	Dextromethorphan	Johnson & Johnson NZ Ltd	14 March 2002
Benadryl PE Dry Cough & Nasal Congestion syrup	Dextromethorphan, Phenylephrine	Johnson & Johnson NZ Ltd	16 Dec 2009
Codral All-In-One Cough, Cold & Flu Day & Night capsule	Dextromethorphan; Paracetamol Phenylephrine; Chlorphenamine	Johnson & Johnson NZ Ltd	22 May 2014
Codral Cold & Flu + Cough Day & Night capsule	Dextromethorphan; Paracetamol Phenylephrine; Chlorphenamine	Johnson & Johnson NZ Ltd	8 Jan 2009
Coldrex PE Phenylephrine Cold & Flu Night & Day tablet	Chlorphenamine; Paracetamol Dextromethorphan; Phenylephrine	GlaxoSmithKline CH NZ Ltd	8 Jan 2009
Congested Cold & Cough oral solution	Brompheniramine Dextromethorphan; Phenylephrine	API Consumer Brands	2 July 2015
Dimetapp Cough & Cold elixir, Colour free elixir	Brompheniramine Dextromethorphan; Phenylephrine	Pfizer NZ Ltd	15 Aug 1996, 18 July 2002
Dimetapp Cough Cold & Flu Daytime/Nighttime capsule	Dextromethorphan; Paracetamol Doxylamine	Pfizer NZ Ltd	23 July 2009
Dimetapp Cough Cold & Flu Decongestant Day & Night capsule	Dextromethorphan; Paracetamol Phenylephrine; Chlorphenamine	Pfizer NZ Ltd	24 May 2012
Dimetapp Cough Cold & Flu Night Relief capsule	Chlorphenamine; Paracetamol Dextromethorphan; Phenylephrine	Pfizer NZ Ltd	24 May 2012
Dimetapp Multi Symptom Cough Cold & Flu capsule	Dextromethorphan; Paracetamol Phenylephrine	Pfizer NZ Ltd	19 July 2012
Dimetapp Multi Symptom Cough Cold & Flu capsule*	Dextromethorphan; Paracetamol Phenylephrine	Pfizer NZ Ltd	19 July 2012
Panadol Cold & Flu Relief + Cough tablet	Dextromethorphan; Paracetamol Phenylephrine	GlaxoSmithKline CH NZ Ltd	10 April 2008
Panadol Flu Strength Day & Night tablet	Chlorphenamine; Paracetamol Dextromethorphan; Phenylephrine	GlaxoSmithKline CH NZ Ltd	10 April 2008
Robitussin Cough & Chest Congestion oral solution	Dextromethorphan; Guaifenesin	Pfizer NZ Ltd	9 April 1998
Robitussin Dry Cough Forte syrup	Dextromethorphan	Pfizer NZ Ltd	14 Oct 1999
Robitussin Dry Cough Liquid Capsules*	Dextromethorphan	Pfizer NZ Ltd	1 Dec 2016
Strepsils Dry Cough Lozenge*	Dextromethorphan	Reckitt Benckiser NZ Ltd	31 Dec 1969
Strepsils Dry Cough Syrup*	Dextromethorphan	API Consumer Brands	24 Dec 2002
Vicks Cough Lozenges Honey Flavour for Dry Cough lozenges*	Dextromethorphan	Procter & Gamble Distr NZ Ltd	4 Oct 2007
Vicks Cough Syrup Honey Flavour for Dry Cough Syrup*	Dextromethorphan	Procter & Gamble Distr NZ Ltd	19 July 2007
Vicks Formula 44 for Dry Coughs Syrup*	Dextromethorphan	Procter & Gamble Distr NZ Ltd	10 Aug 2000
Your Pharmacy Congested Cold & Cough Medicine oral solution	Brompheniramine; Dextromethorphan; Phenylephrine	Orion Laboratories (NZ) Ltd	21 July 2011
Your Pharmacy Dry Cough Syrup*	Dextromethorphan	Orion Laboratories (NZ) Ltd	17 Feb 2011

\*General Sale

The table below shows Gees linctus products currently available in New Zealand:

Product name	Active ingredients	Sponsor	Approval date
Gees Linctus** 200 ml	Opium, squill	API Consumer Brands	14 June 2001
Gees Linctus 200** ml	Opium, squill	API Consumer Brands	12 Feb 2015
Opiate Squill Linctus** 100 ml, 2 L, 2.5 L	Opium, squill	API Consumer Brands	29 May 1980

\*\* contains ethanol

The table below shows pholcodine containing products currently available in New Zealand:

Product name	Active ingredients	Sponsor	Approval date
Pholcodine Linctus BP 1 mg/ml 100 ml, 125 ml, 200 ml, 1 L, 2 L	Pholcodine	AFT Pharmaceuticals Ltd	16 Oct 2003
Pholcodine Linctus BP** 1 mg/ml 100 ml, 2 L, 2.5 L	Pholcodine	API Consumer Brands	29 May 1980
Pholcodine Strong BP** 2 mg/ml 2 L, 2.5 L	Pholcodine	API Consumer Brands	29 May 1980

\*\* contains ethanol

## Sales

As these medicines are sold in pharmacies or by general sale, there is no easy way of following sales over a period. In addition they are sold over the internet. Therefore no statistics of sales or trends in sales in New Zealand is available for this report.

## Labelling

The Label Statements Database (edition 1.21) has the following requirements for dextromethorphan and pholcodine:

Medicine/Group/ Class	Conditions	Statements or requirements
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

These would not change in the event of a reclassification.

There are no label requirements for Gees Linctus in the Label Statements Database.



## Recent international regulatory actions

### Dextromethorphan

#### **EMA**

In 2016, taking into account a Pharmacovigilance Risk Assessment Committee (PRAC) Assessment report on a Periodic Safety Update Report (PSUR) for dextromethorphan, the EMA noted that cases of drug abuse have been reported in adolescents and young adults, as well as in patients with a history of drug abuse. It was therefore considered that a warning should be introduced in the product information (PI) to recommend caution in this patient population. In addition, more information was to be provided about the effect and toxicity of dextromethorphan being dependent of the metabolism of the medicine which is genetically determined.

Regarding abuse, the product information was updated with the following warning: Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances. The EMA considered that the benefit-risk balance of the medicinal products containing dextromethorphan is unchanged subject to the proposed changes to the product information (8).

#### **Sweden**

Dextromethorphan was previously included in cough medicines in Sweden, but these were withdrawn from the market in year 2000. The reason was misuse, especially by young people. However, it was still possible to legally buy dextromethorphan-containing products from the Internet. Over the next years there was a high increase of these products being purchased over the internet and some cases of death of young people associated with consumption of dextromethorphan occurred. In 2008, dextromethorphan was classified as a narcotic (9).

#### **FDA**

In January 2018, FDA issued a safety communication requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. These products will no longer be indicated for use in children, and their use in this age group is not recommended. The message was that a 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 products such as dextromethorphan, as well as prescription benzonatate products (10).

In 2010 an FDA Drug Safety and Risk Management Advisory Committee 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 (11).

### Pholcodine

#### **EMA**

On 28 January 2011, France triggered a referral under Article 31 of Directive 2001/83/EC (5). The Committee for Medicinal Products for Human Use, (CHMP) was requested to give its opinion on whether the marketing authorisations for medicinal products containing pholcodine-containing medicinal products should be maintained, varied, suspended or withdrawn.

The French Agency for the Safety of Health Products (AFSSAPS) concern arose from the potential risk that pholcodine may lead to IgE-sensitisation to neuromuscular blocking agents (NMBAs). Literature has been published suggesting a link between pholcodine consumption and cross sensitisation to NMBAs, resulting in anaphylactic reactions during surgery. The published data refers mainly to Norway and Sweden, where pholcodine is no longer marketed. In France, data from spontaneous reporting suggests a 25% increase in the number of anaphylactic shocks to NMBAs in the period 2008/2009 when compared to the 2003/2004 period. This coincides with a 9% increase in the consumption of pholcodine-containing products in France between the two periods. As a consequence, the French Medicines Agency changed the prescription status of pholcodine-containing medicines to prescription only and triggered this referral.

The Committee considered that evidence of an association between pholcodine use and development of NMBA-related anaphylaxis is circumstantial, not entirely consistent and therefore does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis is needed, and to that end the sponsors shall conduct a case-control study. One member had a divergent position.

This issue was also discussed in Australia where anesthetists argued there is a link between severe allergic reactions to some anesthetics and pholcodine. They wanted the drug to be restricted (either removed from the market or reclassified as prescription only), but TGA shared EMAs opinion described above (12).

## Scientific information

### Abuse and misuse

#### **A cross-sectional examination of medicinal substance abuse and use of nonmedicinal substances among Canadian youth: findings from the 2012-2013 Youth Smoking Survey (13).**

The purpose of this study was to characterize the abuse of medicinal substances, such as prescription medications and selected OTC substances, as well as that of licit and illicit nonmedicinal substances, using a nationally representative sample of young people, age 12-17. Data was obtained using a previous study (Health Canada's 2012-2013 Youth Smoking Survey ( $n = 38\ 667$ )).

In this study, one question was formulated: "If you have ever used or tried any of the following drugs, mark the age at which you first used or tried. Then mark if you have used or tried the drug in the last 12 months," and a subsequent probe that asked participants if they had used the listed substances "to get high and not for medical purposes."

The results showed that almost one-quarter of Canadian youth from grades 7 to 12 reported abusing medicinal or nonmedicinal substances and about 5% reported abusing medicinal substances in the previous year. Dextromethorphan was the most widely abused medical substance (2.9%).

The authors refer to recent estimates in Ontario suggesting an increase in recreational use of dextromethorphan, from 7% to 10% among students in grades 7 through 12 from 2011 to 2013.<sup>21</sup> The question asked in this survey was slightly different: children were asked whether they have used particular substances without a prescription or without a doctor telling them to take it.

### Changes in OTC drug misuse over 20 years: perceptions from Scottish pharmacists (3).

In this study a questionnaire, based on one used previously (1995, 2000 and 2006), was posted to all community pharmacists in Scotland (n=1246) in 2014. The questions related to suspected OTC misuse in their area, products involved and resultant changes in policy. Responses were compared across the four cohorts. OTC in the UK include general sales medicines and pharmacy-only medicines (sold only from a pharmacy, under the supervision of a pharmacist).

The 2014 response rate was 57%. The proportion of pharmacists reporting suspected OTC misuse increased to 80.8% from 70.8% in 2006. Codeine-containing products were most frequently perceived to be misused. Of pharmacists reporting suspected misuse, 91.3% had altered policies, including refusing sales and referring patients elsewhere.

The authors note that other studies on OTC misuse, particularly from the USA, have found dextromethorphan to be a commonly misused substance. This was not particularly reflected in the results of this survey. There may be a cultural difference in Scotland compared with that in USA. However, it is notable that both of these products were more commonly reported in the 2000 survey (71 and 44 responses, respectively), perhaps reflecting a time trend rather than a cultural difference.

#### Dextromethorphan

### Trends in dextromethorphan cough and cold products: 2000–2015 National Poison Data System intentional abuse exposure calls (14).

In this publication recent trends and patterns of calls to poison control centers in the US involving DXM abuse were described by demographics, geography, common brands, and medical outcomes. Data was obtained from the National Poison Data System (NPDS).

From 2000 to 2015, 72,260 DXM cough and cold product intentional abuse calls met inclusion criteria; 55,559 (76.9%) of these were single-substance exposures. The annual rate of single-substance DXM intentional abuse calls tripled from 2000 to 2006 and subsequently plateaued from 2006 to 2015, see figure 1 below:

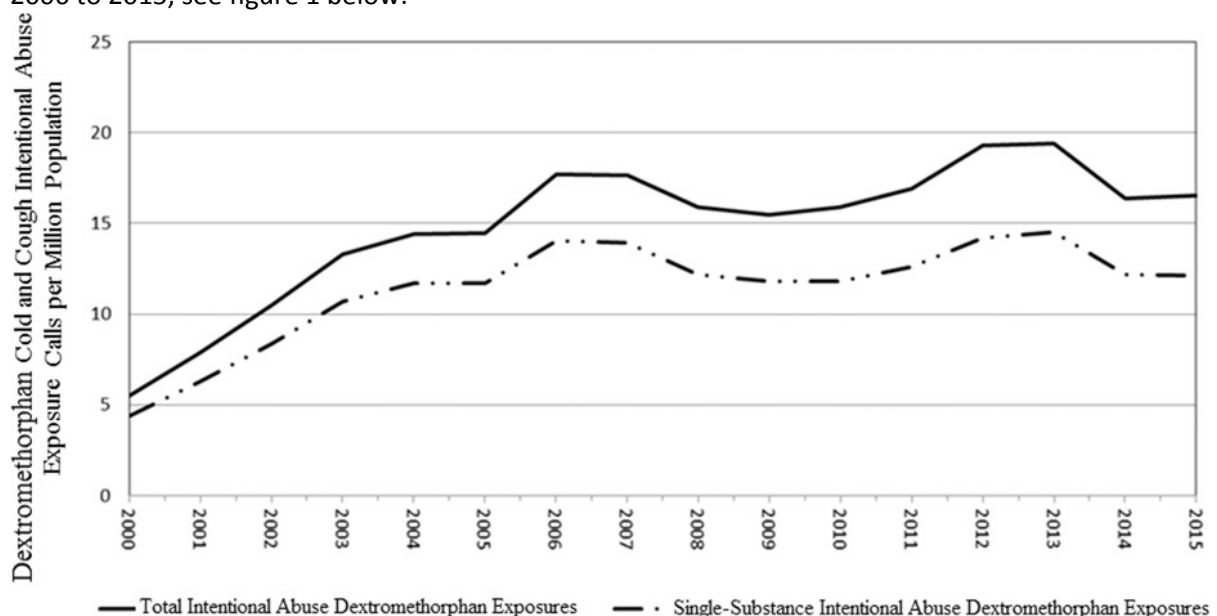


Figure 1. Annual Rate of Dextromethorphan Cough and Cold Intentional Abuse Exposure Calls, AAPCC 2000–2015.

The highest abuse call rate was observed among adolescents 14–17 years old, where the mean annual number of calls was 1761 per year, corresponding to an annual rate of 103.6 calls per million population. From 2006 to 2015, the rate for single-substance DXM abuse calls among adolescents 14–17 years decreased by 56.3%, from 143.8 to 80.9 calls per million population. For 18–21 year olds there was no change in DXM abuse call rates and the rates almost doubled for 22–29 year-olds, see figure 2 below:

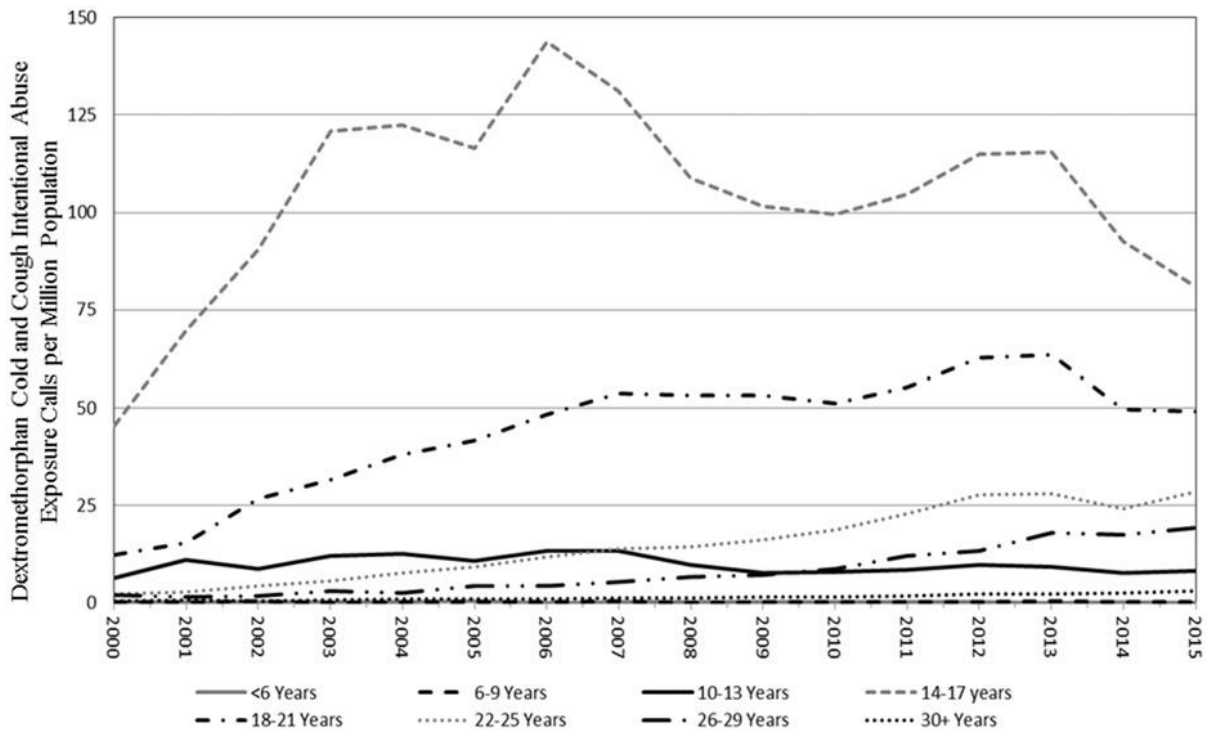


Figure 2. Age-Specific Annual Rate of Single-Substance Dextromethorphan Cough and Cold Intentional Abuse Exposure Calls, AAPCC 2000–2015.

The most common medical outcome associated with DXM abuse was moderate effects (36.6%), followed by minor (30.6%) and no (8.9%) effects. One-quarter of single-substance DXM abuse calls resulted in a hospitalization. A small proportion of DXM abuse calls resulted in major effects (1.3%) or death (0.02%). Of the eight deaths observed, seven were among males and one among a female. Only one fatality, in 2007, occurred among an adolescent, 17 years old.

The authors concluded that although a causal relationship cannot be confirmed, the observed decline in DXM abuse call rates corresponds to a period of growing public health efforts, with some focusing specifically on adolescents, to restrict access to and availability of DXM, including prevention of OTC sales of DXM to individuals under 18 years in 12 states. However, the call data indicates that DXM abuse remains fairly common, and that these exposures are associated with substantial burden to the healthcare system.

### **Dextromethorphan: a case study on addressing abuse of a safe and effective drug (15).**

In 2006, the National Institute of Drug Abuse (NIDA) funded Monitoring the Future survey showed that abuse of DXM-containing OTC cough medicine was concentrated among teens and, to a lesser degree, young adults: 5.4 % of 8th, 10th, and 12th grade students reported non-medical use of OTC cough medicine in the past year.

To address this, an abuse mitigation campaign was introduced in 2010 by Consumer Healthcare Products Association (CHPA, representing manufacturers of OTC medicines and dietary supplements), with specific goals related to awareness of the behavior, perception of risk, social disapproval, and access to the products. The campaign mainly used social media channels and focused on addressing the levers that influence a teen's decision, including changing teen perceptions and attitudes toward abuse behavior; raising awareness among parents, caregivers, and influencers; and limiting teen access to these medicines.

At the same time some states started to apply age-restriction laws that prevented consumers under the age of 18 from purchasing products containing DXM. In March 2016 there were 10 states where this regulation was in use.

Results showed that during the period of 2010–2015, reported abuse of dextromethorphan by 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders (12-17 years of age) decreased 35 %. A true cause-and-effect relationship could not be assured but the authors concluded that the increased awareness of the issue and the subsequent implementation of the campaign contributed to the observed reduction in abuse. It was also concluded that there are more targeted, more effective, and less disruptive interventions to address dextromethorphan abuse than controlled substance scheduling or prescription requirements.

Note that this publication was written by employees of the CHPA and the funding was provided by CHPA member companies.

### **Dextromethorphan in cough syrup: the poor man's psychosis (16)**

This is a case report of a dextromethorphan-induced psychotic disorder in a 40-year-old Caucasian female, whose symptoms remitted only following treatment with a combination of an antipsychotic and mood stabilizer.

The patient had an extensive history of substance abuse. Her typical daily dose for years was 12 tablets of a tablet available in the US containing 30 mg DXM TID (providing 1080 mg/day of DXM total) or 9 tablets another product containing 60 mg DXM TID (providing 1620 mg/day of DXM total). Sometimes she took more.

The authors of this publication note that dextromethorphan has overtaken codeine as the most widely used cough suppressant due to its availability, efficacy and safety profile when taken at directed doses. They conclude that abuse of DXM, a readily available and typically inexpensive agent that is not detected on a standard urine drug screen, may be an under-recognized cause of substance-induced psychosis. It is imperative that clinicians are aware of the potential psychiatric sequelae of recreational DXM use.

## **New Zealand specific information**

### **CARM**

A search of the CARM database revealed 3 case reports involving the cough medicines of interest in this paper in association with drug abuse, drug dependence or substance dependence. In all three reports the cough medicine was Robitussin. Two of the reports are from 2009 and one is from 2011. All three patients were male and they were 22, 31 and 34 years old. Many factors are unknown such

as the doses taken of the cough medicines. The relationship between the cough medicines and the reactions are considered probable or possible.

The Centre for Adverse Reactions Monitoring CARM, however, has indicated 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. Three reports to CARM can in no way reflect that this is the true extent in reality.

### National Poisons Centre data

The National Poison Centre has little information regarding misuse of the three cough medicines. Incoming calls reporting substance exposures are coded based on what callers report and also (if possible) a reason for the exposure – was it after intentional use, unintentional use or abuse. However, the abuse classification is very rarely used. Someone who has abused a substance is not likely to supply that information and therefore it is usually only reported if healthcare professionals make the call.

The National Poisons Centre will not have complete information for every call in regards to the amount of substance taken or which brand or administration form was involved (e.g a caller reporting exposure to “Robitussin” rather than Robitussin Cough & Chest Congestion which contains 30 mg dextromethorphan vs Robitussin Cold & Chesty Cough which does not contain dextromethorphan). During the year 2016 they had 25 calls on dextromethorphan, but as outlined above, it is not possible to know for each case if they relate to misuse.

From 1 August 2011 to 5 June 2018 there were 18 calls to the National Poisons Centre that were classified as “abuse” or “intentional”. Of the calls, 4 involved capsules or tablets and 14 regarded liquids.

The products were:

<b>Product</b>	<b>Amount of calls</b>
Gees linctus oral solution	1
Robitussin cough & chest congestion oral solution	4
Robitussin dry cough forte syrup	6
Robitussin dry cough liquid capsules	4
Vicks formula 44 dry cough syrup	1
Pholcodine	2

The age ranges were:

<b>Age (years)</b>	25	24	17	16	14	Unknown
<b>Amount of calls</b>	1	1	2	2	2	10

All cases resulted in medical referral.

## Benefits and risks

The expected benefits of this proposal are to reduce the risk of intentional misuse of these medicines and improve the information available to consumers about the correct use of the

medicines. In addition pharmacists will have a better opportunity to identify patients who should be referred to a doctor because of additional underlying health problems or severity of their illness.

The risks from this change are that it may become slightly more difficult for legitimate users to access the medicine, other medicines may be misused instead or purchase redirected to internet outlets.

## Discussion

Cough medicine containing dextromethorphan, anhydrous morphine or pholcodine are all readily available in New Zealand and could all potentially be misused. Dextromethorphan most likely possesses the highest risk. A high dose of DXM can cause euphoric, stimulant, and dissociative effects and even be fatal. The effect is highly dependent of the capability of the individual to metabolise the medicine.

DXM has a long history of abuse, especially among teenagers and young people and apart from the toxic effects, DXM abuse may be the first step to abuse of stronger substances.

This medicine has been a problem in many countries. In the US it has been a popular substance for abuse. Worth noting is that many of the available tablets in the US contains 35 mg DXM and therefore are stronger than the New Zealand tablets/capsules. In Sweden DXM was banned and withdrawn from the market in the beginning of this century because of misuse by young people.

New Zealand sales data is not readily available. However, Medsafe has been contacted and provided with details of misuse of dextromethorphan. DXM is easily obtained in New Zealand especially as some products can be bought in the supermarket. Reduction in misuse has been shown internationally to occur with education of healthcare professionals and restrictions on availability.

Medsafe notes that previous research outlined above shows that a fatal outcome can result from misuse of DXM.

Some tablets contain DXM in combination with for example paracetamol which increases the risk of a serious outcome if the product is misused.

Gees linctus, which contains anhydrous morphine, is not available in as many countries and therefore there is little data on misuse. However, the product has a history of misuse in New Zealand and, in addition to anhydrous morphine, also contains a significant amount of alcohol.

The effects of pholcodine are uncertain, but the addictive potential is considered to be low.

## Conclusion

Medsafe has been alerted to concerns within the community about the abuse of DXM containing cough medicines. Since there are other cough medicines containing related ingredients, Medsafe has also considered these in this paper. Medsafe recommends that the MCC considers whether the current classification of cough medicines containing dextromethorphan, opium tincture, squill oxymel and pholcodine is adequate to manage the risk of abuse and need for advice on management of cough.

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