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**Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspects**

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**ABSTRACT**

Dextromethorphan (DXM) is a safe and effective antitussive agent present in several over the counter cough and cold medications. At higher doses, it causes psychoactive effects, making it appealing for abuse. In this work, the pharmacokinetics and pharmacodynamics of DXM with clinical and forensic relevance were extensively reviewed. DXM and related known metabolizing enzymes and metabolites were searched in books and in PubMed (U.S. National Library of Medicine) without a limiting period. Major metabolic pathways include sequential O-demethylation and N-demethylation of DXM, yielding dextrorphan (DXO), the major active metabolite, and 3-hydroxymorphinan, the bi-demethylated product, respectively. The demethylation order described may reverse being the resultant mid product 3-methoxymorphinan. UDP-glucuronosyltranferase produces glucuronide conjugates. Genotypic variations in enzymes and interactions with other drugs can result in large inter-individual variability in the pharmacological and toxicological effects produced. Knowing the metabolism of DXM may help to better understand the inter-individual variability in the pharmacokinetics and pharmacodynamics and to avoid adverse effects.

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**Introduction**

Dextromethorphan (DXM; d-methorphan) is a non-narcotic synthetic analog of codeine (Aumatell and Wells 1993), widely used as an antitussive agent in over-the-counter (OTC) cough and cold medications (El-Naby and Kamel 2015) and is considered safe and effective when taken at therapeutic doses (Spangler et al. 2016). In 2015, in the USA, OTC medicines containing DXM comprised 85–90% of all medicines containing a cough suppressant that were sold, in a total of 235 million packages (Spangler et al. 2016). Codeine, levopropoxyphene, and noscapine are other opioids derivatives also used as antitussive agents (Dinis-Oliveira 2019). DXM may have several other medical uses, such as pain management, treatment of pseudobulbar affect, and psychological applications (El-Naby and Kamel 2015). It is purported to produce less constipation than codeine.

DXM has a wide range of pharmacodynamic effects as consequence of its activity on numerous channels and receptors. DXMs popular antitussive effects are believed to result from its sigma-1 receptors (σ1R) stimulation and N-methyl-d-aspartate (NMDA) antagonism (Brown et al. 2004). Moreover, especially in doses higher than 100–200 mg, DXM has the potential to produce clinical signs and symptoms similar to those of phencyclidine (PCP) and ketamine, such as euphoria and dissociative hallucinations, effects that are probably mediated by a rather nonselective action on serotonin reuptake inhibition and σ1 opioid, α3β4 nicotinic, and NMDA receptors (Logan 2009; Logan et al. 2009, 2012). Although structurally related to opioid agonists, DXM does not have relevant pharmacological activity at opioid receptors (Chen et al. 2005). DXM also is a serotonergic drug having a potential risk for serotonin syndrome (Chyka et al. 2007; Dilich and Girgis 2017), and enhances the analgesic action of morphine and presumably other μ-receptor agonists.

Regarding metabolism, DXM is primarily metabolized by cytochrome P450 (isoenzyme CYP2D6) producing its major active metabolite dextrophorphan (DXO). Nevertheless, DXM is also a pharmacological active compound (Pechnick and Poland 2004). The expression
of CYP2D6 is genetically controlled and this enzyme polymorphism contributes to a variability in drug response and toxicity (Meyer et al. 1990; Burton et al. 2006; Gaedigk 2013). This is even more relevant since DXM is widely consumed and usually ingested licitly when combined with other drugs, or illicitly as mixtures of uncertain composition (Chyka et al. 2007; Banken and Foster 2008; Brown et al. 2018).

Even though DXM has been used as a nonprescription drug since 1958, only recently it has been considered as a seriously emerging substance of abuse, with its recreational use becoming more frequent and widespread since the 1990s (Banken and Foster 2008; Spangler et al. 2016). The availability of DXM, either in OTC formulations or as illicitly manufactured powder or tablets containing DXM, alone or with other drugs, and the easy access through the internet may facilitate the abuse and fatalities (Brown et al. 2018). The reports of abuse involve most commonly teenagers, but also young adults (Spangler et al. 2016). Data from American Association of Poison Control Centers from 2000 to 2015 show a total number of 72,260 calls reporting intentional abuse of a DXM cough and cold product, with a peak in 2006 (Karami et al. 2018). Since antitussive OTC medications that contain DXM are safe and effective, and acute bothersome coughing can impair daily life, self-medication with these products, can contribute to make them about 85–90% of all medicines sold as cough suppressants and a total accounted of around 235 million of packages purchased in 2015 (Spangler et al. 2016).

Therefore, it is important to understand how DXM produces its pharmacological and toxicological effects. This review aims to gather as much information as possible available in the literature concerning its chemical structure, pharmacokinetics, pharmacodynamics, pharmacogenomics and abuse potential, as well as clinical effects, toxicological analysis and treatment of acute intoxications, with special focus on DXM metabolism and its implications in clinical and forensic interpretations.

**Methodology**

A narrative review was performed by searching articles in English, French, Spanish, and Portuguese in PubMed, Scopus, Web of Science, and PsycINFO concerning legal, laboratorial, clinical, ethical, forensic, and safety concerns related to DXM and its known metabolizing enzymes and metabolites, without a limiting period. Furthermore, electronic copies of the full papers were obtained from the retrieved journal articles and books related to this topic, which were further reviewed for possible additional publications related to pharmacokinetics and pharmacodynamics aspects of DXM. Besides these inclusion criteria, the World Health Organization (WHO) pre-review report on DXM was also reviewed to identify possible additional publications related to human and non-human *in vivo* and *in vitro* studies.

**Chemistry of dextromethorphan and analogs**

DXM (3-methoxy-N-methylmorphinan; Figure 1) is the dextrorotatory [d- or (–)] enantiomer of levomethorphan [l- or (+)], which is the methyl ether of DXO (3-hydroxy-N-methylmorphinan) and levorphanol, respectively (Sromek

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**Figure 1.** Chemical structure of dextromethorphan and analogs.
et al. 2014). Although former levorotatory compounds are both opioid analgesics, only levorphanol was clinically developed (Gudin et al. 2016; Le Rouzic et al. 2019). Moreover, levorphanol is the levorotatory isomer of racemic 3-hydroxy-N-methylmorphinan (Dromoran®) and named as Levo-Dromoran®. DXM is named according to IUPAC rules as (+)-3-methoxy-17-methyl-9α,13α,14α-morphinan. It is also the d-isomer of methorphan (racemic mixture), but unlike the l-isomer, it does not have opioid activity. Methorphan presents as two isomeric forms, each with differing pharmacology and effects with respect to its two enantiomers. The DXM is used as an antitussive drug in cough medicines (and in high doses, it is a dissociative hallucinogen), whereas the levorotatory enantiomer levomethorphan, a prodrug of levorphanol, is a strong opioid analgesic that is listed as a schedule II drug in the USA (Wong and Sunshine 1996; Bortolotti et al. 2013; Gudin et al. 2016). Levorphanol binding affinity for the mu (MOR; μ) opioid receptor, 0.42 nM, is greater than the affinity of morphine, 1.24 nM and also presents longer $t_{1/2}$ (Bortolotti et al. 2013). As DXM is approved for use in OTC drugs, accurate control of enantiomeric purity is essential to assure that commercial DXM preparations do not contain the l-enantiomer.

Therefore, DXM is chemically an opium alkaloid derivative but since it does not act pharmacologically at opioid receptors, it is not an opioid and does not have analgesic, euphoriant, and respiratory depression effects, such as codeine and morphine (Bem and Peck 1992; Jasinski 2000; Pechnick and Poland 2004). In other words, DXM and DXO, both dextrorotatory enantiomers, are non-opioid opium alkaloid derivatives. Racemethorphan is the racemic mixture composed by the two enantiomers DXM and levomethorphan (Wong and Sunshine 1996). Racemorphor or morphorphan refers to the racemic mixture of DXO and levorphanol, both with pharmacological and toxicological effects similar to their correspondent methyl ether derivatives (Aumatell and Wells 1993). This enantiomeric behavior is characteristic of other opioids. Indeed, dextrorotatory opioids have very different pharmacological profiles than their levorotatory isomers. Unlike the levorotatory opioids, dextrorotatory generally have little or no affinity to the mu (MOR; μ), delta (DOR; δ), or kappa (KOR; κ) opioid receptors, and thus do not carry the same abuse and addiction potential as their levorotatory enantiomers (Sromek et al. 2014). Dextrorotatory enantiomers typically act as weak to moderate noncompetitive NMDA receptor antagonists and have affinity to the $\sigma_1$ and $\alpha_2\beta_4$ nicotinic receptors (Glick et al. 2001). Both dextrorotatory and levorotatory opioids have antitussive properties.

DXM has been synthesized from a benzylisoquinoline by a process known as Grewe’s cyclization to give the corresponding morphinan with a three-dimensional structure. The isoquinoline is 1,2,3,4,5,6,7,8-octahydro-1-(4-methoxybenzyl) isoquinoline (there is just one residual double bond at the fusion position of the two rings of the isoquinoline) and it is converted into the N-formyl derivative, cyclized to the N-formyl normorphinan, and the formyl group reduced to an N-methyl group, to give 3-methoxy-17-methylmorphinan, or race-methorphan (WHO 2012).

**Licit and illicit formulations**

Accordingly to PubChem Database (CID = 5360696), in its pure form, DXM exists as an odorless, opalescent white powder, freely soluble in ethanol 96% and poorly water soluble. It is available most often as the monohydrated hydrobromide salt, making it water soluble (Loyd et al. 2014; Jayachandra et al. 2018). The monohydrated hydrobromide salt is water-soluble up to 1.5 g/100 mL at 25°C. Some formulations, as extended-release ones, can present DXM bound to an ion-exchange resin based on polystyrene sulfonic.

Licit DXM is typically available as an oral drug in liquid, tablet, lozenges, and capsule formulations of cough and cold (and other pathologies) OTC medicines. These products can contain DXM alone or in combination with guaifenesin, brompheniramine, pseudoepephrine, phenylephrine, promethazine, codeine, acetaminophen, and/or chlorpheniramine. Benylin® Delsym® Sucrets®, Bromfed-DM®, Robitussin®, Vicks Formula 44-D®, Coricidin®, Bisolussin®, TYLENOL-DM®, Tussilene®, Romilar®, Dr. Rentschler tuss hustenstiller retard kapseln®, Comtrex®, Sucrets DM®, Vicks Nyquil®, Medicin® are the most common trade names in different countries. OTC cough products containing DXM alone have been discontinued as a response to the perceived abuse risk.

Traditionally, DXM is abused in the form of the OTC liquid cough preparations. Nevertheless, nowadays, it can be seen in other presentation forms such as tablet and gel capsule preparations, illicitly manufactured DXM powder and tablets of DXM alone or in combination with other drugs for recreational purposes such as 3,4-methylenedioxymethamphetamine (MDMA; ecstasy), methamphetamine, and cocaine (Banken and Foster 2008; El-Naby and Kamel 2015; Brown et al. 2018), which composition and dose are uncertain. ‘CCC’, ‘triple C’, ‘rojos’, ‘red devils’, ‘skittles/skittling’, ‘dекс’, ‘robo-tripping’, ‘ro-bowing’, ‘robo-copping’, ‘robo’, ‘velvet’, ‘poor man’s PCP’ are common street
names that come from the most abused products Robitussin® and the red tablet formulation in Coricidin® cough & cold products (Banken and Foster 2008; Logan 2009; Logan et al. 2009, 2012; Ritter et al. 2019). Nevertheless, color pink due to dilution of other beverages, have also been described, making it difficult to ascertain what dose is being administered. Lean also known as purple drank and other street names (Agnich et al. 2013; Hart et al. 2014), is a recreational drug, created by combining prescription-grade cough sirup with a soft drink (e.g. Sprite, Mountain Dew, or grape-flavored Fanta) and hard candy. The term ‘lean’ refers to the posture that abusers assume when intoxicated, namely difficulty in standing up straight. The term ‘purple drank’ is a nod to its purple hue, as most cough sirups are purple in color, and drank is an informal term for a beverage, especially an intoxicating drink. Although, traditionally, the base for lean has been cough sirup, containing promethazine and codeine, DXM has also been used, as it can produce similar effects, is cheaper and eliminates the need for a doctor’s visit (Schwartz 2005). Nevertheless, hallucinogenic effects are more prevalent, rather than the sedative effects of the traditional form of purple drank containing codeine and promethazine.

Experienced DXM abusers extract the DXM from the sirup and offer it as a powder in capsules. Two extraction techniques are widely described in the internet aiming to purify the DXM and therefore to avoid co-ingestant toxicity (e.g. ethanol, guaifenesin, saccharin, propylene glycol, coloring agents, sweeteners) present in combination cold preparations (Hendrickson and Cloutier 2007): (i) a single-phase acid–base extraction with sodium hydroxide that yields a freebase crystalline powder (i.e. ‘crystal dex’) and (ii) a two-phase acid–base extraction with ammonia resulting in a liquid (i.e. ‘DXemon juice’ or ‘agent lemon’). This last technique has become more popular because it yields a more palatable liquid product, it avoids the use of lye, and it eliminates the hazards of heating flammable solvents in enclosed spaces.

Absorption

DXM is usually administered per os, the typical dose as antitussive being in patients over 12-years-old, 10–30 mg taken three to six times per day or extended release formulations 60 mg twice per day, in a maximum of 120 mg per day, without concern with meals (Collins 2018). On the other hand, a single dose for recreational users can range from 240 to 1500 mg (Banken and Foster 2008). Heavier users have been known to ingest up to three or four bottles per day (Wolfe and Caravati 1995). Alternatively, powders and tablets have been used since they produce an effect similar to sirups without the need to consume large quantities of the substance in a short time period (Banerji and Anderson 2001; Chyka et al. 2007; Romanelli and Smith 2009). Besides ingestion, DXM snorting has also been reported among abusers (Banken and Foster 2008). In a retrospective review of 47 patients admitted in an adolescent inpatient psychiatric unit for depression and/or psychosis related to Coricidin HBP® abuse, the number of tablets used per episode ranged from 2 to 42 with 14% of the patients abusing this product daily (Dickerson et al. 2008).

DXO is almost completely absorbed by the gastrointestinal tract and its brain-to plasma ratio ranges from 25 to 500 (Desmeules et al. 1999). Kanaan et al. (2008) demonstrated in vitro Caco-2 cell monolayer model that neither DXM and DXO are P-glycoprotein (P-gp) substrates, but pH-mediated efflux mechanisms, probably Na+/H+ exchangers, may be involved in limiting DXM gastrointestinal absorption and DXO transmembrane passage when a pH gradient is present. Another study showed an enhanced cerebral uptake of DXM in rats by concomitant administration of the P-gp inhibitor verapamil but no effect on its systemic biodisposition (Uhr et al. 2004; Marier et al. 2005). As suggested by Kanaan et al. (2008), DXM might possibly interact with transporters other than P-gp, possibly present at the blood–brain barrier but not at the intestinal barrier. But several contradictory results exist, since grapefruit juice (i.e. an CYP3A4 and efflux transporters inhibitor in the small intestine) can in some concentrations decrease DXM bioavailability by delaying the gastric emptying (Strauch et al. 2009). Therefore, it is obvious that further studies are needed to explore the role of these efflux transporters in the transepithelial transport of DXM and its active metabolite DXO.

The first pass effects in the gastrointestinal tract and in the liver limit oral bioavailability (Wu et al. 1995). Most published results regarding the bioavailability and disposition of DXM are based on analysis of DXO, in plasma and urine. In humans, it has been suggested to be in the order of 1–2% in extensive metabolizer (EM) subjects and would arise to 80% in poor metabolizer (PM) subjects, expressing a large variation in the intrinsic clearance of DXM (Capon et al. 1996). Moreover, the plasma concentrations of DXM were reported to be greater for the slow metabolizers when compared to the immediate metabolizers, due to the greater metabolic capability of the intermediate metabolizers (IMs) (Woodworth et al. 1987). Furthermore, since DXM is
usually administered in combination with other substances, its bioavailability may depend on the drug formulation. Indeed, DXM bioavailability can increase approximately 20-fold when administered with quinidine, a potent inhibitor of hepatic CYP2D6 (Chez et al. 2018; Fralick et al. 2019). Other authors also demonstrated that the coadministration of DXM with a low dose of quinidine inhibits DXM metabolism, yielding greater bioavailability (Taylor et al. 2016). Pathological conditions can also influence bioavailability (Gao et al. 2015). Indeed, besides genetic factors, drug oxidation may depend on liver function, and particularly cirrhosis is associated with approximately a 50% decrease in hepatic cytochrome P450 (Howden et al. 1989). Larrey et al. (1989) have demonstrated that DXM oxidation capacity is impaired in patients with chronic liver disease. Moreover, in inflammation and infection, CYP enzyme activities are also downregulated. The comparison between human immunodeficiency virus (HIV)-infected patients and healthy people evidenced that overall CYP3A activity was approximately 50% lower in HIV-infected patients than in healthy volunteers. The CYP2D6 activity was highly variable, but on average was not different between groups (Jetter et al. 2010). In another study, aimed to quantify the inhibition of CYP3A, CYP2D6, and P-gp in HIV-infected patients receiving an antiretroviral therapy containing ritonavir boosted lopinavir, it was demonstrated that in CYP2D6 EM, the AUC plasma ratio DXM/DXO increased to 2.92-fold (Wyen et al. 2008). Nevertheless, in other study, it was claimed that the effect of low-dose ritonavir on CYP2D6 will not require standard dose reductions for CYP2D6 substrates (Aarnoutse et al. 2005).

**Distribution**

DXM has a higher liposolubility (Log P: 4.11 ± 0.4) than DXO (Log P: 3.46 ± 0.3) and a blood/plasma ratio of 1.5, resulting in a volume of distribution of 5–6 L/kg (Roos et al. 1991; Wu et al. 1995). Its plasma protein binding is approximately 60–70% (Taylor et al. 2016) and following oral administration DXM achieves peak serum concentration in 2–3 hours, whereas peak serum concentrations of DXO occur within approximately 1.5–3 hours, independently if it is a liquid, tablet, or an extended-release formulation (Barnhart and Massad 1979; Chyka et al. 2007). Steinberg et al. (1993) showed a good intestinal absorption and brain accumulation of DXM in a clinical trial involving neurosurgical patients receiving high oral doses of DXM. DXM brain levels were more than 13-fold higher than those of DXO and DXO brain-to-plasma ratio was fivefold lower than that of DXO, suggesting a poor brain bioavailability of DXO. In comparison to DXM, the lower liposolubility of DXO may contribute to a lower cerebral bioavailability and anti-NMDA neuromodulatory effect. Even though DXM probably crosses the placental barrier due to its low molecular weight, it has no teratogenic effect.

**Metabolism**

The metabolic pathways of DXM are shown in Figure 2. DXM is primarily rapid and extensively O-demethylated by CYP2D6 to DXO, its major active metabolite (Nagai et al. 1996; Zhou and Meibohm 2013). Nevertheless, the therapeutic activity is believed to be caused by both DXM and DXO (Braga et al. 1994). Indeed, in vitro studies showed that DXM was a more potent NMDA antagonist than DXO (Szekely et al. 1991; Dematteis et al. 1998; Nicholson et al. 1999). Additionally, experimental and clinical evidence suggests that the antinociceptive, neuromodulatory and neuroprotective in vivo effects of DXM result mainly from a central action of unchanged DXM rather than from its more active metabolite DXO (Steinberg et al. 1993; Desmeules et al. 1999). This metabolic reaction can also be, at lower extent, catalyzed by CYP2C9 and CYP3A4/5 (Takashima et al. 2005). CYP3A4, CYP3A5 are the major enzymes (with certain contribution from CYP2D6) implicated in the N-demethylation of DXM to 3-methoxymorphinan and DXO to 3-hydroxymorphinan (Jacqz-Aigrain et al. 1993; Yu and Haining 2001; Takashima et al. 2005). 3-Methoxymorphinan undergoes further O-demethylation mediated by CYP2D6 to 3-hydroxymorphinan (Strauch et al. 2009). Subsequently, DXO and 3-hydroxymorphinan are subjected to glucuronide and sulfate conjugation and then excreted (Nagai et al. 1996). In fact, the major urinary excretion products are the glucuronide conjugates of DXO and 3-hydroxymorphinan, dextrophan-O-glucuronide and 3-hydroxymorphinan-O-glucuronide (Strauch et al. 2009).

Using human liver microsomes, differences between PM and EM subjects in N-demethylation of either DXM to 3-methoxymorphinan and DXO to 3-hydroxymorphinan were not obtained; hence it was concluded that CYP2D6 is not significantly involved in these reactions (Kerry et al. 1994). Indeed, when grapefruit juice was co-administered with DXM, accumulation of the CYP3A4 substrates, DXM and DXO, and a diminished production of 3-methoxymorphinan, 3-hydroxymorphinan, and hydroxymorphinan-O-glucuronide were obtained (Strauch et al. 2009). Particularly, 3-hydroxymorphinan, which formation depends also on the CYP2D6 activity, had a dose-dependent decrease. The
excretion of the glucuronides suffered also a significant decrease only at the top grapefruit juice concentration (Strauch et al. 2009). Interestingly, there was no increase of DXM systemic availability, since the inhibition of CYP3A4 was counterbalanced by the short-term decrease in DXM absorption from the gastrointestinal tract, both effects attributed to grapefruit juice (Strauch et al. 2009). Moreover, a massive effect on CYP3A4 dependent metabolites was not registered, since 3-methoxymorphinan and DXO are further metabolized to 3-hydroxymorphinan. DXO has significant pharmacological activity, particularly at N-methyl-D-aspartate receptor. P450 isoform is indicated for each metabolic route. UGT: uridine 5’-diphospho-glucuronosyltransferase; SULT: sulfotransferase.

To identify the UDP-glucuronosyltransferase (UGT) isoforms responsible for DXO glucuronidation, DXO was incubated with a panel of 12 recombinant UGT isoforms. All four UGT2B isoforms studied (2B4, 2B7, 2B15, 2B17) were found to mediate glucuronidation of DXO, with UGT2B17 being the most active. In contrast, UGT2B1, 2B2, 2B3, 2B10, and 2B11 did not show detectable activity. The enzyme kinetics of DXO glucuronidation by UGT2B17 were characterized, and the Michaelis-Menten constant (Km) and maximum velocity (Vmax) were determined. The reaction was found to be substrate-dependent, with DXO as the preferred substrate. The results provide insights into the metabolic pathways of DXO and suggest potential targets for the development of inhibitors of DXO glucuronidation.
and 2B17), but none of the eight UGT1A isoforms studied (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, and 1A10), formed DXO-O-glucuronide, suggesting that DXO glucuronidation is catalyzed mainly by the UGT2B subfamily in vivo (Lutz and Isoherranen 2012), similarly to other related opioids such as morphine and codeine (Dinis-Oliveira 2019). DXM-O-glucuronide is permanently charged and less permeable to the blood–brain barrier than unconjugated DXM, and therefore is unlikely to produce significant pharmacological effects in the brain at clinically used doses even though it may be present at higher total (bound and unbound) plasma concentrations than DXM. Furthermore, glucuronide compounds are usually rapidly eliminated by the kidneys (Wu et al. 1995).

**The relevance of CYP2D6 in dextromethorphan metabolism**

CYP2D is expressed in hepatic and brain microsomes, both in humans and rats, and although the expression in the brain being approximately 1–4% of the liver expression, its activity can alter the pharmacologic responses of a centrally acting drug (DuBois and Mehvar 2018). Particularly, the genetic polymorphism of responses of a centrally acting drug (DuBois and Mehvar 2018). Particularly, the genetic polymorphism of.

Therefore, it is possible to measure the activity of CYP2D6 through DXM O-demethylation by measuring urinary metabolic ratios after DXM ingestion (Burton et al. 2006). This analysis can also be done on the basis of saliva samples and obtaining a salivary metabolic ratio, although it requires a higher dose of DXM with the higher risk for side effects (Hou et al. 1991). The phenotype identification has also been performed by plasma metabolite analysis (Mortimer et al. 1989), that would be more rapid and accurate (Yeh et al. 2003). Nevertheless, it should be born in mind that although DXM is not a sensitive CYP3A4 substrate, most of the routinely used CYP2D6 substrates (e.g. desipramine, metoprolol, tolterodine) do show clinically significant CYP3A4 effects (Tornio et al. 2019). Indeed, in this interesting review, it is made clear that an optimal index inhibitor would be selective (i.e. only inhibits one enzyme), meaning that direct mechanistic conclusions could be drawn from the result with reasonable confidence. In opposition, if the index inhibitor inhibits several enzymes and/or transporters, the observed effects on victim drug pharmacokinetics cannot be attributed to a single pathway without further studies (Tornio et al. 2019).

A study conducted in Swiss subjects showed a bimodal distribution of the metabolic ratio of DXM/DXO for the first eight hours, expressing the rates of O-demethylation of DXM, which indicated that there were two phenotypes (i.e. PM and EM) for the DXM metabolism (Schmid et al. 1985). The threshold of 0.3 for the metabolic ratio of DXM/DXO was used as a criteria to differentiate PM (<0.3; the antimode) and EM (>0.3) (Schmid et al. 1985). However, this test is sensitive to co-medications which inhibit CYP2D6 and may yield a phenotype from an EM to a PM phenotype. In the context of DXM, an EM might be more likely to achieve the dissociative effects at lower doses. Indeed, DXO, besides anticonvulsant, sedative, and antitussive properties, has an affinity for the ligand-gated channel of the NMDA receptor complex similar to ketamine (Wong et al. 1988).

Similarly to the above described Caucasian study, a population of 75 healthy Japanese subjects was phenotyped using the metabolic ratio to determine the percentage of PM. The study concluded 1–3% of the population were PM (Nagai et al. 1996). Moreover, differences in the pharmacokinetics between European Caucasians and Japanese EM were identified, namely larger 3-hydroxymorphinan formation in the Japanese population (Nagai et al. 1996). East Asian populations present the lowest incidence of poor metabolism (0–2%) (Gaëdigk 2013). For Caucasians, this value was...
first obtained using sparteine or debrisoquine as the test compound and was estimated to be 3–10% (Küpfer and Preisig 1983). Subsequently, using DXM as a CYP2D6 O-demethylation probe, the frequency of PM in a white French population was 3.9%, meaning that Caucasians Europeans are the group with higher incidence (3–10%) for the PM phenotype (Larrey et al. 1987; Gaedigk 2013). Indeed, Black Africans and African Americans have a 2–7% incidence of PM (Gaedigk 2013).

In PM, the area under the plasma concentration–time curve (AUC) and urinary recovery of 3-methoxymorphinan were increased, and a decrease of O-demethylation to 3-hydroxymorphinan via CYP2D6 was described (Nagai et al. 1996). On the other hand, in EM, there was almost nonexistent quantification of 3-methoxymorphinan due to the rapid conversion to 3-hydroxymorphinan catalyzed by CYP2D6. Still in the Japanese population, the ratios of the cumulative amounts of free and conjugated DXO to DXM excreted in the urine suffered extensive inter-subject variation, most probably related to the fact that the catalysis of DXM to DXO is mediated by CYP2D6; the ratios of DXO to 3-hydroxymorphinan were almost constant, as this reaction is CYP3A4 dependent. The percentages of conjugate metabolites to total metabolites (free and conjugated) were around 86.3–98.9% for both DXO and 3-hydroxymorphinan conjugates, in accordance with data from a French population. DXO and 3-hydroxymorphinan conjugative capacities were similar (mean of 95.7% and 96.7%, respectively), allowing to infer that this step might not be the rate limiting step in the DXM metabolic pathway (Nagai et al. 1996).

**Metabolic interactions**

Besides grapefruit juice, several other metabolic interactions have been described. *Curcuma longa* is used as a traditional medicine and can significantly inhibit human CYP2D6 and CYP3A4 activities. As a result, it was shown that *Curcuma longa* extracts inhibited the enzyme CYP2D6 and CYP3A4 mediated O- and N-demethylation of DXM into DXO and 3-methoxymorphinan, respectively, in a dose-dependent and linear fashion (Al-Jenoobi et al. 2015).

Rolapitant is a potent selective and competitive substance P/neurokinin-1 (NK-1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed chemotherapy-induced nausea and vomiting. *In vivo* rolapitant moderately inhibits CYP2D6 for at least seven days after one 180 mg dose, but the relevance of this finding is yet to be fully clarified (Glass et al. 2019). Nevertheless, a significant increase of DXM systemic exposure with clinical relevance was reported after a single oral dose of rolapitant 180 mg (Wang et al. 2019).

Quinidine can be used to inhibit the rapid DXM metabolism and consequently increase its serum concentrations and its t\(_{1/2}\) (Pope et al. 2004; Garnock-Jones 2011; Taylor et al. 2016; Collins 2018). In other words, quinidine has the potential to temporarily transform a CYP2D6 phenotypic EM into a PM subject. Indeed, a single dose of 50 mg of quinidine caused a partial inhibition of the formation of DXO in the EM group (Capon et al. 1996) and increased DXM elimination t\(_{1/2}\) from approximately four hours (Kazis et al. 2009) to approximately 13 hours (Pope et al. 2004) in volunteers with an EM phenotype, allowing a twice-daily administration to maintain adequate DXM plasma concentrations. This DXM plus quinidine sulfate association (Nuedext\(\text{®}\)) has a therapeutic effect on pseudobulbar affect in patients with amyotrophic lateral sclerosis by diminishing its manifestations (Pope et al. 2004; Garnock-Jones 2011; Taylor et al. 2016; Collins 2018). It is also important to note that the daily dose of quinidine in this combination (20 mg of DXM and 10 mg of quinidine) is much lower than the antiarrhythmic dose of quinidine that is used to block cardiac sodium channels. In another study, DXM 50 mg plus quinidine sulfate 50 mg produced, in PM, an increase in DXM concentrations accompanied with a subjective and objective increase in pain threshold of 35% and 45%, respectively; in EM only a slight and short-lasting increase in the subjective threshold was seen (Desmeules et al. 1999). This highlights the importance of CYP2D6 polymorphisms in the effect of DXM as well as its role in the balance between the analgesic effect of DXM and the hallucinogenic effect of DXO. Authors concluded that the use of CYP2D6 inhibitors combined with DXM interferes with this balance contributing to a higher risk for serotonergic and narcotic related adverse effects (Desmeules et al. 1999).

Amiodarone and selective serotonin reuptake inhibitors may as well interfere with DXM metabolism leading to toxicity (Collins 2018). Clinical interactions of DXM/quinidine with paroxetine have been observed in healthy subjects (Schoedel et al. 2012). The combination increases the AUC of paroxetine by 30% and paroxetine increases the AUC of DXM and quinidine by 50% and 40%, respectively (Schoedel et al. 2012). There is a decrease of 12.3% for the AUC of DXO. The side effect events are increased. Therefore, paroxetine should not be used with DXM/quinidine, patients should be monitored for potential side effects and
Dosage adjustment considered when combining these two agents. Otton et al. (1996) have compared the inhibitory potency of several selective serotonin reuptake inhibitors for CYP2D6-catalyzed DXM O-demethylation. The authors have found that paroxetine, fluoxetine, norfluoxetine, fluvoxamine, and sertraline are potent inhibitors of CYP2D6-catalyzed DXM O-demethylation with Ki values of 0.065–1.8 μM (Otton et al. 1996). Lansoprazole proved to be more potent (Ki = 44.7 μM) than omeprazole (Ki = 240.7 μM) as an inhibitor of CYP2D6-mediated conversion of DXM to DXO (Ko et al. 1997).

DXM has been suggested as an adjuvant for the methadone maintenance therapy for the treatment of opioid dependence (Lee et al. 2015; Fluyau et al. 2020), aiming at reducing methadone tolerance and needed dose, withdrawal symptoms from acute opioid detoxification and inhibiting ‘conditioned reactions to drug-related cues’ (Cornish et al. 2002). There would be a potential interaction between these two drugs, since methadone is both a substrate and a CYP2D6 inhibitor (Dinis-Oliveira 2016; Dilich and Girgis 2017). Investigators propose that the beneficial effects from this combination would come from the increase of plasma methadone concentration, although further research is necessary (Lee et al. 2015; Dilich and Girgis 2017). An 83-year-old woman on methadone 20 mg daily, developed delirium, hypersomnia, confusion, lethargy, impaired concentration, and poor food intake after taking DXM at therapeutic doses of 60 mg per day for cough. Her symptoms resolved soon after discontinuing of DXM (Lotrich et al. 2005).

Amitriptyline is a tricyclic antidepressant, for what inhibits serotonin and norepinephrine uptake. It is an important substrate of CYP2D6 (Courts et al. 1994) and has been proven to inhibit CYP2D6 competitively (Forget et al. 2008). Moreover, it competes with DXM at σ1R but with a lower affinity (Werling et al. 2007) and may block NMDA receptors (Sawynok and Reid 2003). Given this pharmacodynamics, amitriptyline interacts with DXM and may even have a therapeutic adjuvant effect (Sawynok and Reid 2003). A case was described of a possible life-threatening DXM intoxication related with an interaction with amitriptyline in a PM (Forget et al. 2008).

DXM use is not recommended in children younger than 4-years-old, for the doses that would be safe in this age range are not known (Chyka et al. 2007; Collins 2018). There has not been noted any age-related precaution concerning DXM use in the elderly (Collins 2018). DXM is considered safe for use during pregnancy within recommended doses and is commonly used in this context (Chyka et al. 2007).

MAOIs and DXM concurrent use, or if at least two weeks of MAOIs discontinuation are not respected, may cause psychosis, serotonin syndrome, with hypertension or hyperpyrexia, and even death, since DXM also blocks serotonin neuronal uptake (Meoni et al. 1997; Dy et al. 2017; Kongpakwattana et al. 2018; Ahmed et al. 2019). Co-ingestion with SSIRs, tricyclic antidepressants, meperidine, clonazepam, sibutramine, lithium, and antihistamines such as chlorpheniramine and, to a lesser extent, diphenhydramine (Logan 2009; Logan et al. 2009, 2012), can as well increase the risk of inducing a serotonin syndrome (Chyka et al. 2007; Collins 2018). Clinical effects associated with the serotonin syndrome are dose-related and include signs of autonomic instability (hypertension, hyperpyrexia, diaphoresis, tachycardia), muscular hypertonicity (tremor, clonus, myoclonus, hyperreflexia), and mental status changes (agitation, disorientation, confusion). SSIRs, such as fluoxetine, can also inhibit CYP2D6 enzyme (Cazet et al. 2018).

In another study, the inhibition and recovery half-life of CYP2D6 and CYP3A4 activity was assessed in female subjects by administering the probe drug DXM before and repeatedly after MDMA administration, which is a potent mechanism-based inhibitor of CYP2D6 (de la Torre et al. 2004). Results evidence that in women the pretreatment with MDMA resulted in a decrease in DXM clearance. CYP2D6 activity recovered after 10 days to 90% of baseline activity. Regarding CYP3A4 activity, there is an apparent decrease in its activity after MDMA use. These results also highlight that physicians should be criterious when prescribing drugs metabolized by CYP2D6 (Yubero-Lahoz et al. 2011). In men, DXM Cmax and AUC increased approximately 10-fold with corresponding decreases in DXO pharmacokinetic parameters. The metabolic ratio also increased almost 100-fold after MDMA administration, with 67% of the subjects having a value greater than the antimode of 0.3 for assigning the PM phenotype (O’Mathuna et al. 2008). Interactions with ethanol were also reported. Indeed, acute ethanol exposure had the largest effect on the pharmacokinetics of DXM (was doubled), of all studied compounds clearly indicating an inhibitory effect on CYP2D6 (Gazzaz et al. 2018).

**Pharmacological interactions**

There are some drugs that should not be administered with DXM due to the potential of interactions, namely monoamine oxidase inhibitors (MAOIs), SSIRs, central nervous system depressants, and the CYP2D6 inhibitors amiodarone and quinidine (Collins 2018).
Elimination

DXM onset of action is about 15–30 minutes and has a half-life of 1.4–3.9 hours as a parent compound and as DXO of 3.4–5.6 hours (Collins 2018). The duration of action is 5–6 hours and is influenced by the individuals CYP2D6 enzyme activity (Brown et al. 2018). DXM is primarily excreted in urine, mostly as conjugates metabolites of DXO and 3-hydroxymorphinan, dextrorphan-O-glucuronide, and 3-hydroxydextrorphan-O-glucuronide. Traces of the unmetabolized drug were found in urine after oral administration (Ramachander et al. 1977; Pfaff et al. 1983). In the first four hours post DXM administration, approximately one-third of the ingested dose was recovered in urine, mostly as glucuronides conjugates (Strauch et al. 2009); this fraction had been reported to rise to 55% in 12 hours (Schadel et al. 1995) and more than 85% of the dose is excreted in urine within 24 hours (Pfaff et al. 1983). Both DXO and 3-hydroxymorphinan conjugates were found to have a lower mean renal clearance value than the mean glomerular filtration rate, suggesting that renal reabsorption might take a part in the overall excretion process for conjugated metabolites (Nagai et al. 1996). Also, urinary pH is considered a significant covariate for DXM renal clearance (Abduljalil et al. 2010). Moreover, mean plasma concentrations of dextrorphan-O-glucuronide increased by approximately 45% following concomitant administration of DXM and verapamil. Since DXO is mainly eliminated in its glucuronide form in the urine (Zysset et al. 1988), the increase in plasma concentrations of dextrophan-O-glucuronide may be attributed to an inhibitory effect of verapamil on the P-gp-mediated renal excretion of dextrophan-O-glucuronide. Another study pointed out that the urinary recovery in the form of either DXM or its metabolites would not be complete, suggesting that a small percentage could be excreted in feces, as already reported in rats. Moreover, enterohepatic recirculation of DXO has been described (Zysset et al. 1988; Schadel et al. 1995). Furthermore, in PM, in comparison to EM, the urinary recovery was increased, since there was an higher fraction of DXM and 3-methoxymorphinan as excretion products, of which fecal excretion in rats was minimal (Capon et al. 1996).

Pharmacodynamics and therapeutic actions

DXM has several pharmacodynamic mechanisms being, a σ1R agonist (Chou et al. 1999), a δ3β4 nicotinic receptor antagonist, a noncompetitive NMDA receptor antagonist, a NAPDH oxidase inhibitor, a serotonin reuptake inhibitor (Kaplan et al. 2011) and also stimulates its release (Gaikwad et al. 2005), and has competitive 5-HT1 agonist activity (Kamei 1996). Major pharmacodynamic aspects of DXM are resumed in Figure 3. Even though it is structurally similar to other morphine derivatives it is devoid of narcotic proprieties (Spangler et al. 2016). Indeed, DXM does not show any significant affinity for the µ and σ1 opioid receptors, which are responsible for analgesic and central nervous system depressant effects, except in overdoses (Wang et al. 1977).

DXM also blocks voltage-activated Ca2+ and Na+ channels (Netzer et al. 1993), being the last involved in local anesthetic effect. Indeed, DXM was found to produce a dose-dependent local anesthetic effect on the sciatic nerve blockades of motor function, proprioception, and nociception. The same is true for DXO and 3-hydroxymorphinan, and therefore these three compounds may potentially be the novel local anesthetics for peripheral neural blockade (Hou et al. 2006). Another study indicates that DXM induces anti-hyperalgesia through NMDA receptors antagonism and that DXO would play a weaker role; they can prevent the induction of neuronal hyper-excitability and also reverse established neuronal sensitization, but has no effect on acute pain (Duedahl et al. 2005). Some studies suggest that combining NMDA receptor antagonists such as DXM, especially with gabapentin could provide synergistic effect to alleviate neuropathic pain and reduce side effects (Pickering et al. 2014; Aiyer et al. 2018; Shi et al. 2018).

The mechanism of DXMs cough suppressant proprieties is not completely clarified but it is thought to result from depressing the medullary cough center through σ1R stimulation and NMDA receptors antagonism (Brown et al. 2004), thus decreasing the cough reflex sensitivity (Ramsay et al. 2008) and elevating the threshold for cough initiation (Bolser 2006; Spangler et al. 2016).

Fast-acting antidepressant activity is also associated to σ1R signaling by DXM, hypothesis that was raised because of the drug pharmacodynamics similarities to the NMDA antagonist ketamine (Dinis-Oliveira et al. 2010; Dinis-Oliveira 2017). Moreover, it was shown that DXM itself would sufficiently produce this antidepressant-like effect, not requiring conversion to the metabolite DXO (Nguyen et al. 2014). It has been suggested that, when at higher doses namely if over 1500 mg/day, DXM σ1R activation could induce a schizophrenic-like mental state (Martinak et al. 2017).

Also, in mice, DXM shown to elicit stimulant actions (namely locomotor activity) by σ1R dependent mechanisms, which would be independent of the antidepressant-like effects of DXM and would not be increased by
the addition of the CYP2D6 inhibitor quinidine (Wang et al. 2007). Both Food and Drug Administration and European Medicines Agency have approved in 2010 and 2013, respectively, this DXM plus quinidine scheme for the treatment of pseudobulbar affect, whose main symptom is emotional lability (Nguyen et al. 2014).

Anticonvulsant and neuroprotective effects in several experimental models have also been attributed to DXM probably associated with its proprieties as a low-affinity noncompetitive NMDA receptors antagonist and/or high-affinity \( \sigma_1 \)R agonist in the brain (Chou et al. 1999; Shin et al. 2005).

DXM has been proposed for the treatment of nonketotic hyperglycinemia. Nonketotic hyperglycinemia is a genetic defect of glycine metabolism, in which deficiency of glycine cleavage system leads to increased levels of glycine in all tissues, including the brain (Bjoraker et al. 2016). Among other effects, and because glycine is an allosteric co-activator of the NMDA receptor, the high levels of glycine over-stimulate these NMDA receptors, causing an excitotoxic response (Bjoraker et al. 2016; McQueen 2017). Progressive neurodegeneration and recurrent uncontrollable seizures are usually present in this syndrome (McQueen 2017). DXO has a higher affinity for the noncompetitive binding domain of the NMDA receptor (Franklin and Murray 1992), and electrophysiological data show that DXO is a more potent NMDA receptor antagonist than DXM both in vitro and in vivo (Church et al. 1985, 1989; Ishmael et al. 1998; Pechnick and Poland 2004). DXM as a weak inhibitor of NMDA receptors, blocks the effect of excess glycine, and can decrease the associated seizures, combined with benzoate to reduce the glycine levels (Bjoraker et al. 2016).

Abuse and tolerance potential

Reports of DXM abuse, especially among teenagers and to a lesser extent by young adults, have been described (Spangler et al. 2016). It is interesting to note that DXM abuse is consistent with the finding that hallucinogens use peaks at 19-years-old and rapidly decreases after (Karch 2008; Karch and Drummer 2016). DXM was approved by the FDA for OTC sale in 1958 and its pattern of abuse was not reported at that time (Kaplan et al. 2011). This could be because these participants were not abusers of \( \mu \)-agonist opioids and the measured outcomes were centered on its potential to produce liking or euphoria and ascertain if it had morphine-like proprieties. Indeed, even if dissociative

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Figure 3. Major pharmacodynamic aspects of dextromethorphan. DXM: Dextromethorphan; DXO: Dextrophan; NMDA: N-methyl-D-aspartate; NADPH: Nicotinamide Adenine Dinucleotide Phosphate.
effects had appeared, the outcome instruments may not have been capable of identifying them. In opposition, these studies reported drowsiness after a large oral single dose up to 800 mg and some ‘confusion’ and ‘loss of memory’ when chronic dosage, symptoms stated as ‘frightening’ by the participants; increases in the pentobarbital-chlorpromazine and alcohol-like drugs (PCAG) and lysergic acid-like drugs (LSD) scales of the Addiction Research Center Inventory were found, measuring sedative-like effects and dysphoric experiences, respectively (Karch 2008; Karch and Drummer 2016).

Especially since the mid-1990s, its abuse has been found to be more frequent and widespread, probably related to the easy and rapid spread of information made possible by the internet (Karch 2008; Karch and Drummer 2016). In the first 30 years, just 15 cases of fatal outcomes involving DXM were reported to the manufacturer, and only one refers therapeutic doses however in concomitant administration with antidepressants (Bem and Peck 1992); from 1999 to 2004, the California Poison Control System data identified a 10-fold increase in DXM abuse cases among all age groups, and in children aged 9–17-years-old this increase was of 15-fold (Bryner et al. 2006). Similar data from American Association of Poison Control Centers from 2000 to 2015 show a total number of 72,260 calls reporting intentional abuse of a DXM cough and cold product, with a peak in 2006 and with the highest frequency among 15- and 16-year-olds (Karami et al. 2018), being the subsequent reduction possibly related to the ‘Paper Talk’ by the Food and Drug Administration in 2005 that notified the public about the abuse on DXM (Desai et al. 2006). Even though this abuse has been decreasing since 2006, a significant reduction in OTC cold medications abuse was registered since 2010. Although the cause is not absolutely clear, it is thought to be related to the increased awareness resulted from 2010 Food and Drug Administration Advisory Committee meeting, followed by implementation of the mitigation plan targeting decisive factors in youth behavior (Spangler et al. 2016). In Korea, zipeperol is another centrally acting cough suppressant that is abused with DXM for stronger hallucinogenic effects, predominantly by teenagers (Chung et al. 1998).

Currently, DXM is not scheduled under the Controlled Substances Act (CSA), nonetheless along the years there has been some controversy on whether DXM should be or not a scheduled substance (Banken and Foster 2008; Spangler et al. 2016). DXM can be used recreationally since at higher doses produces a dissociative/hallucinogenic experience or simply an intoxicating effect (Karch 2008; Karch and Drummer 2016). These effects, combined with being relatively inexpensive and easily available for consumption and since extensive information on how safely abuse DXM over the internet, may explain its widespread popularity (Banken and Foster 2008; Spangler et al. 2016). However, it shows little recurrence of abuse when researched with other psychoactive substances such as cocaine and heroin (El-Naby and Kamel 2015; Spangler et al. 2016). In opposition to DXM and DXO, their enantiomers levmorphan and levorphanol, respectively, are potent narcotic analgesics and have much greater abuse potential and are both Class A controlled drugs.

DXM and DXO both act as antagonists of the NMDA receptor, reducing neural activation (Logan 2009; Logan et al. 2009, 2012). These differ biochemically from high-affinity NMDA antagonists such as PCP and ketamine (Spangler et al. 2016), but when administered in high doses, the pharmacology of DXM is similar to these controlled substances and hallucinogenic and dissociative effects may appear (Logan 2009; Logan et al. 2009, 2012). This NMDA antagonism might also be related to the adrenergic effects accompanying a high dose intake of DXM due to an inhibition of catechol-amine reuptake (Chyka et al. 2007). DXM is a stronger \( \sigma_1 \)R agonist than DXO and DXO is a stronger NMDA receptor antagonist than DXM. Both these compounds are capable of inducing psychoactive effects; however, it may be DXO, the major responsible compound for the psychotic and dissociative states (Miller 2005; Logan 2009; Logan et al. 2009, 2012).

Even though DXM has no significant addiction liability (El-Naby and Kamel 2015), as with most opioids, long-term users can develop tolerance and in few cases dependence (Chyka et al. 2007). Regarding DXM tolerance, there seems to be a correlation with the individual’s metabolizer phenotype. One pilot study demonstrated that EM tolerated 3–6 mg/kg of DXM, while PM barely tolerated 3 mg/kg without significantly undesirable symptoms emerging justifying lower doses (Zawertailo et al. 1998). Authors also demonstrated that PM had greater psychomotor impairment, as measured by a joystick tracking task, compared with EM. At this dose, EM also reported greater abuse potential compared with PM, and PM reported greater sedation and dysphoria compared with EM. These data provide preliminary evidence that DXO contributes to DXM abuse liability, and therefore PM may be less likely to abuse DXM. Indeed, since PM produces less DXO, maintaining DXM level elevated, experience more pronounced side effects, such as nausea, vomiting, dysphoria, and subsequently having less tendency for abuse. On the other
hand, since EM produces more DXO, which has higher affinity for the NMDA receptor than the parent compound, experiences the ‘desirable’ psychoactive and euphoric effects, presenting with a higher risk for abuse (Zawertailo et al. 1998). Other reports also demonstrated the relationship between CYP2D6 activity and the plasma drug levels, the psychoactive drug effects and the abuse liability and therapeutic utility of DXM (Zawertailo et al. 2010).

**Clinical signs and symptoms**

DXM is widely available on OTC products and its adverse effects are rarely observed if it is taken within recommended dosing parameters (Spangler et al. 2016). Occasionally, drowsiness, dizziness, nausea and abdominal discomfort, flatulence, diarrhea or constipation are observed (Collins 2018). However, constipation, a frequent opioid side-effect, is much less pronounced since DXM has no relevant activity on μ-opioid receptor and σ₁R (Grattan et al. 1995; Farmer et al. 2018).

Given its potential for abuse, it is important to be aware of the overdose risk by DXM and the resulting visual and auditory hallucinations, dissociative effects, mania, delusions, aggression, euphoria, and dysphoria effects (Banken and Foster 2008; Brown et al. 2018), similarly to what is observed in ketamine or PCP abuse (Logan 2009; Logan et al. 2009, 2012). In these cases, some physiological changes can often be noticed, such as diaphoresis, hyperthermia, and tachycardia, requiring early and appropriate recognition and management (Brown et al. 2018). In overdoses, ataxia, nystagmus, mydriasis, muscle spasticity, increase or decrease in blood pressure, blurred vision, blue fingernails and lips, nausea, vomiting, respiratory depression, seizure, stupor, and coma have also been described (Banken and Foster 2008; Kaplan et al. 2011; Spangler et al. 2016). QT interval prolongation in DXM overdose with ethanol (Kaplan et al. 2011), myoclonus after therapeutic DXM use in a patient on peritoneal dialysis with chronic renal failure (Tanaka et al. 2011), and a serotonin syndrome with therapeutic doses of DXM in a 77-years-old patient with chronic hepatitis (Chyka et al. 2007; Kinoshita et al. 2011) were also reported. If symptoms are not developed within the first four hours after DXM ingestion, those are unlikely to appear later, unless it comes from toxicity related to a concomitantly ingested drug like paracetamol.

DXM abuse can cause several other serious health complications not directly related to DXM itself, but due to other drugs found in OTC medications (Woo and Hanley 2013). Indeed, when abuse occurs using the formulations containing antihistamines (chlorpheniramine, brompheniramine, pheneramine), analgesics (paracetamol, acetyl salicylic acid), decongestants (phenylephrine, pseudoephedrine), and/or expectorant mucolytic agents; additional toxicity of these compounds is a concern and predisposes to fatal overdoses (Karch 2008; Karch and Drummer 2016). Some liquid DXM preparations also contain ethanol concentrations up to approximately 25% (Bisaga and Popik 2000). Thus, a high level of suspicion is needed when detected an increase in blood pressure possibly due to pseudoephedrine, a delayed liver damage related to high doses of paracetamol or central nervous system depression, cardiovascular and anticholinergic toxicity from antihistamines (Gunn et al. 2001; Banken and Foster 2008; Woo and Hanley 2013).

**Dose-dependent signs of intoxication by dextromethorphan**

DXM clinical signs of intoxication are dose-dependent and manifest classically in four separate stages or plateaus (Table 1) and once the next is reached the effects may completely change (Logan 2009; Logan et al. 2009, 2012; Brown et al. 2018). Also, for each plateau, effects can often vary and recreational effects may be different depending on the relative quantity of DXM and DXO, since they produce different effects, with DXMs being more subtle (Logan et al. 2012; Brown et al. 2018). The comedown can start suddenly and is noticeable by the user by the return of normal sensory processing; however, it may be prolonged in time (Logan 2009; Logan et al. 2009, 2012; Brown et al. 2018). During the first plateau, ingestion of approximately 100–200 mg DXM produces mild stimulant effects similarly to methylene-dioxyamphetamine (MDA), whereas mild hallucinations develop during the second level following the ingestion of about 200–400 mg DXM, similarly to a combination of alcohol and marijuana intoxication. Dysphoria can occur when DXM doses exceed 200–250 mg. The third plateau is the ‘out of body’ experience, with physical distortion and hallucinations for DXM doses of 300–600 mg; the ingestion of doses > 600 mg is associated with complete dissociation similarly to ketamine. If doses exceed the ‘fourth plateau dosage’ full anesthesia, psychosis, coma, and/or death can occur (Aytha et al. 2013). Another interesting effect is that music enhances DXM sense of euphoria, something that is not quite true with other dissociative drugs, being listening to music probably the most common fun thing to do on DXM (Logan 2009; Logan et al. 2009, 2012; Brown et al. 2018). Given this euphoria specifically linked to
music, which is set and setting dependent, DXM presents as a popular drug within the rave culture (Abanades et al. 2004; Parks and Kennedy 2004; Logan 2009; Logan et al. 2009, 2012; Brown et al. 2018).

After discontinuation of use, rapid and complete remission of symptoms is expected (Miller 2005). DXM withdrawal can occur, manifesting both psychological and physical signs, and is usually long and accompanied by nausea, vomiting, diaphoresis, myalgias, and diarrhea, especially during the first three days after discontinuation of use. Also, anxiety, dysphoria, insomnia, nonspecific malaise, and suicidal ideation have been described as part of DXM withdrawal (Miller 2005; Stanciu et al. 2016).

Since DXM can be found in the form of a bromide salt, bromide poisoning may occur if large quantities are taken. Bromide poisoning, known as bromism, is primarily a chronic neuropsychiatric disorder manifested by behavior changes, headaches, apathy, irritation, slurred speech, psychosis, tremors, ataxia, hallucinations, and coma (James et al. 1997; Frances et al. 2003; Hsieh et al. 2007). It can also cause weight loss and bromoderma characterized as an acneiform rash mimicking a pyoderma gangrenosum (Kunze 1976; Battin and Varkey 1982; Hung 2003; Maffeis et al. 2008; Oda et al. 2016).

### Dextromethorphan DNA interaction

The first study aiming to evaluate the interaction between DXM hydrobromide and DNA was published very recently (Bi et al. 2018). The results showed a spontaneous DXM–DNA interaction, through van der Waals force or hydrogen bond, with a static fluorescence quenching process between the two; DXM binding affected DNA structure and the stability of the complex DXM–DNA decreased when increasing in temperature occurred (Bi et al. 2018). The preferred binding mode of DXM to DNA was intercalation binding, indicated by UV/VIS absorption and CD spectroscopy and further confirmed by the effect of ionic strength, the increase in DNA viscosity and stability in the presence of DXM, a smaller binding constant of DXM with dsDNA than with ssDNA, cyclic and differential pulse voltammogram, and molecular docking that suggests that the chromophore of DXM could slide into the DNA enriched G-C region (Bi et al. 2018).

### Interpretation of toxicological analysis, results, and forensic aspects

DXM is not usually contemplated in the basic immunoassays toxicological screenings. Moreover, since these analysis can result in false positive results for PCP, more frequently, but also for opiates, confirmation and quantification by other specific techniques such as high-performance liquid chromatography coupled to mass spectrometry (LC–MS) and gas chromatography–mass spectrometry, and less commonly by electrophoresis, fluorimetry, ELISA, and spectrophotometry, are required (El-Naby and Kamel 2015). Also, the use of potentiometric sensors for determination of DXM has been investigated (El-Naby and Kamel 2015) and different samples tested such as urine, blood, and oral fluid (Rodrigues et al. 2008). Cross reactivity is also obtained for the DXM enantiomer levomethorphan that presents potent narcotic proprieties (Wong and Sunshine 1996).

Therapeutic dosing regimens generally produce DXM blood concentrations below 50 ng/mL. Generally, plasma concentration range of 0.5–5.9 ng/mL (mean 2.4) for EM and 182–231 ng/mL (mean 207) for PM has been described (Cochems et al. 2007). The reference blood level list of therapeutic and toxic substances of The International Association of Forensic Toxicologists and provided by other comprehensive collection of

<table>
<thead>
<tr>
<th>Table 1. Dose-dependent signs of intoxication by dextromethorphan classically manifested in four separate stages or plateaus.</th>
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<tbody>
<tr>
<td><strong>Stage 1 (1.5–2.5 mg/kg)</strong></td>
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<tr>
<td>Restlessness</td>
</tr>
<tr>
<td>Altered sense of movement and position, disturbances in balance and body position</td>
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<tr>
<td>Mood enhancement and intensified emotions</td>
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<tr>
<td>Visual and auditory sensitization</td>
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<tr>
<td>Impaired short-term memory</td>
</tr>
<tr>
<td>Generalized euphoria, specifically linked to music and motion</td>
</tr>
<tr>
<td>No mental confusion</td>
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<tr>
<td><strong>Stage 2 (2.5–7.5 mg/kg)</strong></td>
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<tr>
<td>Disturbed time-continuous sensory input (‘Flanging’)</td>
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<tr>
<td>Exaggerated auditory and visual sensations followed by periods of deprivation</td>
</tr>
<tr>
<td>Disrupted sense of balance, body position and kinetic sense</td>
</tr>
<tr>
<td>Hallucinations and eidetic imagery</td>
</tr>
<tr>
<td>Impaired working and intermediate-term memory</td>
</tr>
<tr>
<td>Increased energy and excitability</td>
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<tr>
<td>Hallucinations</td>
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<tr>
<td>Periods of semiconsciousness</td>
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<tr>
<td>Delayed reaction and response time</td>
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<tr>
<td>Impaired cognitive ability</td>
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<tr>
<td>Impaired short-term memory, and working memory to a lesser extent</td>
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<tr>
<td>Mania and/or panic</td>
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<tr>
<td>Partial disassociation</td>
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<tr>
<td>Stage 4 (&gt;15 mg/kg)</td>
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<tr>
<td>Complete disassociation</td>
</tr>
<tr>
<td>Hallucination/delusions</td>
</tr>
<tr>
<td>Ataxia</td>
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Adapted from Brown et al. (2018), Logan (2009), Logan et al. (2009), Logan et al. (2012), Romanelli and Smith (2009).
data report serum concentrations of 10–40 ng/mL (Repetto and Repetto 1998, 1999; Bailey et al. 2000; Schulz et al. 2012). Due to extensive metabolism of DXM to DXO, the first is found in low concentrations and the second in high concentrations in the blood, resulting in a blood DXM/DXO ratio of less than 0.11; however, in PM subjects, this ratio can invert and rise up to 2.5 or higher (Mortimer et al. 1989). Blood concentrations were described to be toxic at 0.1–2.8 mg/L and lethal at 1.8–18 mg/L; for humor vitreous and liver, concentrations of 0.7 mg/L and 19–230 mg/kg were obtained, respectively (Repetto and Repetto 1998, 1999; Logan 2009; Logan et al. 2009, 2012; Schulz et al. 2012). Several deaths were reported in Pakistan after consuming cough sirups containing DXM. In an important casuistic of 30 deaths caused by DXM, toxicological analysis revealed concentrations ranging from 7.3 to 41.7 mg/L in the peripheral blood, 4.2–92.6 mg/kg in the liver and 9.9–349.6 mg/L in the gastric content. All subjects tested positive for the presence of opiates, eight for cannabinoids, and two for benzodiazepines. Gastric contents of one deceased also contained 1.1 g/dL ethanol. Table 2 provides a compilation of toxic and lethal concentrations in several reported cases.

A study in rats showed that some postmortem redistribution of DXM can occur, characterized by a mean of sixfold increase and maximum of 15-fold; this was not studied for DXO, but previous studies with other drugs show a tendency for the metabolites to undergo the same extent of postmortem redistribution as the corresponding parent drug (Bailey et al. 2000). The relative distribution of DXM and DXO in skeletal tissues of rats having undergone acute or repeated exposure to DXM in different microclimates was assessed (Unger and Watterson 2016; Morrison et al. 2017). In this study, the drug exposure patterns were shown to be distinguishable from bone drug levels after decomposition, in other words, it was possible to discern acute from repeated drug exposure. Both DXM levels and the ratio of the levels of DXO to DXM were useful in discriminating acute from repeated drug exposure. Moreover, analyte levels and analyte ratios did not differ significantly between different microclimates during bone decomposition. Further investigation is necessary to evaluate physiochemical differences during differential decomposition (Morrison et al. 2017).

The postmortem findings in individuals dying from DXM intoxications are nonspecific, and similar to other opioid intoxications, namely cerebral edema, pulmonary edema, and frothy foam in the major airways without evidence of trauma or antecedent natural disease (Logan 2009; Logan et al. 2009, 2012). The most likely mechanisms of death are serotonin syndrome and generalized CNS depression (Logan 2009; Logan et al. 2009, 2012).

The diagnosis of a dissociative condition should not only take into account the elevated blood concentrations of the DXM and DXO, but should also consider a DSM-V psychiatric criteria (Logan 2009; Logan et al. 2009, 2012). Although evaluation by drug recognition experts indicated that drivers had poor psychomotor performance on standardized field sobriety tests, horizontal gaze nystagmus, vertical gaze nystagmus, and overall signs of central nervous system depression, 96% of these samples contained other drugs (Cochems et al. 2007). Logan (2009) and Logan et al. (2009) described cases of eight drivers arrested for driving under the influence of the combined effects of DXM and chlorpheniramine, and a further four drivers under the influence of DXM alone. Drivers generally displayed symptoms of CNS depression, gross evidence of impairment in their driving, including weaving, leaving the lane of travel, failing to obey traffic signals, and involvement in collisions. To evaluate DXM related-deaths, it is relevant to consider the potential significance of a co-administrated or co-ingested drug, since DXM is frequently abused combined with other substances, and some of the effects following that DXM abuse might be caused or exacerbated by those other concomitant substances (Chyka et al. 2007). Several DXM-related deaths had been reported in impaired drivers (Cochems et al. 2007), where whole blood DXM concentrations averaged 51 μg/L (range 5–1800 μg/L). In another incident, five drivers died after consuming 1500 mg DXM (Logan 2009; Logan et al. 2009). All of them had documented abuse histories of recreational DXM abuse and their blood DXM concentration averaged 790 μg/L (range 470–1220 μg/L). It is also important to highlight that that toxicological analysis should also include metabolite DXO levels, since as mentioned above, DXO has a longer half-life than DXM and it also has increased pharmacological action and potentially increased impairment effects in relation to driving.

In another study, cannabidiol e-liquids used in electronic cigarettes (e-cigarettes) revealed unexpectedly 5-fluoro MDMB-PINACA (5F-ADB) in four of the products and DXM in one of the products. The analysis of these products illustrates the potential quality control issues that can occur in an unregulated industry (Poklis et al. 2019). DXM has also been used as cutting agent of heroin, increasing the risk of adverse health effects on consumers, possibly due to the synergistic effect of the adulterants laced with substances of abuse (Solimini et al. 2017).
Table 2. Therapeutic, toxic, and lethal concentrations of dextromethorphan (DXM) in different biological samples.

<table>
<thead>
<tr>
<th>Biological samples</th>
<th>[Dextromethorphan] and additional toxicological data</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>0.1 mg/L toxic</td>
<td>(Repetto and Repetto 1998, 1999)</td>
</tr>
<tr>
<td></td>
<td>3 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>3 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15 mg/L lethal (infant; age not described)</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0.15–1.22 mg/L toxic</td>
<td>(Logan 2009; Logan et al. 2009)</td>
</tr>
<tr>
<td></td>
<td>Association with chlorpheniramine and in one case temazepam, lorazepam, oxazepam, clonazepam, trazodone, venlafaxine, and bupropion at therapeutic or sub therapeutic concentrations were also found</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0.67 mg/L toxic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Association with chlorpheniramine, Nor-9-carboxy-Δ9-tetrahydrocannabinol and fluoxetine 20-years-old</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0.19–1 mg/L toxic</td>
<td>Association with ethanol</td>
</tr>
<tr>
<td>Blood</td>
<td>1 mg/L toxic, plus guaifenesin and Nor-9-carboxy-Δ9-tetrahydrocannabinol 22-years-old</td>
<td></td>
</tr>
<tr>
<td>Heart blood</td>
<td>3.23 mg/L lethal, association with cannabinoids; 17-years-old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.89 mg/L lethal, association with diphenhydramine and cannabinoids; 19-years-old</td>
<td></td>
</tr>
<tr>
<td>Iliac blood</td>
<td>1.3 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Vitreous humor</td>
<td>0.7 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>19 mg/kg lethal</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>&gt;20 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Iliac blood</td>
<td>0.95 mg/L lethal</td>
<td>Association with alprazolam; 19-year-old</td>
</tr>
<tr>
<td></td>
<td>3.08 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>5.09 mg/L, 1.4 mg/L DXO lethal</td>
<td>(Kintz and Mangin 1992)</td>
</tr>
<tr>
<td>Urine</td>
<td>3.29 mg/L, 3.09 mg/L DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Bile</td>
<td>3.48 mg/L, 1.86 mg/L DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>10.74 mg/kg, 4.81 mg/kg DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>2.38 mg/kg, 1.72 mg/kg DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>4.27 mg/kg, 2.09 mg/kg DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>3.47 mg/kg, 1.58 mg/kg DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Blood from femoral vein</td>
<td>9.2 μg/g, 2.9 μg/g DXO lethal</td>
<td>(Rammer et al. 1988)</td>
</tr>
<tr>
<td>Liver</td>
<td>31.2 μg/g, 11.5 μg/g DXO lethal</td>
<td>18-years-old</td>
</tr>
<tr>
<td>Blood from femoral vein</td>
<td>3.3 μg/g, 1.5 μg/g DXO lethal</td>
<td>27-years-old</td>
</tr>
<tr>
<td>Liver</td>
<td>230 μg/g, 29.2 μg/g DXO lethal</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>2.6 mg/L lethal</td>
<td>(Yoo et al. 1996)</td>
</tr>
<tr>
<td>Gastric contents</td>
<td>25.5 μg/g lethal</td>
<td>Association with zipeprol; 21-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>1.2 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Gastric contents</td>
<td>243.7 μg/g lethal</td>
<td>Association with zipeprol; 20-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>4.1 mg/L lethal</td>
<td>Association with zipeprol; 19-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>1.8 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Gastric contents</td>
<td>2.1 μg/g lethal</td>
<td>Association with zipeprol; 21-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>1.4 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Gastric contents</td>
<td>3.4 μg/g lethal</td>
<td>Association with zipeprol; 19-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>1.8 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Gastric contents</td>
<td>15 μg/g lethal</td>
<td>Association with zipeprol; 29-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>18.3 mg/L lethal</td>
<td>Association with zipeprol; 22-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>2.9 mg/L lethal</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>1.1 mg/L lethal</td>
<td>Association with zipeprol; 21-years-old</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>4.74 mg/L lethal</td>
<td>(Logan et al. 2012)</td>
</tr>
<tr>
<td>Blood</td>
<td>0.3 mg/L toxic</td>
<td>31-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>0.05 mg/L toxic</td>
<td>23-years-old</td>
</tr>
<tr>
<td>Blood</td>
<td>1.05 mg/L toxic</td>
<td></td>
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<tr>
<td>(continued)</td>
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</tbody>
</table>
Interestingly, Olives et al. (2019) reported a patient with persistent DXM hydrobromide abuse at escalating doses whose mean serum chloride concentration increased, on average, by 0.00232 mEq/L every day over a 110-month period. This case demonstrates progressive spurious hyperchloremia secondary to bromide interference in hospital-based ion-selective chloride assays, supporting the patient’s reported need to dose escalate to the same desired effect. Although this artefactual hyperchloremia laboratory finding is a well-documented result of bromide ingestion (Emancipator and Kroll 1990; Ng et al. 1992; Hsieh et al. 2007), authors claimed that this artifact may be useful in identifying patterns of DXM hydrobromide use that suggest tolerance.

### Treatment of acute intoxications

Recognition of DXM abuse is difficult in emergency context, since the signs and symptoms are not specific for DXM and can even precipitate a psychiatric diagnose, and because DXM is not routinely tested in standard toxicological urine drug assays (Dilich and Girgis 2017). Thereby, the early identification of its use and whether other drugs were co-ingested may be challenging. Careful anamnesis collected either from the patient or other people who may have essential information or inspection of the patient’s belongings can help on the identification of the drug causing the acute intoxication (Chyka et al. 2007).

When addressing a DXM acute intoxication, monitoring of vital signs and respiratory, cardiovascular, and

<table>
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</tr>
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<tbody>
<tr>
<td>Peripheral blooda</td>
<td>2.42 mg/L, toxic</td>
<td>(Boland et al. 2003)</td>
</tr>
<tr>
<td>Peripheral blooda</td>
<td>19.5 mg/L, lethal</td>
<td>(Marinetti et al. 2005)</td>
</tr>
<tr>
<td>Blooda</td>
<td>0.5 mg/L, lethal</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.07 mg/kg, lethal</td>
<td></td>
</tr>
<tr>
<td>Cavity blooda</td>
<td>0.55 mg/L, toxic</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1.3 mg/kg, toxic</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>2.9 mg/L, toxic</td>
<td></td>
</tr>
<tr>
<td>Peripheral blooda</td>
<td>0.06 mg/L, toxic</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.58 mg/kg, toxic</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.9 mg/kg, toxic</td>
<td></td>
</tr>
<tr>
<td>Heart blood</td>
<td>0.04 mg/L, lethal</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.29 mg/kg, lethal</td>
<td></td>
</tr>
<tr>
<td>Heart blood</td>
<td>0.03 mg/L, toxic</td>
<td></td>
</tr>
<tr>
<td>Cavity blood</td>
<td>0.09 mg/L, lethal</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.55 mg/kg, lethal</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>7.3–41.7 mg/L, positive for the presence of opiates, 8 were tested positive for cannabinoids, and 2 were tested positive for benzodiazepines. Gastric contents of one deceased also contained 1.1 g/dL ethanol. 18- to 45-years (30 fatal cases)</td>
<td>(Shaﬁ et al. 2016)</td>
</tr>
<tr>
<td>Liver gastric contents</td>
<td>4.2–92.6 mg/kg, 9.9–349.6 mg/L, 17- to 45-years-old (7 cases)</td>
<td>(Shafi et al. 2016)</td>
</tr>
</tbody>
</table>
neurological status are essential. Additionally, supportive and symptomatic care should be provided according to the needs (Chyka et al. 2007), followed by identification and treatment of any psychiatric or medical conditions that may be simultaneous (Logan 2009; Logan et al. 2009). Particularly, the treatment of anxiety, agitation, seizures, and psychosis by the administration of short-action benzodiazepines or a low-dose of short-term antipsychotics, should be considered. Many patients may benefit from pharmacological aid for insomnia or sleep cycle dysregulation (Logan 2009; Logan et al. 2009, 2012). External cooling measures can be used for hyperthermia that may result from serotonin syndrome.

The benefit of using naloxone in a DXM intoxication is not clear; however, if the patient is sedated or comatose, particularly if there is respiratory depression, its use may be considered, given its low risk for adverse effects. Likewise, although the benefit of charcoal use is not proven, it can be considered in specific circumstances, especially if less than one hour since ingestion (Chyka et al. 2007). Intravenous fluids should be given as indicated.

Since DXMs abuse can occur using co-formulated preparations of cough sirup, checking for intoxication by these other drugs should be done and treatment should be directed according to the findings (Gunn et al. 2001; Woo and Hanley 2013); for example, if suspected co-ingestion of paracetamol, its levels should be measured and toxicity treated appropriately, with N-acetylcysteine (Brown et al. 2018).

Conclusions and future perspectives

DXM is widely available, present in approximately 140 prescription and nonprescription cough and cold medications (Chyka et al. 2007), and it is known to be safe and effective at therapeutic doses (Spangler et al. 2016). DXM has little recurrence of abuse (Spangler et al. 2016), has no significant addiction liability (El-Naby and Kamel 2015), and follows other hallucinogen abuse pattern with a peak of use at 19-years-old and a rapid decrease afterwards (Karch 2008; Karch and Drummer 2016). Nevertheless, reports show a decrease of abuse of OTC cough and cold medication containing DXM since 2006, and quite markedly since 2010, possible due to an increased awareness with FDA ‘Talk Paper’ issued in 2005 (Desai et al. 2006) and to a variety of education initiatives in the form of a mitigation plan lead by CHPA in 2010 (Spangler et al. 2016). Currently, DXM is not scheduled under the CSA (Banken and Foster 2008), and it is thought that restrictions over these OTC formulations access would mostly interfere with its legitimate use (Spangler et al. 2016).

When intoxication occurs, effects on central nervous system are predominant (Chyka et al. 2007), with other important symptoms emerging, such as nausea, vomiting, tachycardia, and hypertension (Kaplan et al. 2011; Spangler et al. 2016). Since DXM is usually not detected by routine toxicological screens, a high suspicion is required for its identification (El-Naby and Kamel 2015), thus enabling appropriate patient management, including supportive and symptomatic care (Chyka et al. 2007). Also, these patients should be checked for intoxication by other drugs that can have been co-ingested with DXM, such as acetaminophen or antihistamines (Woo and Hanley 2013), providing treatment accordingly.

DXM has a wide range of effects and its pharmacokinetics and pharmacodynamics are complex. The metabolism of DXM is affected by inter-individual variability, namely polymorphisms in genes encoding enzymes involved, as is the case for CYP2D6, the main enzyme involved (Meyer et al. 1990; Takashima et al. 2007). Also, these patients should be checked for intoxication by other drugs that can have been co-ingested with DXM, usually as substrates or inhibitors of the metabolic pathways (Coutts et al. 1994; Pope et al. 2004; Garnock-Jones 2011; Taylor et al. 2016; Collins 2018). Other, non-metabolic interactions have also been described and are relevant once DXM is usually not ingested alone (Chyka et al. 2007; Banken and Foster 2008; Brown et al. 2018), as they can precipitate a serotonin syndrome or a central nervous system depression (Dy et al. 2017; Baldo 2018; Moss et al. 2019).

DXM stimulates σ1R and blocks NMDA receptors, mechanism that may be underlying its cough suppressant properties (Brown et al. 2004), and may also be the basis for its anticonvulsant and neuroprotective effects (Chou et al. 1999; Shin et al. 2005). Additionally, σ1R activation is associated with antidepressant-like activity (Nguyen et al. 2014) and, when high doses of DXM are present, may induce a schizophrenic-like mental state (Martinak et al. 2017); these elevated DXM doses act on NMDA receptors, and can induce euphoria and hallucinogenic and dissociative effects, as seen with PCP and ketamine (Logan 2009; Logan et al. 2009, 2012). Some of these effects are also carried by DXM’s metabolites, and DXO, its main active metabolite, may be the major responsible compound for the psychotic and dissociative states (Miller 2005; Logan 2009; Logan et al. 2009, 2012). Serotonin enhancement contributes to its abuse
potential and to the risk of serotonin syndrome, that can increase with certain drug interactions (Chyka et al. 2007), as pointed above.

Taken together all these issues contribute concurrently to a diversity in DXM clinical and toxicological aspects, and better understanding these may help delineate strategic uses of this drug, considering its potential applications, allowing a more efficient and safe use of DXM (Gaedigk 2013). Moreover, CYP2D6 genotype analysis would be clinically very useful; however, it is not so simple given the big number of allelic variants and presence of structural and copy number variation. Also, even amongst individuals with the same genotype there is some important inter-individual variability due to other interfering factors, such as age, comorbidities, and concomitant therapies.

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References


