What Did My Patient Actually Take? An Overview of Dextromethorphan/Levorphanol Results

Accurate interpretation of dextromethorphan/levorphanol results should take into account the patient's prescription and over-the-counter (OTC) drug regimen and the specimen type being utilized. Review of drug test results should be supplemented by a conversation with the patient concerning recent drug use.

Dextromethorphan Overview

Dextromethorphan (DXM) is one the most used over-the-counter cough suppressants worldwide. It is found in more than 120 OTC cold medication formulations either as the sole ingredient or in combination with other drugs.[1] Aegis offers testing for dextromethorphan in urine and oral fluid. When dextromethorphan is detected, it does not necessarily indicate abuse of the drug. A patient may be temporarily using a dextromethorphan-containing drug for self-treatment of cough or cold symptoms, so further conversation with the patient is recommended, along with a holistic evaluation of the patient's history and current presentation. The concentration of dextromethorphan present in a sample cannot be used to determine the amount ingested. Time since ingestion, other drugs being metabolized concurrently, liver and kidney function, and extent of drug absorption are among the multiple clinical factors that preclude such a correlation. More information on this topic is available in the Aegis Clinical Reference Guide (see chapter titled, "Interpretation of Drug Test Results to Decipher Dose Adherence.")

Dextromethorphan Abuse

Approved by the Food and Drug Administration in the 1950s, dextromethorphan has a longstanding history of abuse, especially in the adolescent population.[2] While there are minimal side effects associated with DXM at therapeutic doses, high doses may yield hallucinogenic and euphoric effects.[1] Intentional misuse of DXM is referred to as "Robo-tripping" (in reference to the brand name Robitussin) or "skittling" (in reference to the brand name Coricidin).[1]

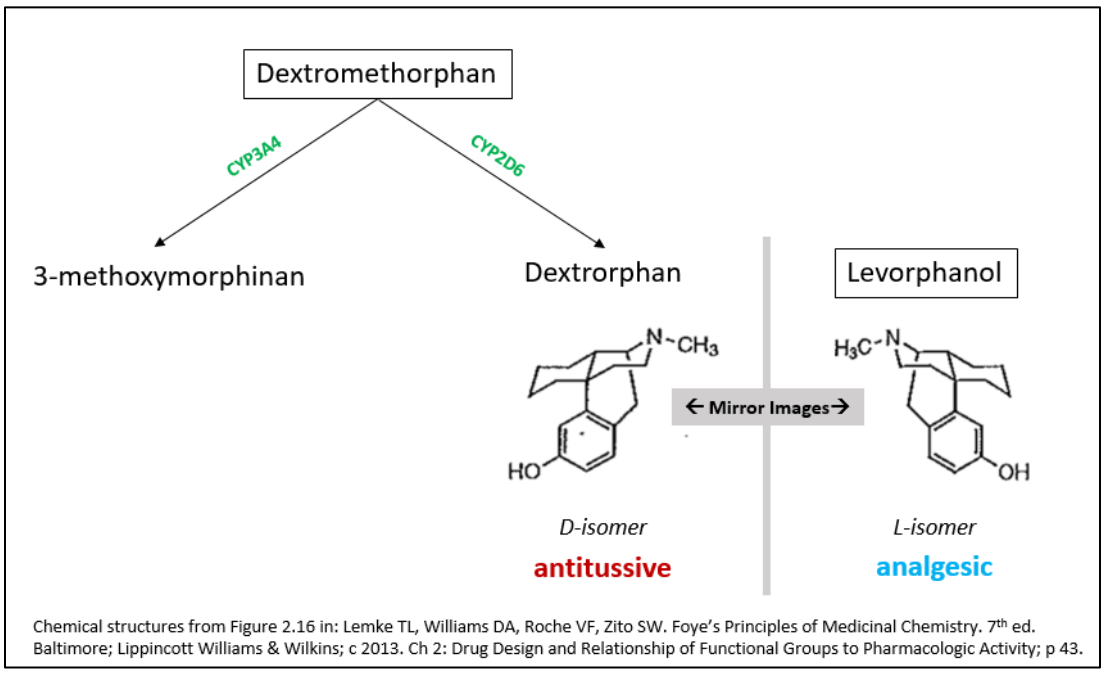
Abusers of the drug report altered time perception and visual hallucinations. Additionally, a series of four "plateaus" have been described: 1) mild stimulation, 2) euphoria and hallucinations, 3) distorted visual perceptions, and loss of motor coordination, and 4) dissociative sedation.[1] At high doses, DXM acts similarly to PCP (phencyclidine) and ketamine due to its antagonism of the N-methyl-d-aspartate (NMDA) receptor; this may explain the hallucinogenic and dissociative effects.[1-3] The agent exerts adrenergic effects by inhibiting catecholamine uptake, and it also acts as an agonist at serotonergic receptors.[4] Signs of intoxication may include hyperexcitability, ataxia, slurred speech, sweating, hypertension, and/or nystagmus. Toxic effects include irregular heartbeat, seizure, serotonin syndrome, and hyperthermia.[1-5]

DXM may be abused in the form of a tablet, gel, or liquid. Uncontrolled access (available as OTC) and minimal cost are two of the reasons it may be appealing to users as a drug of abuse.[1,2] Specific examples of OTC products containing DXM include Robitussin, Pediacare, Delsym, Vicks DayQuil and NyQuil, and Tylenol Cough & Cold along with several others.[6] DXM powder has been purchased through internet sources and deaths have been linked to its intentional ingestion.[1] It may also be sold for illicit use as a tablet containing both DXM and other drugs such as ecstasy or methamphetamine.[1]

Although DXM is abused by individuals of all ages, abuse tends to be more common among adolescents and college-aged persons.[2] According to the American Association of Poison Control Centers, there were 12,077 case mentions, 9,223 single exposures, and one death associated with DXM in 2016.[1] However, in 2017 there was a decline in toxic exposures with 11,931 case mentions, 8,986 single exposures, and no deaths reported.[1] The 2017 Monitoring the Future (MTF) Report estimated the annual prevalence of nonmedical use of cough and cold medicine among 8th, 10th, and 12th graders was 2.1%, 3.6%, 3.2% respectively.[1] Abuse of OTC cough and cold medicines to get high was reported to decrease overall from 2016 to 2017 when comparing the rates between the two years for the three grades combined.[7] According to the National Poison Data System (2000-2015), the annual rate of DXM cases reported tripled from 2000 to 2006 then plateaued from 2006-2015.[8] The use of this drug in the younger population is particularly concerning as research has shown that earlier initiation of drug use increases the likelihood of abuse and/or dependence in the future.[9] Several states have implemented age restrictions on the sale of dextromethorphan products, which is a positive step toward decreasing non-medical use of the drug in children and adolescents.

Dextromethorphan/Levorphanol Metabolism

Dextromethorphan is extensively metabolized by both CYP2D6 and CYP3A4 enzymes (refer to figure below), thus, potential for variation in metabolism due to both genetic differences and drug interactions exists.[10] Interestingly, dextrorphan, the major metabolite of dextromethorphan, is also the d-isomer of levorphanol (Levo-Dromoran®); this means the structures are mirror images of each other as shown below.[11,12] Despite their structural relationship, they vary in pharmacologic activity with dextrorphan being an active antitussive metabolite and levorphanol being a potent synthetic opioid analgesic.[11]



Chemical structures from Figure 2.16 in: Lemke TL, Williams DA, Roche VF, Zito SW. Foye's Principles of Medicinal Chemistry. 7th ed. Baltimore; Lippincott Williams & Wilkins; c 2013. Ch 2: Drug Design and Relationship of Functional Groups to Pharmacologic Activity; p 43.

Assessing Compliance with Dextromethorphan or Levorphanol Prescriptions

Aegis currently offers dextromethorphan testing as an add-on test in urine and oral fluid. Including 3-methoxymorphinan and dextrorphan in testing helps extend the period of detection of the drug and can also increase detection when metabolism may be altered physiologically or by other drugs. Dextromethorphan and

3-methoxymorphinan are both unique markers for dextromethorphan ingestion; their presence indicates recent ingestion of dextromethorphan. Dextrorphan may also indicate dextromethorphan use and will be used to assess compliance with dextromethorphan prescriptions. However, given that the liquid chromatography/tandem mass spectrometry analysis of dextrorphan is not isomeric, dextrorphan alone can indicate use of either dextromethorphan or levorphanol. When dextrorphan is present in the absence of one of the unique markers for dextromethorphan (dextromethorphan and/or 3-methoxymorphinan), then "Dextromethorphan/Levorphanol" will be reported as present. Thus, test results showing presence of dextrorphan alone are not exclusively indicative of specifically dextromethorphan or levorphanol use.

Clinicians wishing to assess levorphanol compliance should utilize urine testing rather than oral fluid. Levorphanol is extensively glucuronidated as a means of clearance from plasma.[14] Concentrations of this conjugated metabolite peak at more than five times the concentration of the unbound drug. Because only free and unbound drug crosses over into saliva from plasma, the glucuronidation pathway decreases the amount of detectable drug in oral fluid significantly. Glucuronidated drug passes freely into urine, however, and the conjugated metabolite is hydrolyzed during urine testing to detect the levorphanol parent drug.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References:

1. Dextromethorphan. U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control. Web site. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/index.html.
2. Romanelli F, Smith KM. Dextromethorphan Abuse: Clinical Effects and Management. *J Am Pharm Assoc*. 2009;49:e20-e27.
3. Desai S, Aldea D, Daneels E, Soliman M, Braksmajer AS, Kopes-Kerr CP. Chronic Addiction to Dextromethorphan Cough Syrup: A Case Report. *J Am Board Fam Med*. 2006;19(3):320-323.
4. Boyer EW. Dextromethorphan Abuse. *Pediatric Emergency Care*. 2004;20(12):858-863.
5. Logan BK, Goldfogel G, Hamilton R, Kuhlman J. Five Deaths Resulting From Abuse of Dextromethorphan Sold Over the Internet. *J Anal Toxicol*. 2009;33:99-103.
6. What is DXM? Stop Medicine Abuse. https://stopmedicineabuse.org/what-is-dxm/.
7. Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. Monitoring the Future National Survey Results on Drug Use, 1975-2017: Overview, Key Findings on Adolescent Drug Use. *The University of Michigan, Institute for Social Research*. 2018. https://eric.ed.gov/?id=ED589762
8. Karami S, Major JM, Calderon S, Mcaninch JK. Trends in Dextromethorphan Cough and Cold Products: 2000-2015 Nation Poison Data System Intentional Abuse Exposure Calls. *Clinical Toxicology*. 2018;56(7):656-663. doi.org/10.1080/15563650.2017.1416124.
9. Drugs, Brains, and Behavior: The Science of Addiction. National Institute on Drug Abuse Web site. http://www.drugabuse.gov/publications/science-addiction/drug-abuse-addiction.
10. Spanakis M, Vizirianakis IS, Mironidou-Tzouveleki M, Niopas I. A Validated SIM GC/MS Method for the Simultaneous Determination of Dextromethorphan and its Metabolites Dextrorphan, 3-Methoxymorphinan and 3-Hydroxymorphinan in Biological Matrices and its Application to In Vitro CYP2D6 and CYP3A4 Inhibition Study. *Biomed Chromatogr*. 2009; 23: 1131-37.
11. Baselt RC. Disposition of Toxic Drugs and Chemicals in Mman. 9th ed. Chemical Toxicology Institute, Foster City, CA. 2011.
12. Lemke TL, Williams DA, Roche VF, Zito SW. Foye's Principles of Medicinal Chemistry. 7th ed. Baltimore; Lippincott Williams &Wilkins; c 2013. Ch 2: Drug Design and Relationship of Functional Groups to Pharmacologic Activity; p 42-43.
13. Kikura-Hanajiri R, Kawamura M, Miyajima A, Sunouchi M, Goda Y. Chiral Analysis of Dextromethorphan/Levomethorphan and their Metabolites in Rat and Human Samples Using LC/MS/MS. *Anal Bioanal Chem*. 2011; 400: 165-174.
14. Dixon R, Crews T, Inturrisi C, Foley K. Levorphanol: pharmacokinetics and steady-state plasma concentrations in patients with pain. *Res Commun Chem Pathol Pharmacol*. July 1983;41(1):3-17