

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 1-I-04

Subject: Dextromethorphan Abuse
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Referred to: Reference Committee J
(Brooks F. Bock, MD, Chair)

1 Substitute Resolution 708 (I-03), introduced by the Florida Delegation and adopted at the 2003
2 American Medical Association (AMA) Interim Meeting, asked that our AMA study, in consultation
3 with the Food and Drug Administration (FDA), the U.S. Drug Enforcement Administration (DEA),
4 the over-the-counter (OTC) pharmaceutical industry, and other appropriate organizations, the status
5 of abuse of medications containing dextromethorphan among adolescents in the United States, with a
6 report back at the 2004 AMA Interim Meeting, including recommendations on dissemination of the
7 findings to physicians and the general public. Subsequently, Resolution 528, introduced by the
8 Illinois Delegation and adopted at the 2004 AMA Annual Meeting, asked that our AMA express
9 concern about the sale of bulk dextromethorphan to the general population and support legislation
10 outlawing this practice. The AMA's House of Delegates had previously raised concerns about the
11 misuse of dextromethorphan (Resolution 407, adopted at the 1997 Interim Meeting), and AMA staff
12 briefly addressed the issue of dextromethorphan abuse at that time.¹

13
14 This report summarizes the current status of dextromethorphan use and abuse, and offers
15 recommendations for appropriate AMA actions.

16
17 Methods

18
19 Literature searches were conducted in the MEDLINE and Lexis-Nexis databases for English-
20 language articles published between 1966 and October, 2004 using the search terms
21 "dextromethorphan," "dextrorphan," "Robitussin," "human," "toxicity," "adverse reaction," and
22 "abuse." One hundred seventy-six articles were retrieved for analysis. Additional citations were
23 culled from the bibliographies of these references. Web sites of the FDA, the DEA, the National
24 Institute on Drug Abuse, and the Consumer Healthcare Products Association (CHPA) also were
25 searched for information on abuse of dextromethorphan-containing products. Additionally, staff at
26 the FDA, DEA, and CHPA were consulted for insight and information.

27
28 Dextromethorphan Pharmacology

29
30 Dextromethorphan (*d*-3-methoxy-N-methylmorphinan) is the *dextro* isomer of levomethorphan, a
31 semisynthetic morphine derivative. Dextromethorphan has no agonist activity at opioid receptors, but
32 the drug acts centrally to elevate the threshold for coughing.²

33
34 Glutamate is found in high concentrations in the central nervous system (CNS) and exerts excitatory
35 effects on neurons throughout the CNS. Glutamate receptors are classified functionally as ligand-
36 gated ion channels or as G-protein-coupled (metabotropic) receptors.³ The ligand-gated ion channels
37 are further classified according to the identity of agonists that selectively activate each receptor

1 subtype.⁴ Dextromethorphan, and its metabolite dextrorphan, antagonize the N-methyl-D-aspartate
2 (NMDA) receptor subtype. Dextromethorphan binding sites in the CNS, however, are not limited to
3 the known NMDA sites; autoradiographic localization of ³H-dextromethorphan binding sites extends
4 beyond the distribution of NMDA-labeled sites.⁵

5
6 NMDA receptors mediate rapid synaptic transmission in the CNS. Dextromethorphan (150 mg)
7 acutely decreases the excitability of the human cerebral cortex.⁶ Activation of NMDA receptors also
8 is closely associated with synaptic plasticity, and the phenomenon of long-term potentiation, a
9 process believed to be important in learning and memory. Functioning NMDA receptors appear to be
10 essential for early development and experience-dependent-wiring of brain circuits.

11
12 Excessive activation of NMDA receptors can trigger Ca²⁺ influx in sufficient quantities to trigger
13 neuronal apoptosis and cause cell death (excitotoxicity). Additionally, NMDA receptors appear to play
14 a role in central pain mediation.⁷ In animal models of pain, dextromethorphan inhibits spinal cord
15 pain sensitization, and also inhibits the development of secondary cutaneous hyperalgesia after tissue
16 trauma.⁸

17
18 Pharmacokinetics of Dextromethorphan. Dextromethorphan undergoes O-demethylation to an active
19 metabolite dextrorphan, which like phenycyclidine (PCP) blocks the open channel of the NMDA
20 receptor, and in large enough doses can cause PCP-like dissociative effects.⁹ Dextrorphan has a
21 higher affinity than dextromethorphan for the NMDA site, and is comparable to ketamine in this
22 regard.¹⁰ In addition to producing PCP-like behavioral effects in animals, dextrorphan exhibits
23 anticonvulsant and neuroprotective properties in a variety of experimental models.¹¹

24
25 The metabolism of dextromethorphan to dextrorphan is mediated by cytochrome P-450 2D6
26 (CYP2D6), a genetically polymorphic enzyme in humans. The dextromethorphan-O-demethylation
27 reaction has been used as a probe (indicator) of *in vivo* CYP2D6 activity.¹¹ The human population is
28 divided into so-called extensive metabolizers (EM) or poor metabolizers (PM), based on their relative
29 CYP2D6 activity. Approximately 5% to 10% of Caucasian patients are deficient in CYP2D6 activity.
30 The half-life of dextromethorphan is relatively short in EMs (~3 hours) but may exceed 24 hours in
31 PMs.^{12,13} After oral administration of dextromethorphan to extensive metabolizers, the major
32 metabolite present in plasma is conjugated dextrorphan.^{14,15} Elimination half-life values for
33 dextrorphan have not been reported.

34
35 CYP3A4 and CYP3A5 form smaller amounts of the 3-hydroxy and 3-methoxy (morphinan)
36 derivatives. The CYP3A pathways may assume increasing importance when toxic doses are
37 consumed, in individuals who consume inhibitors of CYP2D6 (eg, quinidine), and in poor
38 metabolizers. Because of differences in individual pharmacokinetics, the effects of large doses of
39 dextromethorphan reported by PMs may differ qualitatively from those experienced by EMs.¹⁶

40 41 Dextromethorphan-containing Products

42
43 Regulatory Status. Over-the-counter (OTC) dextromethorphan-containing cough and cold
44 preparations are regulated by an OTC Drug Monograph. This monograph was initially offered as a
45 proposed rule in 1976 based on recommendations of the FDA Advisory Review Panel on OTC Cold,
46 Cough, Allergy, Bronchodilator and Antiasthmatic Products. The monograph establishes conditions
47 under which such products are generally recognized as safe and effective and not misbranded.¹⁷ In
48 reaching its conclusion that dextromethorphan was safe and effective for use as an antitussive, the
49 Advisory Panel reviewed 23 studies on the toxicity and efficacy of dextromethorphan, including
50 double-blind crossover studies of experimentally induced cough, controlled studies in pathologic
51 cough using both subjective and objective endpoints, and uncontrolled subjective studies in a variety

1 of disease states associated with cough. Many of these studies predate the MEDLINE database. A
2 comprehensive review of the pre-MEDLINE data supporting the antitussive efficacy of
3 dextromethorphan is available.¹⁸ The Advisory Panel concluded that dextromethorphan is comparable
4 to codeine on a mg-to-mg basis for cough suppression, and “because of its low order of toxicity” is
5 probably the safest antitussive presently available. After the administrative record was reopened in
6 1980, a tentative final monograph covering antitussives was proposed in 1983.¹⁹ The final antitussive
7 monograph was published in 1987.²⁰ The final monograph was amended in 1993 to include a
8 warning about the use of dextromethorphan in patients taking monoamine oxidase inhibitors.²¹
9

10 Dextromethorphan Hydrobromide. At least 12 OTC products contain dextromethorphan
11 hydrobromide. These products are available in various formulations including gelcaps (15 or 30 mg);
12 lozenges (5 or 7.5 mg); liquids (7.5 to 30 mg/5 ml); syrups (7.5 or 10 mg/5 ml); or as an extended-
13 release oral suspension (30 mg).²²
14

15 Combination Products. More than 100 antitussive combination products containing
16 dextromethorphan are available over-the-counter in combination with decongestants
17 (pseudoephedrine 10 to 60 mg or phenylephrine) and/or analgesics (acetaminophen 108 to 1000 mg),
18 and/or antihistamines (brompheniramine; chlorpheniramine; diphenhydramine; doxylamine;
19 pyrilamine), and/or an expectorant (guanifenesin).²²
20

21 Abuse of combination products introduces additional hazards, including increased blood pressure
22 from pseudoephedrine; potential hepatotoxicity from acetaminophen; and CNS, cardiovascular, and
23 anticholinergic toxicity from antihistamines.²³
24

25 Clinical Uses

26

27 At recommended doses, dextromethorphan is well tolerated and produces few adverse reactions,
28 primarily gastrointestinal discomfort or nausea in susceptible individuals.²⁴ As an antitussive, the
29 recommended daily dosage for adults and children aged 12 years and older is 60 to 120 mg in 4
30 divided doses.
31

32 A recent Cochrane review questioned the effectiveness of OTC medications as antitussives in the
33 ambulatory setting, but did not conclude that dextromethorphan was ineffective.^{25,26} The American
34 Academy of Pediatrics warns against the use of dextromethorphan-containing products in children
35 because of adverse reactions, including case reports of adverse reactions and fatalities, and lack of
36 data regarding antitussive effectiveness in children.²⁷ Results of other trials conducted in children
37 support this stance.²⁸⁻³⁰ There is little evidence to support age-based dosing practices, although a
38 recent study suggested that a dextromethorphan dose of 0.5 mg/kg should be considered in future
39 assessments of the antitussive effect of dextromethorphan in children.^{27,31}
40

41 Since dextromethorphan achieved OTC status, several studies have been published on its antitussive
42 efficacy, including some that were conducted in patients with chronic cough, even though
43 dextromethorphan is indicated for acute, uncomplicated cough. Studies examining single doses of
44 dextromethorphan in chronic cough and in patients with upper respiratory tract infections (URTI)
45 have produced mixed results.³²⁻³⁴ A longer-term, office-based practice study that relied on patient
46 report found that dextromethorphan and codeine were comparable in patients with uncomplicated
47 URIs.³⁵ In a placebo-controlled, double-blind trial, daytime use of dextromethorphan alone in
48 patients with acute URTI was no more effective than placebo.³⁶ Another double-blind, crossover trial
49 comparing dextromethorphan with codeine in patients with chronic stable cough found that
50 dextromethorphan and codeine, at a dose of 20 mg, were similarly effective in reducing cough
51 frequency.³⁷ In subjects with artificially-induced cough, dextromethorphan 30 mg was more effective

1 than placebo, and comparable to codeine 20 mg.³⁸ In a meta-analysis published by the manufacturer
2 of an OTC dextromethorphan-containing cough syrup, single doses of dextromethorphan 30 mg were
3 more effective than placebo in patients with uncomplicated URTI. Antitussive effects were measured
4 by computerized cough acquisition and analysis.³⁹

5
6 Dextromethorphan is being investigated as an adjunctive or preventive analgesic in reducing
7 postoperative pain; as a treatment for bone or neuropathic pain, including diabetic peripheral
8 neuropathy; and, in the treatment of phantom limb pain, where hyperexcitability of NMDA receptors
9 may play a role.^{7,8,40-48} Clinical trials of dextromethorphan's possible neuroprotective effects have
10 been largely disappointing.

11 Information on Abuse Trends

12
13
14 Abuse of dextromethorphan among youth was first reported more than 30 years ago.⁴⁹ Subsequently,
15 reports of sporadic abuse of dextromethorphan have surfaced, including isolated case reports of
16 overdose and death, and attention has been devoted to the issue in the popular press and media.⁵⁰⁻⁵⁴

17
18 In the early 1990s, the FDA Advisory Committee on Drug Abuse (since renamed the Drug Safety and
19 Risk Management Advisory Committee) held hearings on dextromethorphan abuse in response to
20 certain community epidemics. The Committee issued recommendations for community-based,
21 educational interventions.

22
23 The December 2001 Advance Report of the Community Epidemiology Work Group (CEWG) noted
24 evidence of increasing abuse of dextromethorphan-containing products in adolescents located in
25 Denver, Detroit, Seattle, and Minneapolis-St. Paul, and in Texas.⁵⁵ Sponsored by the National
26 Institutes of Health and the National Institute on Drug Abuse, CEWG is a network of epidemiologists
27 and researchers in the United States that meets biannually to review current and emerging substance
28 abuse problems. Reports of dextromethorphan abuse originated from community-based treatment
29 programs, school personnel, hospitals, poison control centers, and medical examiners. Subsequent
30 CEWG reports have not specifically noted dextromethorphan abuse except for its appearance in
31 products that were represented as methylene dioxamphetamine (MDA) or its methylated derivative
32 (MDMA or "Ecstasy").

33
34 The Drug Abuse Warning Network (DAWN), operated by the Substance Abuse and Mental Health
35 Services Administration (SAMHSA) Office of Applied Studies (OAS), includes data on drug-related
36 emergency room visits, with estimates for the nation and 21 metropolitan areas, as well as drug-
37 related deaths for 40 metropolitan areas. Publicly reported DAWN data do not specifically identify
38 dextromethorphan, but rely on a broader category of "respiratory" agents, including upper respiratory
39 combinations or respiratory agents not specified in other categories. These data do not permit
40 evaluation of dextromethorphan abuse trends.

41
42 Results of other school surveys and reports from individual poison control centers also support an
43 increasing trend of abuse; however, reliable estimates of dextromethorphan abuse are unavailable.⁵⁶⁻⁵⁸
44 In an effort to compile current data about dextromethorphan abuse, the CHPA informed the AMA
45 that it intends to conduct a more comprehensive national survey of poison control centers and will
46 share that information with our AMA (personal communication, Lorna Totman, CHPA, September
47 2004). At the time this report was finalized, these data were not available.

1 Dextromethorphan Intoxication

2
3 Dextromethorphan intoxication also may be referred to as "Robo-ing," a term derived from a common
4 form of dextromethorphan--Robotussin®. Among combination products, Coricidin HBP® Cough and
5 Cold tablets (CCC or triple C's) have been identified as subject to abuse.⁵⁹ Recently, some abusers of
6 dextromethorphan have opted for a powdered form of the drug because of the large volumes of cough
7 syrup that need to be ingested to achieve intoxication. Bulk sales of powdered dextromethorphan
8 hydrobromide from chemical supply companies and the publication of a recipe-like extraction
9 procedure used to separate dextromethorphan from cough syrups have led the DEA to increase its
10 field monitoring of dextromethorphan-based activities.

11
12 Controlled dose-response information is not available. Web sites dedicated to dextromethorphan
13 abuse describe an apparent dose-response to the drug in the form of "plateaus."^{60,61} The Drug and
14 Human Performance Fact Sheet from the National Highway Transportation Safety Administration
15 contains similar information. Recreational doses are divided into (1) threshold dose, 80 to 100 mg;
16 (2) "light" dose, 100 to 200 mg; (3) "common" dose, 200 to 400 mg; (4) "strong" dose, 400 to 600
17 mg; and (5) "heavy" (dissociative) dose, 600 to 1500 mg.⁶²

18
19 Based on these anecdotal reports, dextromethorphan users describe a set of distinct dose-dependent
20 phases ranging from a mild stimulant effect at low doses to altered sensory perceptions to complete
21 dissociative effects (mind out of body-like experiences) at larger doses. The effects attributable to
22 dextromethorphan typically last 6 to 8 hours in individuals with normal metabolizing capacity.

23
24 Dextromethorphan intoxication also may be confused with the effects of phencyclidine, and
25 dextromethorphan has been reported to result in a false-positive drug screen for phencyclidine.^{63,64}

26 Current Activities Addressing Dextromethorphan Abuse

27
28
29 The CHPA and the Partnership for a Drug-Free America (PDFA) are involved in an educational
30 campaign directed at the various audiences that are in position to influence young people's attitudes
31 toward drug abuse or to recognize when a substance abuse problem might occur. Specifically, the
32 CHPA and PDFA are reaching out to parents, educators, health care and substance abuse
33 professionals, poison prevention centers, and law enforcement entities. An educational brochure
34 (http://www.drugfreeamerica.org/dxm/dxm_brochure.pdf) for parents is being distributed, and a
35 parent-oriented Web site (<http://www.drugfreeamerica.org/dxm/>) is operational.

36 Sale of Dextromethorphan

37
38
39 Bulk dextromethorphan is available for sale from chemical supply companies. The FDA does not
40 regulate the bulk sale of chemical ingredients such as dextromethorphan, which are approved for use
41 as OTC products. The FDA would have jurisdiction if individuals were purchasing bulk
42 dextromethorphan and then reselling dosage forms that were not properly labeled, but the Agency is
43 unaware of any prosecutions that relied on this approach for dextromethorphan, or any other OTC
44 product. One potential remedy to bulk sales of this substance to individuals would rely on the DEA
45 scheduling bulk dextromethorphan as a controlled substance. This action would complicate
46 commerce involving legitimate manufacturers of dextromethorphan-containing products.
47 Alternatively, the Federal Trade Commission could seek enforcement actions against purveyors who
48 supply bulk dextromethorphan to individuals via the Internet.

1 Some state legislatures have considered banning the sale of dextromethorphan-containing products to
2 those under the age of 18 years, and some pharmacies have independently taken steps to limit the
3 number of Coricidin HBP® tablets that can be purchased.

4
5 Summary and Comment

6
7 Dextromethorphan is a widely used OTC cough suppressant available alone or in combination with
8 other products that are used for symptomatic relief by patients with various upper respiratory
9 ailments. The American Academy of Pediatrics cautions against the use of dextromethorphan-
10 containing products in children. The ability of large doses of dextromethorphan to cause altered
11 consciousness was recognized soon after it became available over-the-counter and was described
12 more than 30 years ago.

13
14 Consuming large amounts of dextromethorphan from combination products that include
15 acetaminophen, pseudoephedrine, or antihistamines is more dangerous because of the ancillary toxic
16 effects of these other compounds. The availability of bulk dextromethorphan creates an additional
17 concern for dealing with the increasing trend for abuse. Repackaging of bulk powdered
18 dextromethorphan for resale as dextromethorphan or as counterfeit PCP or Ecstasy may be a criminal
19 act subject to the jurisdiction of either the FDA (misbranding) or the DEA (counterfeit controlled
20 substance).

21
22 Potential remedies include states prohibiting or limiting the sale of dextromethorphan-containing
23 products to minors; increasing the penalties for misbranded use; requiring registration and
24 cataloguing of mail order and Internet-based sales; reclassifying bulk dextromethorphan as a
25 controlled substance; and the expanded use of traditional educational campaigns.

26
27 RECOMMENDATIONS

28
29 The Council on Scientific Affairs recommends that the following statements be adopted in lieu of
30 Resolution 708 (I-03) and that the remainder of this report be filed:

- 31
- 32 1. That our AMA recommend that the Federal Trade Commission consider taking actions against
33 purveyors of bulk dextromethorphan for sale to individuals, particularly those committing unfair
34 or deceptive acts in conducting business over the Internet. **(Directive to Take Action)**
 - 35
36 2. That our AMA assist the Consumer Healthcare Products Association and the Partnership for a
37 Drug-Free America in publicizing their educational efforts and resources on dextromethorphan
38 abuse. **(Directive to Take Action)**
 - 39
40 3. That our AMA support legislation preventing the over-the-counter sale of dextromethorphan
41 products to individuals under the age of 18. **(Directive to Take Action)**
 - 42
43 4. That this report be publicized by our AMA and be made readily available to physicians who
44 treat adolescents and to the public. **(Directive to Take Action)**
 - 45
46 5. That our AMA monitor emerging data on the extent of dextromethorphan abuse and respond
47 as appropriate. **(Directive to Take Action)**

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