

REPORT OF COUNCIL ON SCIENTIFIC AFFAIRS

The following report was presented by Melvyn L. Sterling, MD, Chair:

1. DEXTROMETHORPHAN ABUSE

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS AND REMAINDER OF REPORT FILED

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

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

METHODS

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

DEXTROMETHORPHAN PHARMACOLOGY

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

Glutamate is found in high concentrations in the central nervous system (CNS) and exerts excitatory effects on neurons throughout the CNS. Glutamate receptors are classified functionally as ligand-gated ion channels or as G-protein-coupled (metabotropic) receptors. The ligand-gated ion channels are further classified according to the identity of agonists that selectively activate each receptor subtype. Dextromethorphan, and its metabolite dextrorphan, antagonize the N-methyl-D-aspartate (NMDA) receptor subtype. Dextromethorphan binding sites in the CNS, however, are not limited to the known NMDA sites; autoradiographic localization of ³H-dextromethorphan binding sites extends beyond the distribution of NMDA-labeled sites.

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

Excessive activation of NMDA receptors can trigger Ca^{2+} influx in sufficient quantities to trigger neuronal apoptosis and cause cell death (excitotoxicity). Additionally, NMDA receptors appear to play a role in central pain mediation. In animal models of pain, dextromethorphan inhibits spinal cord pain sensitization, and also inhibits the development of secondary cutaneous hyperalgesia after tissue trauma.

Pharmacokinetics of Dextromethorphan

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

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

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

DEXTROMETHORPHAN-CONTAINING PRODUCTS

Regulatory Status

Over-the-counter dextromethorphan-containing cough and cold preparations are regulated by an OTC Drug Monograph. This monograph was initially offered as a proposed rule in 1976 based on recommendations of the FDA Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. The monograph establishes conditions under which such products are generally recognized as safe and effective and not misbranded. In reaching its conclusion that dextromethorphan was safe and effective for use as an antitussive, the Advisory Panel reviewed 23 studies on the toxicity and efficacy of dextromethorphan, including double-blind crossover studies of experimentally induced cough, controlled studies in pathologic cough using both subjective and objective endpoints, and uncontrolled subjective studies in a variety of disease states associated with cough. Many of these studies predate the MEDLINE database. A comprehensive review of the pre-MEDLINE data supporting the antitussive efficacy of dextromethorphan is available. The Advisory Panel concluded that dextromethorphan is comparable to codeine on a mg-to-mg basis for cough suppression, and "because of its low order of toxicity" is probably the safest antitussive presently available. After the administrative record was reopened in 1980, a tentative final monograph covering antitussives was proposed in 1983. The final antitussive monograph was published in 1987. The final monograph was amended in 1993 to include a warning about the use of dextromethorphan in patients taking monoamine oxidase inhibitors.

Dextromethorphan Hydrobromide

At least 12 OTC products contain dextromethorphan hydrobromide. These products are available in various formulations including gelcaps (15 or 30 mg); 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-release oral suspension (30 mg).

Combination Products

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

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

CLINICAL USES

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

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

Since dextromethorphan achieved OTC status, several studies have been published on its antitussive efficacy, including some that were conducted in patients with chronic cough, even though dextromethorphan is indicated for acute, uncomplicated cough. Studies examining single doses of dextromethorphan in chronic cough and in patients with upper respiratory tract infections (URTI) have produced mixed results. A longer-term, office-based practice study that relied on patient report found that dextromethorphan and codeine were comparable in patients with uncomplicated URIs. In a placebo-controlled, double-blind trial, daytime use of dextromethorphan alone in patients with acute URTI was no more effective than placebo. Another double-blind, crossover trial comparing dextromethorphan with codeine in patients with chronic stable cough found that dextromethorphan and codeine, at a dose of 20 mg, were similarly effective in reducing cough frequency. In subjects with artificially-induced cough, dextromethorphan 30 mg was more effective than placebo, and comparable to codeine 20 mg. In a meta-analysis published by the manufacturer of an OTC dextromethorphan-containing cough syrup, single doses of dextromethorphan 30 mg were more effective than placebo in patients with uncomplicated URTI. Antitussive effects were measured by computerized cough acquisition and analysis.

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

INFORMATION ON ABUSE TRENDS

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

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

The December 2001 Advance Report of the Community Epidemiology Work Group (CEWG) noted evidence of increasing abuse of dextromethorphan-containing products in adolescents located in Denver, Detroit, Seattle, and Minneapolis-St. Paul, and in Texas. Sponsored by the National Institutes of Health and the National Institute on

Drug Abuse, CEWG is a network of epidemiologists and researchers in the United States that meets biannually to review current and emerging substance abuse problems. Reports of dextromethorphan abuse originated from community-based treatment programs, school personnel, hospitals, poison control centers, and medical examiners. Subsequent CEWG reports have not specifically noted dextromethorphan abuse except for its appearance in products that were represented as methylene dioxamphetamine (MDA) or its methylated derivative (MDMA or "Ecstasy").

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

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

DEXTROMETHORPHAN INTOXICATION

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

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

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

Dextromethorphan intoxication also may be confused with the effects of phencyclidine, and dextromethorphan has been reported to result in a false-positive drug screen for phencyclidine.

CURRENT ACTIVITIES ADDRESSING DEXTROMETHORPHAN ABUSE

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

SALE OF DEXTROMETHORPHAN

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

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

SUMMARY AND COMMENT

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

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

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

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following be adopted and that the remainder of this report be filed:

1. That our AMA recommend that the Federal Trade Commission consider taking actions against purveyors of bulk dextromethorphan for sale to individuals, particularly those committing unfair or deceptive acts in conducting business over the Internet.
2. That our AMA assist the Consumer Healthcare Products Association and the Partnership for a Drug-Free America in publicizing their educational efforts and resources on dextromethorphan abuse.
3. That our AMA support legislation preventing the over-the-counter sale of dextromethorphan products to individuals under the age of 18.
4. That this report be publicized by our AMA and be made readily available to physicians who treat adolescents and to the public.
5. That our AMA monitor emerging data on the extent of dextromethorphan abuse and respond as appropriate.