Dextromethorphan

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SaeRam Oh, Suneil Agrawal, Sarah Sabir, Preeti Patel, Alan Taylor

Continuing Education Activity

Dextromethorphan is a centrally acting, nonopioid antitussive widely used for cough suppression and increasingly recognized for its therapeutic potential in neuropsychiatric care. Commonly found in over-the-counter cough and cold products, it has multiple central nervous system effects, including *N*-methyl-D-aspartate receptor antagonism and sigma-1 receptor agonism. These properties support its FDA-approved use for pseudobulbar affect when combined with quinidine and for major depressive disorder when combined with bupropion, highlighting the importance of understanding its mechanisms and clinical applications.

This activity provides a focused review of dextromethorphan, covering pharmacology, pharmacokinetics, therapeutic indications, and key safety considerations. The activity also reviews factors affecting metabolism, including cytochrome P450 2D6 variability, clinically relevant drug interactions, and the risk of serotonin syndrome, offering guidance for safe and effective clinical use. Additionally, recognition and management of misuse and overdose are addressed, including common clinical presentations and recommended interventions. By examining these aspects, healthcare professionals are equipped with the knowledge needed to optimize patient care and ensure the responsible use of dextromethorphan in both cough management and emerging neuropsychiatric therapies.

Objectives:

- Apply evidence-based indications for dextromethorphan in cough suppression, pseudobulbar affect, and major depressive disorder.
- Assess patients for risk factors related to serotonin syndrome, drug interactions, and metabolic variability.
- Differentiate normal and abnormal responses to dextromethorphan therapy, including expected therapeutic effects versus adverse reactions.
- Strategize with the interprofessional healthcare team to develop protocols for early recognition, management, and follow-up of dextromethorphan-related adverse events.

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Indications

Dextromethorphan is a centrally acting antitussive and a nonopioid morphinan derivative. Dextromethorphan also demonstrates additional neurologic and psychotropic applications beyond its role in cough suppression. Since the US Food and Drug Administration (FDA) approved dextromethorphan in 1958, its clinical use has expanded. The expanded therapeutic indications for dextromethorphan now include the treatment of pseudobulbar affect (PBA) when combined with quinidine. Additionally, the medication is used in a fixed-dose combination with bupropion for the treatment of major depressive disorder.

FDA-Approved Indications

Antitussive: Dextromethorphan was approved by the FDA in 1958 as a nonopioid antitussive.

Pseudobulbar affect: In 2010, the FDA approved the use of dextromethorphan combined with quinidine for the treatment of PBA. PBA is a neurologic dysfunction of emotional expression characterized by outbursts of crying or laughing inappropriately and disproportionately to mood. Neurological diseases, including traumatic brain injury, multiple sclerosis, amyotrophic lateral sclerosis, and brain tumors, are associated with PBA. The pathology of PBA is still incompletely understood. Still, the leading hypothesis is that it results from a loss of descending cortical control over brainstem motor nuclei and the cerebellum, thereby disrupting inhibitory mechanisms for motor control of emotional expression.

Major depressive disorder: The fixed-dose combination of dextromethorphan 45 mg and bupropion 105 mg is FDA-approved for adults with major depressive disorder (MDD). Clinical data support its rapid antidepressant effect, which is believed to be related to dextromethorphan's activity at multiple central nervous system (CNS) targets, including *N*-methyl-D-aspartate (NMDA) receptors and sigma (σ)-1 receptors, although the precise mechanism remains unclear. This pharmacologic profile differentiates it from conventional monoaminergic antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Off-Label Uses

Many other potential therapeutic uses for dextromethorphan are currently under investigation in clinical studies. Most of these uses exploit dextromethorphan's neuroprotective properties, as mentioned below.

- Stroke: Studies have shown that dextromethorphan has a role in improving some neurological and psychiatric complications, though not necessarily overall functional outcomes.[11]
- Traumatic brain injury: Although the effects are limited, proposed mechanisms include activation of NMDA and σ-1 receptors, conferring neuroprotection.

- Seizure: Some clinical reports indicate efficacy for refractory seizures; overdose cases highlight risks such as status epilepticus.[12]
- Analgesia: Analgesic effects are studied for cancer-related, postoperative, neuropathic, and gastrointestinal pain. Dextromethorphan may be valuable as an opioid-sparing medication in postoperative settings.[13][14][15]
- Methotrexate neurotoxicity: Dextromethorphan showed complete resolution of neurological deficits associated with methotrexate toxicity in a case series.[16][17][18]
- Parkinson disease: Studies have reported amelioration of primary Parkinson disease symptoms. Dextromethorphan may be effective in levodopa-induced dyskinesia; further research is required.[19]
- Autism: Data on behavioral improvement are contradictory and under further evaluation.[20]
- Pulmonary fibrosis: Recent translational studies suggest potential antifibrotic properties of dextromethorphan, and early clinical trials are exploring the drug as a treatment for progressive pulmonary fibrosis.[21][22]

This summary reflects the expanding clinical interest in dextromethorphan beyond its traditional use, supported by emerging evidence of diverse pharmacological effects.

Mechanism of Action

Dextromethorphan is a synthetic dextrorotatory morphinan derivative structurally related to levorphanol, and its primary active metabolite is dextrorphan. Although occasionally described as a “codeine analog,” it lacks the phenanthrene structure of classical opioids and has minimal mu (μ)-opioid receptor activity. The precise antitussive mechanism of dextromethorphan remains incompletely defined. Still, current evidence suggests involvement of brainstem pathways regulating the cough reflex, including the nucleus tractus solitarius, where vagal afferents terminate. Dextromethorphan also acts as an agonist at the σ-1 receptor, a chaperone protein that modulates neuronal excitability, and this effect is thought to contribute to its cough-suppressing effects, independent of opioid pathways. The drug is lipophilic, contains an ionizable amine group, and engages multiple CNS targets in a dose-dependent manner.

Although structurally similar to opioids, dextromethorphan does not directly act on the μ-, kappa (κ)-, or delta (δ)receptors, which are responsible for the typical CNS effects of opioid agonists. Dextromethorphan primarily acts as a noncompetitive antagonist at NMDA receptors; however, studies have identified multiple additional targets for both dextromethorphan and its active metabolite, dextrorphan. These include high-affinity σ-1 receptor agonism, which contributes to its antidepressant-like effects; inhibition of nicotinic acetylcholine receptor subtypes (α3β4, α4β2, and α7); inhibition of serotonin and norepinephrine transporters; and blockade of voltage-gated calcium channels. This multimodal pharmacology underlies dextromethorphan’s diverse clinical effects, including cough suppression, neuroprotection, treatment of PBA, and rapid antidepressant properties. In comparison, opioid antitussives such as codeine primarily act through μ-opioid

receptors and carry a risk of greater dependence and respiratory depression. Peripherally acting agents, such as benzonatate, work by anesthetizing stretch receptors in the respiratory tract rather than by altering central neural pathways.

Pharmacokinetics

Absorption: Dextromethorphan has low oral bioavailability in the general population because of extensive first-pass hepatic metabolism by cytochrome P450 2D6 (CYP2D6). In CYP2D6 extensive metabolizers, the oral bioavailability of dextromethorphan is low. A single 30 mg oral dose has a median elimination half-life of approximately 2 to 3 hours, whereas CYP2D6 poor metabolizers (seen in ~8%–10% of some populations) have substantially increased systemic exposure, with oral bioavailability reported to be markedly higher (up to ~60%–80% in some studies); a prolonged half-life on the order of approximately 15 to 20 hours; and several-fold higher plasma concentrations of the parent drug.

Distribution: Dextromethorphan and its metabolites are lipophilic and distribute into the CNS, although the extent of CNS penetration depends on CYP2D6 metabolic status. The major circulating metabolite, dextrorphan-*O*-glucuronide, is highly polar and permanently charged, limiting its permeability across the blood-brain barrier.

Metabolism: Dextromethorphan is primarily metabolized in the liver through *O*-demethylation by CYP2D6 to produce dextrorphan, its principal active metabolite. Dextrorphan undergoes further metabolism via uridine diphosphate-glucuronosyltransferase enzymes to form dextrorphan-*O*-glucuronide, which accounts for approximately 98% of circulating dextrorphan in plasma. A secondary metabolic pathway involves cytochrome CYP3A4, which converts dextromethorphan to 3-methoxymorphinan. CYP2D6 phenotype is the primary determinant of exposure: ultrarapid and extensive metabolizers show rapid clearance of the parent drug, whereas poor metabolizers exhibit markedly reduced clearance and prolonged half-life.

Excretion: Dextromethorphan and its metabolites are eliminated mainly via the kidneys, predominantly as glucuronide and sulfate conjugates. Less than 1% of the parent compound is excreted unchanged in urine in extensive metabolizers.

Administration

Available Dosage Forms and Strengths

Dosing and administration of dextromethorphan primarily occur via the oral route. Several formulations are available for this administration, as mentioned below.

- Combination liquid cough syrups: The common over-the-counter (OTC) formulation contains 15 mg/5 mL of dextromethorphan. The recommended adult dosage is 2 tsp (10 mL) every 4 hours.

- Sustained-release cough syrup suspensions: These OTC formulations contain 30 mg/5 mL of dextromethorphan.
- Liquid-filled capsules: These capsules contain 15 mg or 30 mg doses of dextromethorphan.
- Oral strips: These strips contain 7.5 mg or 15 mg of dextromethorphan.
- Lozenges: These lozenges contain 5 mg, 7.5 mg, or 10 mg of dextromethorphan.

The recommended dosage for dextromethorphan is 0.5 mg/kg up to 30 mg, administered 3 or 4 times daily. Some animal studies have suggested that achieving the potential neuroprotective effects requires doses higher than those typically used for antitussive effects (60–120 mg/d).

Adult Dosage

Antitussive: The typical adult dosage is 10 mg to 20 mg every 4 hours or 30 mg every 6 to 8 hours, not exceeding 120 mg in 24 hours.

Pseudobulbar affect: The recommended dosage of dextromethorphan/quinidine is 1 capsule containing 20 mg of dextromethorphan and 10 mg of quinidine, taken once daily for 7 days, followed by 1 capsule every 12 hours as tolerated.

Major depressive disorder: For MDD, the fixed-dose combination of dextromethorphan/bupropion is initiated as 1 tablet containing 45 mg of dextromethorphan and 105 mg of bupropion once daily for 3 days. If tolerated, the dose is increased to 1 tablet twice daily, not to exceed 2 tablets per day. All labeled contraindications and precautions must be followed as per the prescribing information.

Specific Patient Populations

Hepatic impairment: The manufacturer provides no specific dose-adjustment recommendations for patients with hepatic impairment; therefore, the drug should be used with caution in this population.

Renal impairment: The manufacturer provides no specific dose-adjustment recommendations for patients with renal impairment; therefore, the drug should be used with caution in this population.

Pregnancy considerations: Dextromethorphan is a former FDA pregnancy category C medication and is mainly metabolized in the liver via CYP2D6 and CYP3A, both of which exhibit increased activity in pregnant women. Standard therapeutic doses of dextromethorphan are generally considered acceptable for use in pregnant patients; however, alcohol-containing dextromethorphan formulations should be avoided during pregnancy.

Breastfeeding considerations: Dextromethorphan and its active metabolite are excreted in very low amounts in breast milk and are not expected to cause adverse effects in infants. Nonetheless, it is recommended that dextromethorphan products with high alcohol content be avoided.

Pediatric patients: The safety and efficacy of dextromethorphan in infants and very young children (aged 4 or younger) have not been established in systemic clinical trials. According to the American College of Chest Physicians, in pediatric patients aged 1 to 18 with cough due to common cold, honey may provide greater relief of cough symptoms than no treatment, diphenhydramine, or placebo; however, it is not more effective than dextromethorphan. Infants younger than 1 year should not be given honey, and dextromethorphan is not recommended for the treatment of cough in children younger than 2 years.

Older patients: The American Geriatrics Society (AGS) Beers Criteria considers dextromethorphan/quinidine combinations for use with caution in older adults due to cardiac risks associated with the quinidine component (eg, QT prolongation), potential drug-drug interactions, and CNS adverse effects. In older adults, minimize the use of multiple CNS-active agents, review concomitant serotonergic/opioid medications, and monitor for increased sedation, falls, and cognitive effects.

Adverse Effects

Adverse effects from cough suppressants are rare. The most commonly reported reactions include nausea and gastrointestinal discomfort, with drowsiness and dizziness also occurring in some patients.

Astudy showed that at high doses (>4 mg/kg), up to 64% of patients experienced euphoria, and some developed various CNS effects such as visual hallucinations and persecutory delusions. In addition, these episodes were associated with agitation, leading to patient management difficulties.

The most common adverse effects in this study were a sensation of being "drunk" or "high" (20%), nausea and vomiting (17%), nystagmus (15%), and dizziness (15%). Most adverse effects resolved within a day of the final dose, and no cardiorespiratory compromise was reported. Serum dextromethorphan levels exceeding 400 ng/mL were observed in 87.5% of patients with these adverse effects. Additionally, more than 60% of patients who experienced adverse effects with dextromethorphan had serum levels exceeding 120 ng/mL and brain levels exceeding 700 ng/g.

Drug-Drug Interactions

Monoamine oxidase inhibitors: Dextromethorphan must not be used with monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, isocarboxazid, selegiline, linezolid, or methylene blue, as the combination can trigger life-threatening serotonin syndrome. A 14-day washout period is required after discontinuing an MAOI before dextromethorphan can be administered.

CYP2D6 inhibitors: Potent CYP2D6 inhibitors such as fluoxetine, paroxetine, terbinafine, duloxetine, and ritonavir can increase dextromethorphan plasma concentrations, leading to dissociation, hallucinations, and CNS toxicity even at normal cough-suppressant doses. It should be noted that FDA-approved fixed-dose combinations of dextromethorphan/quinidine and dextromethorphan/bupropion are specific exceptions. These products are carefully formulated to exploit CYP2D6 inhibition by quinidine or bupropion to achieve the desired, higher therapeutic dextromethorphan plasma concentrations for the specified indications. The dosing regimens for these combinations are precisely calibrated and should be followed strictly as labeled to ensure safety and efficacy.

Serotonergic drugs: Coadministration of dextromethorphan with SSRIs, SNRIs, tricyclic antidepressants, trazodone, mirtazapine, tramadol, lithium, triptans, or St John's wort increases the risk of serotonin syndrome due to additive serotonergic effects.

Central nervous system depressants: Concurrent use of dextromethorphan with alcohol, benzodiazepines, opioids, or gabapentinoids may result in additive CNS and respiratory depression, particularly in cases of overdose, misuse, or in patients with underlying respiratory compromise.

Contraindications

Dextromethorphan is contraindicated in patients with known or established hypersensitivity or idiosyncratic reactions to the drug or any constituents of combination products. Use with other serotonergic drugs, including SSRIs, carries an increased risk of serotonin syndrome and requires close monitoring. Additionally, coadministration with MAOIs or use within 14 days of discontinuation of MAOIs is strongly contraindicated because this combination may cause serious and potentially fatal reactions, including serotonin syndrome, hypertensive crisis, hyperpyrexia, and convulsions. Since dextromethorphan is often formulated with other medications, it is essential to consider the contraindications of each component to ensure safe prescribing of combination products. These contraindications are critical to preventing severe adverse drug interactions and ensuring patient safety during dextromethorphan administration.

Dextromethorphan/Quinidine

Dextromethorphan/quinidine is contraindicated in patients receiving concomitant therapy with quinidine, quinine, or mefloquine; in those with a history of quinine-, quinidine-, or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions; and in patients with known hypersensitivity to dextromethorphan. The drug must not be used with MAOIs or within 14 days of discontinuing an MAOI, and at least 14 days should elapse after discontinuing dextromethorphan/quinidine before an MAOI is initiated. It is also contraindicated in patients with a prolonged QT interval, congenital long-QT syndrome, a history suggestive of torsades de pointes, or heart failure, as well as in those with complete atrioventricular block without a functioning

pacemaker or in patients at high risk of complete atrioventricular block. In addition, concomitant use with drugs that both prolong the QT interval and are metabolized by CYP2D6, such as thioridazine or pimozide, is contraindicated.

Dextromethorphan/Bupropion

Dextromethorphan/bupropion is contraindicated in patients with a seizure disorder, as bupropion is associated with an increased risk of seizures. It is also contraindicated in individuals with a current or prior diagnosis of bulimia nervosa or anorexia nervosa due to the increased seizure risk associated with bupropion in these populations. The combination must not be used in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs, as this may further lower the seizure threshold. Use with MAOIs or within 14 days of discontinuing an MAOI is contraindicated. Likewise, at least 14 days should elapse after discontinuing dextromethorphan/bupropion before an MAOI is initiated. Dextromethorphan/bupropion is also contraindicated in patients with known hypersensitivity to bupropion, dextromethorphan, or any component of the formulation.

Monitoring

Dextromethorphan is well-tolerated and has a wide therapeutic window, making it suitable for clinical use. Clinical studies and postmarketing surveillance indicate that adverse reactions are generally infrequent and dose-related, primarily affecting the neurological, cardiovascular, and gastrointestinal systems. At therapeutic doses, adverse effects such as slight drowsiness, dizziness, nausea, or vomiting occur in fewer than 10% of patients. In contrast, higher or repeated doses may produce more frequent and diverse symptoms, including dysarthria, nystagmus, memory impairment, and gastrointestinal disturbances. Serious adverse events such as respiratory depression are rare, even at relatively high doses; however, caution is advised, particularly in patients with respiratory disease or those taking multiple medications with CNS effects. The safety margin is further supported by the lack of severe cardiopulmonary compromise in overdose cases unless combined with other CNS depressants.

Overall, the safety profile of dextromethorphan supports its use in both clinical and OTC applications, provided that appropriate dosing and patient monitoring are implemented. A chronic cough that does not respond to antitussives warrants further evaluation to identify other potential causes, such as gastroesophageal reflux disease, postnasal drip, underlying pulmonary disorders, including cough-variant asthma, or angiotensin-converting enzyme inhibitor use.

Toxicity

Signs and Symptoms of Overdose

One significant concern regarding dextromethorphan toxicity is its OTC misuse, which has steadily increased since the early 2000s. This misuse is referred to by slang terms such as "going pharming," "robotripping," and "dexing." In 2006, three specific OTC product formulations accounted for 66% of reported dextromethorphan misuse cases in the United States, with Coricidin HBP Cough & Cold Tablets and Robitussin products being prominent. A life-threatening toxicity associated with dextromethorphan abuse is serotonin syndrome, resulting from its serotonin reuptake inhibition properties. When combined with SSRIs or MAOIs, the risk of serotonin syndrome increases significantly. Symptoms include agitation, confusion, dilated pupils, headache, tachycardia, hypotension, high fever, seizures, irregular heartbeat, and may progress to unconsciousness.

Despite the rise in misuse, public health efforts and legislative actions restricting the sale of dextromethorphan-containing products to minors have helped stabilize or reduce abuse rates in recent years. However, continued vigilance is essential to prevent misuse and associated toxicities, given dextromethorphan's widespread availability and potential for harm. These trends underscore the importance of monitoring and educating patients on the proper use of dextromethorphan-containing medications.

Management of Overdose

Once airway, breathing, and circulation are stabilized, management of dextromethorphan poisoning focuses on identifying and treating its major complications: agitation/psychosis, hyperthermia, rhabdomyolysis, serotonin syndrome, and seizures. Agitation and psychotic symptoms should be managed with benzodiazepines such as lorazepam, which also decrease muscle activity and lower the risk of progression to hyperthermia or seizures. Antipsychotic agents should be avoided because they may worsen anticholinergic effects and impair thermoregulation.

Hyperthermia is treated with active evaporative cooling rather than antipyretics, and patients with core temperatures greater than or equal to 40 °C may require neuromuscular paralysis and endotracheal intubation to halt heat production. Rhabdomyolysis is managed with aggressive isotonic intravenous fluids to maintain a urine output of at least 4 mL/kg/h, with close monitoring for electrolyte abnormalities, particularly hyperkalemia. Please see StatPearls' companion resource, "Dextromethorphan Toxicity," for more information.

Serotonin syndrome is treated with benzodiazepines and, when necessary, cyproheptadine. Seizures are treated first with benzodiazepines, with phenobarbital as a second line. In cases of respiratory depression, naloxone may reverse coma or hypoventilation, particularly when there is concomitant opioid/benzodiazepine ingestion, and mechanical ventilation may be required. Coingestants commonly found in OTC preparations, such as acetaminophen or sympathomimetics, require appropriate antidotes, including *N*-acetylcysteine for acetaminophen toxicity. Most uncomplicated cases resolve within several hours, but severe toxicity warrants

intensive care monitoring. All intentional overdoses require psychiatric assessment before discharge. For the latest recommendations, clinicians should contact the regional poison control center at 1-800-222-1222.

Enhancing Healthcare Team Outcomes

Dextromethorphan is one of the most widely used OTC antitussives. Pharmacists, primary care physicians, and advanced practice providers play a key role in counseling patients on appropriate dosing, potential drug-drug interactions, and the risks associated with combining dextromethorphan with serotonergic medications. In patients with chronic cough unresponsive to dextromethorphan, collaboration among pulmonologists, allergists, and gastroenterologists is essential to evaluate alternative causes such as asthma, gastroesophageal reflux disease, or upper airway cough syndrome.

Since dextromethorphan became available OTC, its misuse and overdose have increased significantly. Diagnosis and management of dextromethorphan overdose require an interprofessional healthcare team including clinicians, advanced practice providers, nurses, pharmacists, and any witnesses or family members. Thorough documentation of the patient's medical history and current medications is vital for identifying major overdose complications such as serotonin syndrome. Treatment for serotonin syndrome involves hydration, drug withdrawal, body temperature management, and seizure control. Without timely intervention, serotonin syndrome and dextromethorphan overdose can be fatal.

Paramedics play a crucial role in gathering information from witnesses and identifying empty pill bottles at the scene. The triage nurse should consider the possibility of a drug overdose and direct patient disposition accordingly. A detailed history is essential for establishing the time of onset and for monitoring the patient's clinical progression or deterioration. Emergency department physicians are responsible for ordering relevant laboratory tests, including blood or urine drug levels, when appropriate. Consultation with pharmacists, toxicologists, radiologists, and hospitalists should be obtained as needed. Psychiatry consultation should be obtained in cases of intentional overdose.

According to the American Association of Poison Control Centers, out-of-hospital management of dextromethorphan overdose includes two grades of recommendation.

- Grade D: This category applies to patients with suicidal ideation, intentional abuse, or malicious intent, who should be referred immediately to the nearest emergency department
- Grade C: This category applies to patients with effects beyond mild or those following an acute ingestion, who should also be promptly referred to an emergency department.

Patients who ingest 5 to 7.5 mg/kg should receive poison control center–initiated treatments, with follow-up every 2 to 4 hours. Any patient exhibiting persistent or worsening symptoms or who ingests more than 7.5 mg/kg should be referred immediately to emergency care. A structured approach that emphasizes interprofessional collaboration, including physicians, advanced practice

providers, pharmacists, and relevant specialists, along with timely referral, is essential for improving healthcare outcomes and reducing morbidity and mortality associated with dextromethorphan misuse and overdose.

Review Questions

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