DEXTROMETHORPHAN

THERAPEUTICS

Brands
- Creo-Terpin, Delsym, Robafen Cough, Robitussin CoughGels, Medicon

Generic?
Yes

Class
- NMDA receptor antagonist

Commonly Prescribed For
(FDA approved in bold)
- Symptomatic relief of coughs caused by the common cold or inhaled irritants
  (Dextromethorphan was approved by the FDA in 1958 as a nonprescription cough suppressant)
- Pain/neuropathic pain

How the Drug Works
- Binds preferentially to NMDA receptors, preventing glutamate from activating these receptors. The excitatory effects of glutamate are postulated to contribute to pain

How Long until It Works
- Roughly 30 minutes

If It Works
- Continue to use

If It Doesn’t Work
- Nonpharmacologic measures
- Change to another agent
- Limit drugs with sedative properties such as opioids, hypnotics, antiepileptic drugs, and tricyclic antidepressants (although may use cautiously)

Best Augmenting Combos for Partial Response or Treatment-Resistance
- May use with acetaminophen
- May utilize cautiously with opioids
- Scant preclinical evidence suggests that cautious use of dextromethorphan and melatonin, ketamine, or clonidine may be beneficial for neuropathic pain

Tests
- None required

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
- Direct effect on NMDA receptors

Notable AEs
- Dysphoria, nausea, GI disturbances, dizziness, confusion, fatigue, dystonia, slurred speech, nystagmus, hallucinations, insomnia, restlessness, irritability, dissociation, paranoia, rash, sedation

Life-Threatening or Dangerous AEs
- Syncope or cardiac arrhythmias can occur although it is unclear that these events are related to dextromethorphan
- Anaphylaxis
- Serotonin syndrome: can even rarely occur with monotherapy at usual doses; mostly occurs with high doses and concomitant SSRI/SNRI or “triptans”

Weight Gain
- Unusual

Sedation
- Common

What to Do about AEs
- For CNS AEs, discontinuation of nonessential centrally acting medications may help. If a bothersome AE is clearly drug-related then reduce the dose or discontinue dextromethorphan

Best Augmenting Agents for AEs
- Most AEs do not respond to adding other medications; however if being used to ameliorate neuropathic pain the addition of low doses of opioids may enable a reduction in the dose of dextromethorphan

DOSING AND USE

Usual Dosage Range
- 30–60 mg daily

Dosage Forms
- Oral: capsule, liquid filled, as hydrobromide – Robafen cough: 15 mg; liquid, as hydrobromide
Robitussin® Cough Gels™

Long-Acting

Oral solution: Delsym-Long-Acting (every 12 hours); dextromethorphan polistirex (equivalent to dextromethorphan hydrobromide) 30 mg/5 mL

How to Dose

- Start at 15 mg extended release in the evening. Increase to twice daily, may slowly titrate upward to 30–60 mg every 12 hours. If AEs occur, titrate more slowly

Dosing Tips

- Slow titration may reduce AEs. Food does not affect absorption

Overdose

- Symptoms may include restlessness, psychosis, hallucinations, and stupor

Long-Term Use

- Safe for long-term use. Effectiveness may decrease over time

Habit Forming

- Possible but infrequent

How to Stop

- Gradually tapering dose to off is best. Abrupt cessation may cause a withdrawal syndrome (craving, diaphoresis, nausea, hypertension, tachycardia)

Pharmacokinetics

- Nearly all (96–99%) of dextromethorphan is O-demethylated by CYP2D6 and converted into dextrophan, which is conjugated with glucuronic acid and excreted in bile
- 1–4% of dextromethorphan is N-demethylated by the CYP3A4/5 pathway and converted into 3-methoxy-morphinan, which is O-demethylated into 3-hydroxymorphinan by CYP2D6, conjugated, and then excreted in the urine
- Duration: immediate release ≤6 hours; extended release ~12 hours
- Half-life elimination: extensive metabolizers 2–4 hours; poor metabolizers 24 hours

Drug Interactions

- Use with caution with drugs that significantly affect CYP2D6
- Use with caution with other drugs which are NMDA antagonists (amantadine, ketamine, memantine)
- Use with caution with drugs that also utilize renal mechanisms of excretion such as ranitidine, cimetidine, hydrochlorothiazide, or nicotine
- Use with caution with drugs that are NMDA antagonists (amantadine, ketamine, memantine)

Other Warnings/ Precautions

- Some products may contain sodium
- Some products may contain sodium benzoate which may cause allergic reactions in certain individuals
- Some products may contain tartrazine
- Concomitant use of proserotonergic drugs (SSRIs/SNRIs [e.g. Fluvoxamine] or triptans) especially with higher dextromethorphan doses may lead to serotonin syndrome

Do Not Use

- Hypersensitivity to the drug
- Concurrent administration with or within 2 weeks of discontinuing MAOIs

SPECIAL POPULATIONS

Renal Impairment

- Drug is renally excreted. Consider dose reduction with moderate impairment and do not use in patients with severe renal insufficiency

Hepatic Impairment

- No known effects

Cardiac Impairment

- No significant change in ECG observed in trials compared to placebo. No known effects

Elderly

- There is reduced drug clearance, but no dose adjustment needed as the dose used is the lowest that provides clinical improvement

Children and Adolescents

- Not studied in children

Pregnancy

- Category C. Decreased birth weight in animal studies. Use only if benefits of medication outweigh risks

Breast-Feeding

- Unknown if excreted in breast milk. Use with caution
**Potential Advantages**
- May be useful to provide additional analgesia when used in conjunction with opioid therapy

**Potential Disadvantages**
- Adverse effects such as dysphoria, sedation, and confusion are not uncommon, especially at high doses

**Primary Target Symptoms**
- May result in confusion, agitation, difficulties performing activities of daily living

**Pearls**
- Dextromethorphan is the d-isomer of levorphanol, an opioid related to codeine

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**Suggested Reading**


