DEXTROMETHORPHAN

**Therapeutics**

**Brands**
- Nuedexta (in combination with quinidine)

See index for additional brand names

**Generic?** No

**Class**
- Noncompetitive NMDA receptor antagonist and sigma 1 agonist

**Commonly Prescribed for** (bold for FDA approved)
- Pseudobulbar affect (PBA)
- Diabetic peripheral neuropathic pain
- Unstable mood and affect in PTSD and mild traumatic brain injury
- Third-line for treatment-resistant depression

**How the Drug Works**
- Dextromethorphan reduces glutamate neurotransmission through blocking NMDA receptors and by acting as an agonist at sigma 1 receptors
- Dextromethorphan also has affinity for the serotonin transporter and may therefore modulate serotonin levels
- Quinidine increases availability of dextromethorphan by inhibiting its metabolism via CYP450 2D6

**How Long Until It Works**
- In clinical trials the rate of pseudobulbar affect episodes was significantly decreased beginning at day 15

**If It Works**
- Reduces the frequency and severity of episodes of uncontrollable laughing and/or crying

**If It Doesn’t Work**
- Consider switching to a TCA or an SSRI

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Often best to attempt another monotherapy prior to resorting to augmentation strategies

**Tests**
- None for healthy individuals

**Side Effects**

**How Drug Causes Side Effects**
- Presumably mechanism related, including central actions at sigma and NMDA receptors causing dissociative symptoms, euphoria, or sedation

**Notable Side Effects**
- Dizziness, asthenia
- Diarrhea, vomiting
- Cough, peripheral edema
- Urinary tract infection
- Euphoria

**Life-Threatening or Dangerous Side Effects**
- Immune-mediated thrombocytopenia
- Hepatotoxicity
- Dose-dependent QT prolongation

**Weight Gain**
- Reported but not expected

**Sedation**
- Reported but not expected

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- In a few weeks, switch to another agent or add other drugs

**Best Augmenting Agents for Side Effects**
- Often best to try another agent prior to resorting to augmentation strategies to treat side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
## DOSING AND USE

### Usual Dosage Range
- 20 mg/10 mg twice per day

### Dosage Forms
- Capsule 20 mg/10 mg (dextromethorphan/quinidine)

### How to Dose
- Initial 20 mg/10 mg once per day; after 7 days increase to 20 mg/10 mg twice per day

### Dosing Tips
- Some patients may tolerate and respond to doses higher than the approved doses, but few controlled studies of high doses

### Overdose
- Nausea, dizziness, headache, ventricular arrhythmias, hypotension, coma, respiratory depression, seizures, tachycardia, hyperexcitability, toxic psychosis

### Long-Term Use
- Not evaluated

### Habit Forming
- No

### How to Stop
- Taper not necessary

### Pharmacokinetics
- Elimination half-life of dextromethorphan is approximately 13 hours
- Elimination half-life of quinidine is approximately 7 hours
- Dextromethorphan is metabolized by CYP450 2D6, while quinidine inhibits CYP450 2D6
- Quinidine is metabolized by CYP450 3A4

### Drug Interactions
- Via CYP450 2D6 inhibition, dextromethorphan/quinidine could increase plasma concentrations of drugs metabolized by CYP450 2D6 (e.g., desipramine), potentially requiring dose reduction of the substrate
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing dextromethorphan/quinidine
- Via P-glycoprotein inhibition, quinidine could increase plasma concentrations of P-glycoprotein substrates such as digoxin, potentially requiring dose reduction of the substrate
- Can theoretically cause serotonin syndrome when combined with serotonin reuptake inhibitors, but not well studied

### Other Warnings/Precautions
- Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal; dextromethorphan/quinidine should be discontinued immediately if thrombocytopenia occurs unless it is clearly not drug-related, and should not be restarted in sensitized patients
- Quinidine has been associated with a lupus-like syndrome involving polyarthritis
- ECG should be monitored if patient must take an agent that prolongs QT interval or that inhibits CYP450 3A4
- Anticholinergic effects of quinidine may lead to worsening in myasthenia gravis and other sensitive conditions

### Do Not Use
- If patient is taking an MAOI
- If patient is taking another medication containing quinidine, quinine, or mefloquine
- If patient has a history of quinidine, quinine, or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reaction
- If patient has prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure
- If patient has complete atrioventricular block (AV) without implanted pacemaker, or patients at high risk of complete AV block
- If patient is taking a drug that prolongs QT interval and is metabolized by CYP450 2D6 (e.g., thioridazine, pimozide)
- If there is a proven allergy to dextromethorphan or quinidine
**Special Populations**

**Renal Impairment**
- Dose adjustment not necessary in patients with mild to moderate impairment

**Hepatic Impairment**
- Dose adjustment not necessary in patients with mild to moderate impairment

**Cardiac Impairment**
- Contraindicated in patients with prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, and heart failure
- Monitor ECG in patients with left ventricular hypertrophy or left ventricular dysfunction

**Elderly**
- Some patients may tolerate lower doses better

**Children and Adolescents**
- Safety and efficacy have not been established
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and strongly consider informing parents or guardian of this risk so they can help observe child or adolescent patients

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Some animal studies have shown adverse effects

**Breast Feeding**
- Unknown if dextromethorphan/quinidine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother

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**The Art of Psychopharmacology**

**Potential Advantages**
- No other approved agent for PBA

**Potential Disadvantages**
- CYP450 2D6 poor metabolizers may require dose reduction
- In patients with past substance abuse, especially of dextromethorphan, ketamine, or PCP

**Primary Target Symptoms**
- Uncontrollable crying
- Uncontrollable laughter

**Pearls**
- Quinidine is intended to increase the actions of dextromethorphan by inhibiting its metabolism by CYP450 2D6; therefore, poor metabolizers of CYP450 2D6 may not benefit as much from this treatment while still experiencing adverse effects associated with quinidine
- Affective instability in Alzheimer disease may be treatable with this agent, including agitation, allowing antipsychotics to be avoided in this population
- Some men express emotional lability as laughter and anger rather than laughter and crying
- Affective instability in PTSD and in mild traumatic brain injury may be improved by dextromethorphan/quinidine
- Similar binding properties to ketamine suggest possible efficacy in both treatment-resistant depression and chronic pain

