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Dextromethorphan: An update on its utility for neurological and neuropsychiatric disorders

Linda Nguyen, Kelan L. Thomas, Brandon P. Lucke-Wold, John Z. Cavendish, Molly S. Crowe, Rae R. Matsumoto

Abstract

Dextromethorphan (DM) is a commonly used antitussive and is currently the only FDA-approved pharmaceutical treatment for pseudobulbar affect. Its safety profile and diverse pharmacologic actions in the central nervous system have stimulated new interest for repurposing it. Numerous preclinical investigations and many open-label or blinded clinical studies have demonstrated its beneficial effects across a variety of neurological and psychiatric disorders. However, the optimal dose and safety of chronic dosing are not fully known. This review summarizes the preclinical and clinical effects of DM and its putative mechanisms of action, focusing on depression, stroke, traumatic brain injury, seizure, pain, methotrexate neurotoxicity, Parkinson’s disease and autism. Moreover, we offer suggestions for future research with DM to advance the treatment for these and other neurological and psychiatric disorders. © 2016 Elsevier Inc. All rights reserved.
1. Introduction

Dextromethorphan (DM) has been a widely used non-opioid antitussive for over 50 years. It was first developed as one of two enantiomers of methorphan, a morphine derivative. DM is available in many over-the-counter (OTC) cough and cold preparations worldwide and does not possess the same central nervous system (CNS) pharmacodynamic effects as other opioids in humans (i.e., analgesia, respiratory depression, addiction or psychotomimetic properties) when taken at therapeutic doses (60–120 mg/day in divided doses). At high doses (from 5 to over 10 times the label-specified maximum dosages), it acts as a dissociative agent similar to the N-methyl-D-aspartate (NMDA) antagonists ketamine and phencyclidine (PCP) (Romanelli & Smith, 2009; Schwartz, 2005; Banken & Foster, 2008). The levorotatory enantiomer of DM, levomethorphan, in contrast, is a low potency opiate analgesic, strictly controlled as a narcotic drug.

Over the past 20 years, accumulating evidence suggests that DM has both anticonvulsant and neuroprotective effects in numerous experimental models of seizure, traumatic brain injury (TBI), stroke, pain, and others (Tortella et al., 1989; Werling et al., 2007b; Shin et al., 2011). Moreover, DM in combination with quinidine, a cytochrome P450 (CYP) 2D6 inhibitor, was recently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of pseudobulbar affect (PBA). Currently, DM is being used in clinical trials for a variety of CNS-related disorders. As more data is obtained on the use of DM in preclinical and clinical trials, questions about mechanisms of action and potential repurposing avenues for this relatively safe drug take on considerable significance.

In this review, a brief overview is given on the pharmacokinetic and pharmacodynamic properties of DM. We also discuss the currently approved indications for DM, followed by its therapeutic potential in a multitude of neurological and neuropsychiatric disorders. For the disorders mentioned herein, we will elaborate on the putative mechanisms of action underlying the effects of DM. Together, the literature suggests that DM not only has many potential therapeutic applications, but also serves as a promising tool in the development of future medical therapies.

2. Pharmacokinetics and metabolism

DM is commonly used as a probe drug for CYP2D6 metabolizer status. It undergoes extensive first-pass hepatic metabolism via O-demethylation to form its active metabolite, dextrorphan (DX) (Capon et al., 1996; Yu & Haining, 2001). DM is also metabolized to a relatively inactive metabolite, 3-methoxymorphinan (3-MM), via CYP3A4 N-demethylation (Yu & Haining, 2001). These DX and 3-MM metabolites can both undergo further metabolism to another relatively inactive 3-hydroxymorphinan (3-HM) secondary metabolite via CYP3A4 and CYP2D6 demethylation, respectively (Yu & Haining, 2001). However, there is minimal free DX available for metabolism since this active metabolite is rapidly glucuronidated and excreted in urine (Pope et al., 2004). A summary of the metabolic pathway for DM is shown in Fig. 1. DM and DX are both metabolized by CYP2D6, so it is useful to stratify pharmacokinetic comparisons by the four possible CYP2D6 phenotypes: ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) or poor metabolizer (PM). In a study of 252 Americans, 84.3% were found to be EMS, 6.8% to be IMs, and 8.8% were PMs for DM (Woodworth et al., 1987). In a different study, EM subjects (N = 6) given a single oral dose of 30 mg DM demonstrated a median half-life of 2.4 h with an oral bioavailability of 1–2%, while PMs (N = 6) had a median half-life of 19.1 h with an oral bioavailability of 80% (Capon et al., 1996). EM subjects also demonstrated a DM median maximum concentration (Cmax) of 1.4 mg/L with an area under the curve (AUC) of 9.0 mg/L·h, while PMs had a median Cmax of 23.0 mg/L with an AUC of 1362 mg/L·h (Capon et al., 1996). After pretreatment with quinidine, a potent CYP2D6 inhibitor, EM subjects demonstrated a DM median Cmax of 24.9 mg/L with an AUC of 383 mg/L·h (Capon et al., 1996). This study demonstrated that PMs may have fourfold higher DM exposure (AUC 1362 vs. 383 mg/L·h, p < 0.05), while peak DM plasma concentration (Cmax 23.0 vs. 24.9 mg/L) remained relatively similar when compared to EMS after pretreatment with quinidine.

Fig. 1. DM demethylation pathways catalyzed by CYP2D6 and CYP3A4. DX is formed by CYP2D6-mediated O-demethylation of DM. N-demethylation of DM to 3-MM is favored over N-demethylation of DX given the relative Km values for the reactions and the ease with which DX is glucuronidated in vivo. Adapted from Blake et al. (2007). 3-HM, 3-hydroxymorphinan; 3-MM, 3-methoxymorphinan; DM, dextromethorphan; DX, dextrorphan.
3. Pharmacodynamics

DM has a complex and unique neuropharmacology that may underlie its apparent efficacy in indications besides cough suppression. Though DM is derived from levorphanol, a mu opioid agonist, it has no direct agonist activity at the classic opioid receptors (mu, kappa, delta); it does not carry the full range of CNS effects common to opioid agonists (e.g., analgesia, euphoria, respiratory depression), nor does it produce typical opioid effects, including dependence (Duman et al., 1995; Banken & Foster, 2008; Shin et al., 2011).

Apart from opioid sites, DM binds to several other receptors and transporters in the brain, many with nanomolar to micromolar affinities (Table 1). DM is a well-established uncompetitive, low affinity NMDA receptor antagonist (Church et al., 1985, 1989; Franklin & Murray, 1992; Netzer et al., 1993). Noteworthy, this low affinity binding to NMDA receptors by DM is therapeutically useful because low affinity (vs. high affinity) NMDA antagonists are, in general, better tolerated by patients (Palmer, 2001). A high affinity NMDA antagonist such as MK801 (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine) can function well as excitotoxicity

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Binding affinities (Kᵢ) for DM or DX. NC = less than 20–30% displacement of specific binding at 1 μM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>DX</td>
</tr>
<tr>
<td>NMDA (PCP)</td>
<td></td>
</tr>
<tr>
<td>2120 ± 84 nM</td>
<td>892 ± 108 nM</td>
</tr>
<tr>
<td>7253 ± 302 nM</td>
<td>906 ± 77 nM</td>
</tr>
<tr>
<td>8945 ± 867 nM</td>
<td>486 ± 68 nM</td>
</tr>
<tr>
<td>8340 ± 495 nM</td>
<td>696 ± 87 nM</td>
</tr>
<tr>
<td>AMPA</td>
<td></td>
</tr>
<tr>
<td>150 ± 47 nM</td>
<td>118 ± 77 nM</td>
</tr>
<tr>
<td>196 ± 74 nM</td>
<td>–</td>
</tr>
<tr>
<td>138 ± 48 nM</td>
<td>351 ± 39 nM</td>
</tr>
<tr>
<td>161 ± 57 nM</td>
<td>481 ± 64 nM</td>
</tr>
<tr>
<td>142 ± 38 nM</td>
<td>344 ± 47 nM</td>
</tr>
<tr>
<td>180 ± 28 nM</td>
<td>294 ± 36 nM</td>
</tr>
<tr>
<td>403 ± 22 nM</td>
<td>–</td>
</tr>
<tr>
<td>214 ± 15 nM</td>
<td>–</td>
</tr>
<tr>
<td>205 ± 42 nM</td>
<td>144 ± 37 nM</td>
</tr>
<tr>
<td>652 ± 33 nM</td>
<td>–</td>
</tr>
<tr>
<td>&gt;10,000 nM</td>
<td>–</td>
</tr>
<tr>
<td>528 ± 6 nM</td>
<td>–</td>
</tr>
<tr>
<td>Sigma-2</td>
<td></td>
</tr>
<tr>
<td>19,976 ± 2144 nM</td>
<td>12,899 ± 2015 nM</td>
</tr>
<tr>
<td>22,864 ± 1917 nM</td>
<td>15,582 ± 2114 nM</td>
</tr>
<tr>
<td>16,873 ± 2234 nM</td>
<td>12,987 ± 1975 nM</td>
</tr>
<tr>
<td>12,079 ± 1638 nM</td>
<td>11,457 ± 1437 nM</td>
</tr>
<tr>
<td>&gt;10,000 nM</td>
<td>–</td>
</tr>
<tr>
<td>&gt;10,000 nM</td>
<td>–</td>
</tr>
<tr>
<td>11,060 ± 1320 nM</td>
<td>11,325 ± 1395 nM</td>
</tr>
<tr>
<td>SERT</td>
<td></td>
</tr>
<tr>
<td>40 ± 7 nM</td>
<td>484 ± 116 nM</td>
</tr>
<tr>
<td>23 nM*</td>
<td>401 nM*</td>
</tr>
<tr>
<td>5-HT1A</td>
<td></td>
</tr>
<tr>
<td>21 ± 17 nM</td>
<td>–</td>
</tr>
<tr>
<td>1 ± 10 nM</td>
<td>–</td>
</tr>
<tr>
<td>5-HT1B/D</td>
<td></td>
</tr>
<tr>
<td>61% at 1 μM</td>
<td>54% at 1 μM</td>
</tr>
<tr>
<td>5-HT2</td>
<td></td>
</tr>
<tr>
<td>&gt;50% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>NET</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>240 ± 10 nM</td>
<td>340 nM*</td>
</tr>
<tr>
<td>Alpha-1 adrenergic</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Alpha-2 adrenergic</td>
<td></td>
</tr>
<tr>
<td>60% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Beta adrenergic</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Mu opioid</td>
<td></td>
</tr>
<tr>
<td>1280 nM</td>
<td>420 nM</td>
</tr>
<tr>
<td>Kappa opioid</td>
<td></td>
</tr>
<tr>
<td>7000 nM</td>
<td>5950 nM</td>
</tr>
<tr>
<td>Delta opioid</td>
<td></td>
</tr>
<tr>
<td>11,500 nM</td>
<td>34,700 nM</td>
</tr>
<tr>
<td>Nicotinic</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Alpha-3/beta-4 nicotinic</td>
<td></td>
</tr>
<tr>
<td>&lt;20% at 100 μM</td>
<td>&lt;20% at 100 μM</td>
</tr>
<tr>
<td>8.9 ± 1.1 μM*</td>
<td>29.6 ± 5.7 μM*</td>
</tr>
<tr>
<td>0.7 ± 0.1 μM*</td>
<td>1.3 ± 0.1 μM*</td>
</tr>
<tr>
<td>Alpha-4/beta-2 nicotinic</td>
<td></td>
</tr>
<tr>
<td>3.9 ± 0.2 μM*</td>
<td>3.0 ± 0.5 μM*</td>
</tr>
<tr>
<td>Alpha-7 nicotinic</td>
<td></td>
</tr>
<tr>
<td>2.5 ± 0.2 μM*</td>
<td>4.3 ± 0.2 μM*</td>
</tr>
<tr>
<td>Histamine-1</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Histamine-2</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Dopamine-1</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>Dopamine-2</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>DAT</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>GABA</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
<tr>
<td>L-type Ca²⁺</td>
<td></td>
</tr>
<tr>
<td>&gt;95% at 1 μM</td>
<td>–</td>
</tr>
</tbody>
</table>
blocks; however, because its “dwell time” in the ion channel is long, critical normal functions are also blocked. An individual taking a neuroprotective dose of MK801 may not only become drowsy, but also lapse into a coma (Lipton, 2004). DM is also thought to act as an agonist at sigma-1 receptors (Nguyen et al., 2014), and an antagonist at nicotinic (alpha-3-beta-4, alpha-4-beta-2, and alpha-7) receptors (Hernandez et al., 2000; Damaj et al., 2005; Lee et al., 2006). It may also inhibit serotonin transporters (SERT) and to a lesser extent norepinephrine transporters (NET) (Codd et al., 1995). DM can also inhibit voltage gated calcium channels (VGCC) (Carpenter et al., 1988; Kim et al., 2001; Kamel et al., 2008), but it is unclear whether inhibition of VGCC is through direct or indirect protein–protein interactions (Carpenter et al., 1988; Kim et al., 2001; Kamel et al., 2008). DM’s activity at other receptors and protein targets remains to be characterized. Based on the currently available data, among the known pharmacodynamic activities of DM, the ones that appear to be most examined as potential mechanisms for its therapeutic effects in the CNS are its NMDA antagonist and sigma-1 agonist actions. Additional details of how these and other interactions are hypothesized to convey therapeutically relevant actions are discussed in further detail in the sections that follow.

4. Approved indications

4.1. Cough suppression

Patented by Hoffmann-La Roche in 1954 as an antitussive, DM was approved by the FDA in 1958 for OTC use. Its cough suppression potency in adults is nearly equal to that of prescribed codeine (Matthys et al., 1983; Aylward et al., 1984). Aside from its non-addictive properties, DM is superior to codeine when used at the recommended antitussive doses (10–30 mg) in that it lacks the gastrointestinal side effects, such as constipation, as well as sedative, analgesic and respiratory depression effects associated with opioids (Shin et al., 2011). Adverse effects with recommended doses of DM are rare, though nausea, other gastrointestinal disturbances, slight drowsiness and dizziness can occur (Bem & Peck, 1992).

DM is believed to preferentially act within the brainstem cough network rather than at peripheral sites to suppress cough (Canning, 2009). Supporting this, DM is 11 to 40 times more effective when given directly into the left vertebral artery than intravenously in a cat cough model (Chou & Wang, 1975; Domino et al., 1985). In addition, more recently, microinjection of DM bilaterally into the nucleus tractus solitarius (NTS) has been shown to dose-dependently inhibit cough without affecting basal respiratory rate (Canning, 2009). The NTS is a site where the pulmonary vagal afferent fibers first synapse with second-order interneurons and an area very close to the cough center in the brainstem (Widdicombe, 1998; Bolser & Davenport, 2002); this region is thought to function as a “gate” for the cough reflex (Widdicombe, 1998). The precise mechanisms by which DM inhibits cough is still unclear and may include blockade of NMDA receptors (Haji et al., 2008; Kamei et al., 1989), and activation of sigma-1 (Kamei et al., 1993; Kotzer et al., 2000; Brown et al., 2004) and serotonin (5-HT) 1B/D receptors (Kamei, 1996; Kamei et al., 1992); selective ligands at these receptors have been shown to elicit cough suppression on their own, while pre-treatment with pharmacological antagonists at the latter two receptors have been shown to block the antitussive effects of DM in certain pre-clinical cough models (Kamei et al., 1993; Kamei, 1996; Kotzer et al., 2000).

4.2. Pseudobulbar affect

In 2010 and 2013, the FDA and EMA, respectively, approved the use of DM in combination with quinidine for the treatment of PBA. The combination dose of 20/10 mg is approved in the United States, while doses of 20/10 mg and 30/10 mg are approved in Europe. PBA is characterized by sudden, unpredictable and involuntary episodes of crying, laughing, or other emotional displays that are exaggerated relative to or incongruent with the mood and feelings of the patients (Miller et al., 2011). It occurs secondary to a neurological disease or brain injury, with an estimated prevalence of up to 50% in amyotrophic lateral sclerosis (ALS) and stroke, 39% in Alzheimer’s disease (AD), 10–29% in multiple sclerosis (MS), 5–17% in Parkinson’s disease (PD), and 5–11% in TBI (A. Miller et al., 2011). Although the underlying pathology of PBA remains incompletely understood, emerging evidence suggests that it is due to a loss of descending cortical control of brainstem motor nuclei and possibly the cerebellum, disrupting inhibitory mechanisms for motor control of emotional expression (Miller et al., 2011; Cummings et al., 2013; Lauterbach et al., 2013). At the neurotransmitter level, evidence of dysfunction has been shown by a variety of neuroimaging studies and from reported efficacy of specific pharmacologic therapies (Miller et al., 2011). Decreased monoamines, particularly 5-HT and dopamine (DA), as well as glutamate excess have been implicated (Miller et al., 2011; Cummings et al., 2013; Lauterbach et al., 2013). The effectiveness of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, levodopa, and anti-glutamatergic agents for the treatment of PBA support this hypothesis, though all of these have been used off-label (Panitch et al., 2006; Miller et al., 2011; Ahmed & Simmons, 2013; Schoedel et al., 2014).

DM/quinidine is the first and currently only approved treatment for PBA, and data on its efficacy and safety have been reviewed previously (Schoedel et al., 2014). The approval was granted on the basis of a 12-week randomized, double blind, placebo-controlled trial in 326 patients (283 completers) with MS or ALS with PBA in which DM/quinidine (20/10 mg twice daily) showed a 49% reduction in PBA episode rate compared to placebo (Pioro et al., 2010). In addition, more DM/quinidine patients reported remission throughout the study’s final 14 days compared to placebo (51% vs. 29%) (Pioro et al., 2010). The most commonly reported adverse events were falls, dizziness, headache, nausea, diarrhea, and weakness, though none occurred at a significantly different rate from the placebo-controlled group (Pioro et al., 2010). A recent 52-week, open-label study in 553 patients (296 completers) with PBA receiving a higher dose of DM/quinidine (30/30 mg twice daily) confirms the apparent safety of long-term administration of DM/quinidine (Pattee et al., 2014). The most frequently reported treatment–related adverse events in this study were nausea (11.8%), dizziness (10.5%), headache (9.9%), somnolence (7.2%), fatigue (7.1%), diarrhea (6.5%), and dry mouth (5.1%) (Pattee et al., 2014). These adverse events occurred early in the treatment course, were largely mild to moderate, and generally did not result in discontinuation (Pattee et al., 2014). There were also no clinically significant treatment-
related electrocardiogram changes, cardiac events, or respiratory distress reported (Pattee et al., 2014).

DM has many pharmacological properties that may be involved in alleviating PBA. DM may bind to SERT and 5-HT1B/D receptors and modulate 5-HT levels; there is electrophysiological evidence that it can increase 5-HT release in rat brainstem slices (Kamei et al., 1992). Of note, neurons in the brainstem and cerebellum are highly enriched with sigma-1 receptors (Gundlach et al., 1986), suggesting that the effect of DM on emotional control may be mediated at least in part through interactions with sigma-1 receptors. Sigma-1 agonists have been shown to inhibit NMDA receptor activity and decrease glutamate release under certain conditions (Lobner & Lipton, 1990; Zhang et al., 2011). In addition to its direct inhibition of NMDA receptors, DM may further blunt NMDA receptor activity through sigma-1 receptors. Reports have shown that DM can decrease potassium-stimulated glutamate release in rabbit hippocampal slices (Annels et al., 1991) as well as electrical-stimulated glutamate release from presynaptic terminals in the NTS in pig brainstem slices (Ohi et al., 2011). Whether DM is attenuating the release of glutamate in these studies through sigma-1 receptors still needs to be investigated. Moreover, sigma-1 agonists can increase the firing of 5-HT neurons in the rat dorsal raphe nucleus (Bermack & Debonnel, 2001; Lucas et al., 2008) and also increase DA release in the rat brain, especially in the striatum, medial prefrontal cortex (PFC) and nucleus accumbens shell (Patrick et al., 1993; Gudelsky, 1995; Kobayashi et al., 1997; Gudelsky, 1999; Garces-Ramirez et al., 2011). The exact mechanisms by which sigma-1 receptors modulate neurotransmitter receptor activity and release are not fully understood. It also remains to be determined whether DM can replicate the effects seen with selective sigma-1 agonists. Taken as a whole, DM may treat PBA by correcting a myriad of neurotransmission abnormalities: increasing 5-HT and DA, inhibiting excessive excitatory glutamate neurotransmission, and enhancing sigma-1 receptor function in specific networks (Schoedel et al., 2014). Additional neuroimaging using magnetic resonance imaging (MRI) to detect structural changes; positron emission tomography and functional MRI to detect functional changes; and magnetic resonance spectroscopy to detect biochemical alterations are needed to better understand the specific neural circuitry disruptions at play both at the systems and cellular level in those with PBA. These neuroimaging techniques or related studies may provide potential markers of disease onset and progression that can be easily adapted to clinical trials. This will help to inform and further improve treatment options for PBA.

5. Potential therapeutic uses

5.1. Depression

Although there are many available pharmaceutical agents for treating depression, most of these are similar in their mechanism of action (i.e., targeting the monoaminergic system), remain ineffective in a third of patients, and have a delayed clinical efficacy of several weeks to months (Berton & Nestler, 2006). DM is postulated to have fast acting antidepressant activity based on pharmacodynamic similarities to the glutamate NMDA receptor antagonist ketamine (Lauterbach, 2012), which has shown rapid (within 24 h) antidepressant effects even in treatment resistant individuals, but whose use remains limited by abuse liability and adverse effects (Aan Het Rot et al., 2012). Indeed, in depressed patients with treatment resistant bipolar type II or bipolar not otherwise specified disorder, some individuals reported improvements in mood within 1–2 days of initiating treatment with DM/quinidine or having the dose increased to twice a day (Kelly & Lieberman, 2014). In preclinical studies, we have found that DM exerts antidepressant-like effects in mice using the forced swim test (FST) and tail suspension test, two of the most validated and widely used animal models for predicting antidepressant efficacy (Nguyen et al., 2014; Nguyen & Matsumoto, 2015). Though the former study was a retrospective chart review and the latter studies were done in stress-naive animals, the results lend credence to DM as a potential antidepressant.

DM has multiple properties in common with as well as distinct from known fast acting and conventional antidepressants, which may provide adequate response in treatment resistant depression (Werling et al., 2007a; Lauterbach, 2012; Stahl, 2013). A side-by-side comparison of DM, ketamine and imipramine based on their putative principal pharmacologic mechanisms of action is shown in Fig. 2. DM has been reported to increase 5-HT levels (Codd et al., 1995), possibly through interactions at SERT and 5-HT1B/D receptors. In contrast to its high affinity for SERT, DM binds weakly with NET (>1 μM) (Werling et al., 2007b), but its reported ability to modulate NE reuptake (Codd et al., 1995) would be expected to also contribute antidepressant effects in humans. This however would not account for its potential fast acting effects. In addition to DM’s interaction with 5-HT and NE transporters and receptors, DM may regulate 5-HT levels through activation of sigma-1 receptors, which has been shown to modulate monoamine neurotransmitter levels (Kobayashi et al., 1997; Bermack & Debonnel, 2001; Lucas et al., 2008). These receptors have been implicated as protein targets for existing and novel antidepressant drugs (Fishback et al., 2010). Note-worthy, compared to existing medications, sigma-1 receptor agonists may facilitate a more rapid onset of antidepressant efficacy (Hayashi & Su, 2008; Fishback et al., 2010). Supporting the involvement of sigma-1 receptors in mediating the antidepressant-like effects of DM, our lab recently showed that pretreatment with behaviorally inactive doses of sigma-1 receptor antagonists attenuates the antidepressant-like effects of DM, at least in the FST (Nguyen et al., 2014). Moreover, in the same study, since the dose response curve for DM shifted to the right in the presence of a sigma-1 antagonist, it is thought that DM is acting in a competitive manner at sigma-1 receptors to elicit the antidepressant-like behaviors (Nguyen et al., 2014).

DM may also elicit antidepressant-like effects through modulation of glutamatergic function, which is increasingly implicated in the pathogenesis and pharmacology of depression (Hashimoto, 2011; Nicu et al., 2013). Similar to ketamine, DM is an NMDA receptor antagonist, which is thought to be the primary mechanism by which ketamine produces its fast acting effects (Monteggia & Zarate, 2015). The NMDA receptors exist in vivo as tetrameric complexes comprising proteins from two families of homologous subunits, designated NR1 and NR2(A–D). In patients with major depressive disorder (MDD), a significant reduction in NR2A and NR2B, but not NR1 subunit expression was found in the PFC, a region that has long been implicated in the pathophysiology of depression (Feyissa et al., 2009). Interestingly, sigma-1 receptor agonists have been shown to up regulate NMDA receptor expression (specifically NR2A and NR2B, but not NR1) in the rat hippocampus (Zhang et al., 2011; Pabba et al., 2014), another area prominently involved in depression (Palazidou, 2012). Whether or not DM may induce changes in the activity or level of specific NMDA subunits in the hippocampus and PFC through sigma-1 receptors remains to be determined.

Along with NMDA receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors also appear critical for antidepressant responses, including rapid effects (Alt et al., 2006; Bleakman et al., 2007). Recent data from our lab suggest that AMPA receptors may also play a major role in mediating the antidepressant-like effects of DM (Nguyen & Matsumoto, 2015). It is not clear how DM may alter AMPA receptor activity, because it does not directly bind to AMPA receptors (Werling et al., 2007). Similar to ketamine, it is thought that the activation of AMPA occurs downstream from binding to initial targets (Jin, 2007; Lu & Bieger, 1996). Interestingly, sigma-1 ligands have been shown to regulate AMPA mRNA and protein expression levels (Guitart et al., 2000) and modulate AMPA receptor neurotransmission (Liang & Wang, 1998). Hence, DM may be activating AMPA receptors indirectly through activation of sigma-1 receptors or antagonism of NMDA receptors.
Finally, neural plasticity is hypothesized to be a final common pathway of different antidepressant therapies and may explain the delay in efficacy with conventional antidepressants (Nestler et al., 2002; Duman, 2014). An important contributor thought to be involved in driving antidepressant-relevant neural adaptations is brain derived neurotrophic factor (BDNF) (Castren & Rantamaki, 2010). Several studies have shown that serum BDNF levels are reduced in unipolar and bipolar depression and can be normalized by successful treatment (Castren & Rantamaki, 2010; Grande et al., 2010). In a double-blind study involving bipolar patients (type I or II) given placebo or DM (30 or 60 mg/day) in combination with valproic acid (VPA) for 12 weeks, participants had lower levels of plasma BDNF compared to healthy controls at baseline (Chen et al., 2014). Subsequent treatment with DM (60 mg/day) plus VPA produced a small increase in plasma BDNF levels from baseline at 12 weeks, and this increase was significantly higher than the increase seen in the placebo plus VPA group (Chen et al., 2014). Although this small increase did not correlate with measured improvements of clinical symptoms in this study, it may benefit other factors of clinical presentation not measured, such as a shorter duration of clinical course or other depressive conditions (Chen et al., 2014).

In the brain, post-mortem studies have reported reductions in BDNF in the PFC and hippocampus of suicide victims who were depressed relative to matched controls or patients taking an antidepressant at the time of death (Dwivedi et al., 2001). There is also normalization/upregulation of BDNF levels in the brains of MDD patients taking antidepressants compared with antidepressant-untreated subjects (Chen et al., 2001). Noteworthy, activation of AMPA receptors has been shown to increase rat hippocampal BDNF mRNA expression within a few hours of treatment compared to the chronic dosing that is typically required of conventional antidepressants (Mackowiak et al., 2002). In addition, in contrast to clinically used antidepressants that promote the transcriptional upregulation of BDNF, activation of sigma-1 receptors has been shown to potentiate its post-translational processing (i.e., the conversion of the precursor form, pro-BDNF, to the mature form, BDNF) without affecting the mRNA level of BDNF (Fujimoto et al., 2012). This provides a novel therapeutic opportunity for the treatment of depression (Fujimoto et al., 2012). Through activation of sigma-1 receptors, DM may also promote increases in other trophic factors such as nerve growth factor (Fishback et al., 2010). It is possible that DM, through these interactions, may facilitate neural adaptations faster than conventional antidepressants and thereby induce therapeutic effects on a faster time scale (Fig. 3).

Other mechanisms may contribute to the antidepressant effects of DM, including possible activity at 5-HT1B/D, alpha-2 adrenergic autoreceptors and nicotinic receptors (Hernandez et al., 2000; Damaj et al., 2005; Werling et al., 2007). The time lag in current SSRI antidepressant medications is believed, at least in part, to be due to desensitization of presynaptic 5-HT1A and 5-HT1B receptor subtypes, which occurs over 2–4 weeks. Similarly, a delay in therapeutic response with conventional antidepressants may be due in part to desensitization of alpha-2 noradrenergic autoreceptors (Estevez et al., 1999; Invernizzi & Garattini, 2004). Notably, mirtazapine, a noradrenergic and specific serotonergic antidepressant, has been found to have a faster onset of antidepressant action (as early as within the first week of treatment) compared to SSRIs and serotonin-norepinephrine reuptake inhibitors (Watanabe et al., 2011). Its primary mechanism of action is thought to be through blockade of alpha-2 noradrenergic autoreceptors and heteroreceptors, resulting in enhanced release of NE from noradrenergic terminals, and increased 5-HT release from serotonergic terminals, respectively (Croom et al., 2009). Whether or not DM may activate or inhibit 5-HT1B and alpha-2 noradrenergic receptors located presynaptically or postsynaptically remains to be determined.

Regarding nicotinic receptors, there is evidence suggesting that hypercholinergic neurotransmission, which is associated with depressed mood states, may be mediated through excessive neuronal nicotinic receptor activation and that the therapeutic actions of many antidepressants may be partly mediated through inhibition of these receptors (Shytle et al., 2002). Supporting this, a recent study in rat pheochromocytoma cells suggested that the therapeutic effects produced by ketamine may be the result of a combination of independent but interrelated pharmacological effects at the alpha-7 nicotinic receptors produced by the parent drug and its metabolites (Paul et al., 2014). DM has been found to act as an antagonist at nicotinic (alpha-3/beta-4, alpha-4/beta-2, and alpha-7) receptors (Hernandez et al., 2000; Damaj
DM has been shown to improve some neurological and psychiatric complications, but not overall functional outcome in stroke patients. Clinicians have successfully used DM off-label for many years, for example, to successfully treat PBA following stroke (Balakrishnan & Rosen, 2008). PBA is relatively common after a stroke; it can arise in up to 50% of cases (Miller et al., 2011) and reduces quality of life for patients (Rosen & Cummings, 2007). Due to the clear benefit of treating PBA following stroke, the FDA has approved a DM/quinidine capsule for use in PBA post-stroke (Yang & Deeks, 2015). A recent case report offers evidence that off-label use of the DM/quinidine capsule can also decrease agitation following a cerebellar stroke (Daly & Caplan, 2012). In a randomized, placebo-controlled trial (N = 40) examining the use of DM (300 mg/day for 5 days) as a neuroprotective agent following acute stroke, DM had no signifi-cant effect on the National Institutes of Health Stroke Severity Score (Mousavi et al., 2011). Of note, in this study, though DM did not worsen the patients’ conditions, DM increased the chance of myocardial infarction and renal failure by almost 5% compared to placebo-treated groups (Mousavi et al., 2011). Future work may need to use prolonged administration to reassess the neuroprotective potential of DM post-stroke, and lower doses to further improve its safety profile. In addition, it remains unclear whether DM will prove benefi-cial in ischemic or hemorrhagic stroke, or both. In children undergoing cardiac surgery with cardiopulmonary bypass (N = 13), who are at high risk for most likely ischemic brain injury, treatment with DM (36–38 mg/kg/day) yielded fewer abnormalities in the electroencephalo-graphy (EEG) and MRI than the placebo group (Schmitt et al., 1997). Though promising, the authors noted that the small number of children and dissimilarities of the treatment groups by chance diminish conclusions to possible protective effects of DM (Schmitt et al., 1997).

In preclinical studies, DM was neuroprotective in numerous models of focal and global ischemia in a variety of animals including rodents, rabbits, and gerbils (Werling et al., 2007b). The neuroprotective effects included reduction of neuronal damage, cortical infarct volume and edema as well as improvements in post-ischemic hypoperfusion and neurological functions (Werling et al., 2007b). As the preclinical results have been well-summarized previously by Werling et al. (2007b), we will focus on the potential mechanisms underlying the neuroprotective properties of DM. In addition, we will briefly highlight potential reasons behind the failure of DM to translate into clinical success for stroke.

In stroke, the infarct activates a cascade of biochemical events that ultimately lead to the death of brain cells. These events are complex and include excitotoxic mechanisms, inflammatory pathways, oxidative damage, cortical spreading depolarization (CSD), calcium imbalances, and apoptosis, most of which may be attenuated with DM treatment following injury to prevent further damage (Fig. 4). To decrease gluta-mate excitotoxicity, DM may inhibit NMDA receptors following ischemic stroke and prevent cell damage in the penumbra region. In primary rat neuronal cultures, DM attenuated glutamate-mediated excitotoxicity in a manner that appeared to correlate with its binding affinity to sigma-1 receptors (DeCoster et al., 1995). DM may also inhibit CSD. CSD is characterized by depression of evoked and spontaneous EEG activity spreading at a rate of 2–5 mm per min across the cortical surface (Lauritzen et al., 2011). These waves of depolarization may appear
spontaneously in the ischemic penumbra region, an area that has been functionally and metabolically compromised but not yet irreversibly damaged (Lauritzen et al., 2011). Though mechanisms initiating CSD remain unclear, studies have shown that the EEG depression coincides with and is caused by a failure of brain homeostasis, particularly potassium, and efflux of excitatory amino acids efflux from nerve cells, especially glutamate (Lauritzen et al., 2011). In rat brain slices, DM at a dose of 100 μM prevented CSD following ischemia, an effect that appeared independent of targeting NMDA receptors and was associated with its agonistic properties at sigma-1 receptors (Anderson & Andrew, 2002). Along with affecting CSD itself, DM may attenuate the hypoperfusion and infarct expansion that can be precipitated by CSD. In a mouse model of acute focal ischemia, DM preserved cerebral blood flow during ischemic depolarizations and prevented expansion of the area of severely hypoperfused cortex, providing a novel hemodynamic mechanism of neuroprotection to improve outcome following focal ischemic depolarizations (Shin et al., 2006).

Another reported benefit of DM is the reduction of reactive oxygen species (ROS) and inflammatory markers post-injury (Liu et al., 2003; Zhang et al., 2004; Feng et al., 2014). DM may decrease ROS by inhibiting nicotinamide adenine dinucleotide phosphate oxidase (Wu et al., 2012; Zhang et al., 2004), which is an important source of intracellular ROS and extracellular superoxide, and a promising target for reducing brain injury after stroke (Tang et al., 2012). In rats subjected to transient cerebral ischemia, DM attenuated the activation of extracellular regulated kinase 5 (ERK5) compared with vehicle controls (Wang et al., 2004). ERK5 activation has been closely related to free radical formation, and modulation of this pathway may help counteract oxidative stress-induced cellular damage (Suzaki et al., 2002). In this study, the authors also reported that nifedipine (an L-type VGCC blocker) prevented ERK5 activation to a similar extent as DM, suggesting that DM may in part inhibit VGCCs to regulate ERK5 activity (Wang et al., 2004).

Interestingly, in a rat model of transient, focal cerebral ischemia, DM attenuated the injury-related increase in rectal temperature, which was associated with its ability to protect neurons in temperature regulating hypothalamic centers (Britton et al., 1997). A strong correlation between rat rectal and brain temperatures has been shown during focal ischemic insults (Zhang et al., 1993), suggesting that DM may improve outcome in certain ischemic cases by limiting the transient increase in body temperature (Britton et al., 1997). Sigma-1 receptors, which have been shown to modulate methamphetamine-induced hyperthermia and neurotoxicity (Matsumoto et al., 2014), could contribute to this beneficial regulation of body temperature and also prevention of neuronal damage by DM.

The discrepancy between the substantial body of evidence indicating efficacy in preclinical studies and the limited and equivocal efficacy seen in clinical studies is not fully understood. One reason may be the limited central bioavailability of DM; while animal studies have typically used doses ranging from 10 to 80 mg/kg (administered via various routes of administration), clinical studies have used much lower oral doses (Werling et al., 2007b). In addition, while animals used in stroke research are a young, homogenous population with no comorbidities, humans who suffer ischemic stroke are usually an elderly, heterogeneous population with numerous comorbidities (Sutherland et al., 2012). This difference in population type may provide another reason for the discrepancy between human and animal studies, for none of the preclinical studies using DM so far have specifically used aged animals. Future work with DM should address this important age factor for preclinical stroke models. Evidence also suggests that gender plays an important role in ischemic stroke, in terms of influencing how patients present in the clinic to how they respond to treatment (Gibson, 2013). This is also supported by preclinical data such as those from mice pups, in which DM protected against ischemic brain injury in males, but not females, following unilateral carotid ligation (Comi et al., 2006). These findings suggest the presence of gender-dependent determinants of outcome which requires further elucidation (Comi et al., 2006). Investigating whether this also applies in adult rodents and other stroke models, as well as characterizing the pathologic mechanisms influenced by gender may inform the design for better
5.3. Traumatic brain injury

The use of DM in the context of TBI has been limited to date. In a patient with head trauma, hypoxia, and seizures refractory to antiepileptic drugs, DM normalized the EEG within 48 h and ceased seizures within 72 h (Schmitt et al., 1994). In TBI patients who developed PBA, the use of DM in combination with quinidine successfully treated PBA with minimal side effects (Pattee et al., 2014). DM administration thus has the potential to limit seizures and behavioral disturbances following TBI, thereby warranting further scientific investigation into its targeted effects.

Similar to stroke, two proposed mechanisms of DM conferring benefits in TBI include its activity at NMDA and sigma-1 receptors. Subsequent to the immediate brain tissue disruption (primary injury), secondary damage may take place hours, days, and weeks after the initial physical impact. These include glutamate excitotoxicity, CSD, oxidative stress and inflammation, which contribute to eventual tissue degeneration and functional loss (Chen & Shi, 2014) and may be attenuated by DM to improve functional outcomes. Indeed, in a penetrating, ballistic-like brain injury preclinical model, DM prevented axonal fiber degeneration and improved motor and cognitive performance in rats when given post-injury (Shear et al., 2009). In rat brain slices subjected to injury by a heavy weight, DM at a dose of 30 μM inhibited CSD and subsequent cellular swelling and damage (Church & Andrew, 2005). In this study, the DM effects were blocked by co-application of a sigma-1 receptor antagonist (Church & Andrew, 2005), suggesting the role of sigma-1 receptors in mediating the DM effects on CSD. In a mouse model of perinatal brain injury, DM (5 or 25 mg/kg, intraperitoneal, or i.p.) administration significantly attenuated excitotoxic lesion size in gray and white matter by reducing cell death (Keller et al., 2008). Moreover, pretreatment with the inflammatory mediators interleukin (IL)-1β or lipopolysaccharide (LPS) sensitized the developing brain to excitotoxic brain damage, causing an increase in lesion size and microglial activation (Keller et al., 2008), which were both abolished by DM treatment (Keller et al., 2008). This is likely due to DM’s NMDA receptor antagonistic effect, as excitotoxic brain injury has been shown to also be mediated by direct NMDA receptor-mediated microglial activation (Kaindl et al., 2012). DM’s neuroprotective effects may also be due to its anti-inflammatory properties, because DM administration has been shown to attenuate the LPS-mediated induction of several inflammation-related genes in vivo, including macrophage inflammatory protein-2, CXC chemokine, thrombospondin-1, intercellular adhesion molecular-1 and IL-6 (Li et al., 2005b). Additionally, Li et al. have demonstrated that DM inhibits the LPS-stimulated production of tumor necrosis factor (TNF)-alpha, nitric oxide and superoxide free radicals in microglial cells (Li et al., 2003). Cheng et al. also showed that DM suppresses activation of nuclear factor-κB, caspase-3 signaling, heat shock protein 60 and heat shock factor-1 and reduces the release of nitric oxide, inducible nitric oxide synthase, TNF-alpha, IL-1β and IL-6 induced by LPS in microglia (Cheng et al., 2015). In a more recent study, rats subjected to a controlled cortical impact injury, DM (30 mg/kg, i.p.) immediately after injury significantly reduced brain edema and neurological deficits, as well as increased neuronal survival (Pu et al., 2015). These effects correlated with a decrease of TNF-alpha, IL-1β and IL-6 protein expression and an increase of glutamate/aspartate transporter and glutamate transporter-1 in the cortex of the brain (Pu et al., 2015), further suggesting DM exerts neuroprotective effects via reducing inflammation and excitotoxicity induced following TBI. Additional studies are needed to examine the neuroprotective potential and therapeutic treatment window of DM on other secondary mediators of damage in TBI, including calcium dysregulation, mitochondria dysfunction, and oxidative stress (Werner & Engelhard, 2007; Andriessen et al., 2010).

5.4. Seizure

DM has shown some efficacy against refractory seizures in human clinical studies (Table 2). For example, in the largest trial to date, which involved an open-label study of DM as an add-on therapy in 16 patients with refractory partial epilepsy, DM (either 160 or 200 mg/day, for 8 weeks) improved seizure control (Kimiskidis et al., 1999). While the mechanisms for the antiepileptic potential of DM remain unclear, the authors also showed that DM had no effect on the anticonvulsant(s) plasma levels (Kimiskidis et al., 1999), suggesting that DM is primarily acting pharmacodynamically (vs. pharmacokinetically) to improve seizure control. It is important to note though that, at high doses, DM may precipitate seizures (Thompson & Wasterlain, 1993; Chyka et al., 2007; Majlesi et al., 2011), and health care providers should be vigilant for manifestation of this potential toxicity, particularly in DM abusers. Kimiskidis et al. posited several possible explanations for this proconvulsant phenomenon: 1) noncompetitive NMDA antagonists such as standard antiepileptic drugs (e.g., phenytoin and carbamazepine) have long been shown to produce clinical and/or electrographic seizures at toxic levels; 2) DM theoretically may lower standard antiepileptic drug levels via a pharmacokinetic interaction; and 3) the patients with increased seizure frequency upon DM administration may have had a decrease of seizure frequency during baseline (Kimiskidis et al., 1999). In contrast to the limited clinical evidence of the therapeutic potential of DM in seizures post-injury and in epilepsy, DM has demonstrated robust anticonvulsant effects in a variety of experimental seizure etiologies in rodents, including those related to NMDA, sound, theophylline, pentylentetrazol (PTZ), cocaine, kainate (KA) and trimethyltin (TMT) (Table 3).

The development of seizures can involve various biological pathways or processes, and structural or functional changes. Moreover, it is often unclear which mechanisms are required or necessary for the genesis of seizures in specific clinical cases, which are often idiopathic.

An important postulated mechanism being targeted by DM in seizure disorders is the dysregulation of glutamate. Glutamatergic molecular mechanisms that are involved during the initiation and progression of epilepsy and other seizures include elevation in extracellular glutamate concentration and abnormalities in glutamatergic transporters, which contribute to excessive glutamatergic activity and hyperexcitability (Hui Yin et al., 2013). DM has been shown to decrease glutamate release (Annels et al., 1991; Ohi et al., 2011) and attenuate NMDA-induced seizures (Ferkany et al., 1988; Sofia et al., 1994). In addition, using an in vitro model of epilepsy, DM (100 μM) blocked interictal bursts and prolonged ictal epileptiform afterdischarges induced by perfusion of guinea pig neocortical brain slices with a magnesium-free solution (Wong et al., 1988). DM also blocked NMDA-induced depolarizations without altering intrinsic membrane properties (Wong et al., 1988). In a similar in vitro study using rat neocortical slices, the potency of a range of PCP-like drugs as NMDA antagonists, including DM, DX, ketamine, MK801 and others, correlated well with their potency in blocking epileptiform activity in magnesium-free medium (Aram et al., 1989). These data suggest that DM may confer anticonvulsant activities partly by antagonizing NMDA receptors.

Another potential mechanism involves sigma-1 receptor activation and subsequent changes in gene expression following brain insults that might be regulated by transcription factors (Hui Yin et al., 2013). Cellular immediate early genes or inducible transcription factors such as members of the Jun family (c-jun, junB, junD) and the fos family (c-fos, fosB and fos-related antigens, fra-1 and fra-2) are believed to be involved in the pathogenesis of seizures (Hui Yin et al., 2013). Both of these gene families encode transcription factors such as c-fos and c-jun, which are major components of the transcription factor...
Table 2
Summary of DM in select human clinical studies and case reports for controlling refractory seizures post-injury and in epilepsy.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Design</th>
<th>Treatment</th>
<th>Main outcomes</th>
<th>Reference</th>
</tr>
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</table>
| Nonketoic hyperglycemia (NKH)    | Pediatric case reports N=4 (3 males) Follow up ranging from 3 months to 6 years | DM 3.5–22.5 mg/kg/day in combination with benzoate 500–750 mg/kg/day         | • Benzoate reduced and normalized glycine concentration in plasma, but not CSF  
• DM improved arousal, decreased or eliminated seizures in some patients (2 of 3 living patients; 1 died of intractable seizures at 3 months)  
• Additional of low-dose DM for 3 months led to improvement in EEG activity, resolution of myoclonus with increased eye contract and modest progression of development milestones  
• DM failed to control new seizures that developed 1 week later                                           | (Hamosh et al., 1998)                                               |
| Refractory temporal lobe epilepsy | Case report 48 yo female with 24-year history of refractory temporal lobe epilepsy with complex partial seizures | DM 6–20 mg/day                                                                 | • Adverse effects were mild and transient  
• DM reduced seizure frequency and severity                                                                       | (Wieser & Beck, 1992)            |
| Refractory epilepsy in brain damage | Pediatric case reports N=4 | DM 20–42 mg/kg/day given by tube between 48 h and 14 days after critical incident | • Taking DM for 3 months did not improve seizure frequency  
• DM arm of study increased monthly complex partial seizures frequency by 25% in 8 of 9 patients compared to placebo arm, but increase was not clinically significant  
• Side effects negligible  
• Children had seizures and frequent epileptiform abnormalities in EEG that were refractory to antiepileptic drugs  
• In 3 patients (with hypoxia, head trauma and hypoxia, or hypoglycemia), following DM, EEG improved within 48 h and seizures ceased within 72 h  
• Patient with neurodegenerative disease had improvement in EEG, but seizures were not controlled  
• Despite EEG improvement, clinical outcome was poor in all children  
• DM plasma concentration varied between 74–1730 ng/ml, DX between 349–3790 ng/ml  
• DM improved seizure control, especially in group of intermediate and slow metabolizers  
• Intermediate and slow metabolizers had greater reductions for Seizure Activity Index than fast metabolizers  
• 2 patients experienced increased seizure frequency and were withdrawn from study  
• DM well-tolerated even in patients with high plasma levels up to 15,020 ng/dl  
• Adverse effects were mild and transient  
• DM reduced seizure frequency and severity  | (Schmitt et al., 1994)         |
| Complex partial seizures         | Double-blind, crossover, add-on N = 9 (5 males; average age 36.4 years) | DM 120 mg/day                                                                | • No significant effects on key lab values (white blood count, hematocrit, platelet count, aspartate aminotransferase) or on primary anticonvulsant drug levels (phenytoin, carbamazepine)  
• DM well-tolerated even in patients with high blood level of DM; epileptiform abnormalities in EEG to relatively normal background activity  
• DM tapered off at 61 days of age  
• DM failed to control new seizures that developed 1 week later  | (Chien et al., 2012)                                               |
| Early myoclonic encephalopathy evolving into migrating partial seizures | Female neonate had erratic myoclonous movements and suppression-burst pattern in EEG initially that evolved later into alternating asymmetric tonic seizures | DM 20 mg/kg/day                                                                | • DM failed to control new seizures that developed 1 week later  
• No significant effects on key lab values (white blood count, hematocrit, platelet count, aspartate aminotransferase) or on primary anticonvulsant drug levels (phenytoin, carbamazepine)  
• Taking DM for 3 months did not improve seizure frequency  
• DM arm of study increased monthly complex partial seizures frequency by 25% in 8 of 9 patients compared to placebo arm, but increase was not clinically significant  
• Side effects negligible  
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• In 3 patients (with hypoxia, head trauma and hypoxia, or hypoglycemia), following DM, EEG improved within 48 h and seizures ceased within 72 h  
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• Adverse effects were mild and transient  
• DM reduced seizure frequency and severity  | (Chien et al., 2012)                                               |

CSF, cerebral spinal fluid; DM, dextromethorphan; DX, dextrorphan; EEG, electroencephalography; yo, year old.

activator protein-1 (AP-1). Increased expression of the AP-1 transcription factor, which generally occurs in parallel with increased AP-1 DNA binding activity, is seen in the rodent hippocampus during seizure activity (Hui Yin et al., 2013). Administration of DM has been found to dose-dependently attenuate KA-induced seizures and increases in hippocampal AP-1 DNA binding activity and AP-1 transcription factors at the level of mRNA and proteins (Kim et al., 1996; Kim et al., 2003a; Shin et al., 2005). Pretreatment with the sigma-1 preferring antagonist BD1047 (N'-[2-(3,4-dichlorophenyl)ethyl]-N,N,N'-trimethylthelane-1,2-diamine), but not the sigma-2 preferring antagonist ifenprodil, blocked the protective effects of DM (Kim et al., 2003; Shin et al., 2005). This suggests that the anticonvulsant properties of DM may involve the activation of sigma-1 receptors, which contrasts with previous reports of the ability of highly selective antagonists and antisense oligodeoxynucleotides for sigma-1 receptors to attenuate cocaine-induced convulsions (Matsumoto et al., 2014) and increased expression of the Fos family genes (Liu et al., 2005; Nguyen et al., 2014). The anticonvulsant actions of DM may therefore not only be dose-dependent, but also context dependent and rely on additional mechanisms. Indeed, in a model of Bay K8644 (methyl 2,6-dimethyl-5-nitro-4-[2-( trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate; a L-type VGCC agonist)-induced seizures, DM also attenuated seizures and
### Table 3

Summary of the behavioral and biochemical effects of DM in rodent seizure models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Species</th>
<th>Treatment</th>
<th>Main outcomes</th>
<th>Reference</th>
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| Amygdala-kindled               | Female Wistar rats             | • DM: 3.75–30 mg/kg, i.p.; 30 min before kindling stimulation  
• DX: 15 or 30 mg/kg, i.p.; 15 min before kindling stimulation | • DM dose-dependently increased focal seizure threshold (i.e., threshold for induction of afterdischarge recorded from amygdala)  
• At 30 mg/kg, DM induced motor impairments and seizures, but no PCP-like adverse effects (e.g., hyperlocomotion, stereotypes)  
• DX less potent in inducing anticonvulsant effects, but more potent in inducing motor impairing effects | (Lorsch & Honack, 1993) |
|                               |                                |                                     | • DM dose-dependently decreased seizure severity;  
• ED$_{50}$ = 59 mg/kg  
• DM (30 mg/kg) produced maximum anticonvulsant effect within 30 min and lasted for 2 h  
• DM (30 mg/kg) retarded the growth of afterdischarge in amygdala and cortex  
• DM (60 mg/kg) accelerated development of kindling and produced spontaneous seizures | (Takazawa et al., 1990) |
|                               | Male Sprague–Dawley rats       | • DM: 10–70 mg/kg, i.p.; 30 min before kindling stimulation | • DM lessened severity of already developed seizures  
• DM inhibited development of seizure activity  
• DM produced mild ataxia of the hind limbs, but no other obvious neurological alterations | (Feese et al., 1988) |
|                               | Male C57BL/6 mice for locomotor activity & CPP | Single administration  
• DM, DX, 3-MM, or 3-HM: 5–45 mg/kg; i.p.; 20 min before electrical stimuli (50 mA, 200 msec)  
Repeated administration  
• DM, DX, 3-MM or 3-HM: 20 or 40 mg/kg, i.p. daily for 7 days  
• DM, DX, 3-MM or 3-HM: 20 or 40 mg/kg, i.p. before placement into white compartment for CPP | • Highest dose produced deaths  
• Time to peak anticonvulsant effect was 1 h for p.o. and 2 h for i.p.  
• ED$_{50}$ for HS test examining neurological motor impairment: 130 mg/kg, p.o. or 71 mg/kg, i.p.  
• ED$_{50}$ for MES-induced seizures: 94 mg/kg, p.o. or 46 mg/kg, i.p.  
• Neurological impairment was about 1.5 times the anticonvulsant doses | (Kim et al., 2003b) |
|                               | Male CF-1 mice                 | • DM: 30, 100, or 300 mg/kg, i.p. or p.o.; at various times (0.5–4 h) before horizontal screen (HS) test and MES (50 mA for 200 msec) | • DM reduced NMDA (200 mg/kg, i.p.)-induced lethality  
• TD$_{50}$ for impaired rotorod procedure = 129 $\mu$mol/kg; ratio TD/ED = 1.21  
• DX: ED$_{50}$ = 102 $\mu$mol/kg; TD$_{50}$ = 70 $\mu$mol/kg; ratio TD/ED = 0.69 | (Ferkany et al., 1988) |
|                               | Male CD-1 mice                 | • DM: varying doses, i.p.; approximately 25 min prior to NMDA (250 mg/kg, i.p.) injection | • DM decreased incidence and intensity of audiogenic seizures and locomotor hyperactivity in ethanol-dependent group at the 6th hour of the ethanol withdrawal  
• DM (40 mg/kg) had no significant effects on locomotor activity in ethanol-naïve group | (Folia et al., 1994) |
|                               | Female albino mice             | • DM: 0.05–0.20 mg/kg, i.p.; 25 min before theephyline (300 mg/kg, i.p.) injection | • DM: ED$_{50}$ = 28.0 $\mu$mol/kg, i.p. or 70 nmol, i.c.v. at 15 min;  
35.5 $\mu$mol/kg, i.p. at 45 min  
• DX: ED$_{50}$ = 18.5 $\mu$mol/kg, i.p. or 35 nmol, i.c.v. at 15 min;  
36.8 $\mu$mol/kg, i.p. at 45 min | (Chapman & Meldrum, 1989) |
|                               | Male Wistar rats               | • DM: 10–40 mg/kg, i.p.; at 3rd hour of ethanol withdrawal; 3 h before sound stimulus (100 dB for 1 min) | • DM decreased incidence and intensity of audiogenic seizures and locomotor hyperactivity in ethanol-dependent group at the 6th hour of the ethanol withdrawal  
• DM (40 mg/kg) had no significant effects on locomotor activity in ethanol-naïve group | (Erden et al., 1999) |
|                               | Long Evans rat pups exposed to hypoxia | • DM: 30 mg/kg, i.p.; within 20 min of exposure to hypoxic condition (8% oxygen for 3 h on P7)  
• PTZ (2 mg/kg, i.v.) infused into lateral tail vein at P7–P90 | • DM prevented decrease in cortical thickness in hypoxia-exposed group at P14  
• DM prevented decrease in seizure threshold at P70–P90 | (Laroia et al., 1997) |
|                               | Male Sprague–Dawley rats prenatally exposed to morphine | • DM: 3 mg/kg, i.p. twice a day from P7 to P14  
• PTZ (10 mg/kg, i.p.) injected every 5 min at P14 until onset of status epilepticus | • Prenatal morphine exposure upregulated alpha-1 and downregulated beta-2 and gamma-2 subunits of GABA-A receptor in hippocampal CA1 region and temporal cortex in association with increased seizure susceptibility at P14  
• DM reversed the prenatal morphine-induced alterations, suggesting the altered subunit compositions of GABA-A receptor may contribute, at least in part, to increased seizure susceptibility in these rat offspring | (Wang et al., 2011) |

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<td></td>
<td>Male Fischer 344 rats</td>
<td>• DM: 12.5–75 mg/kg, p.o.; 15 min before KA (8 mg/kg, i.p.) injection</td>
<td>• KA-induced seizure activity correlated with increase in hippocampal opioid peptide mRNA levels; • DM dose-dependently decreased preenkephalin and prodynorphin mRNA levels</td>
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<td>• DM: 12.5–75 mg/kg, p.o.; 15 min before KA (8 mg/kg, i.p.) injection</td>
<td>• DM dose–dependently decreased seizure activity; • DM dose–dependently decreased seizure activity and mortality; • DM blunted cell loss in CA1 and CA3 of hippocampus, increase of AP-1 DNA binding activity, and c-jun/FRA expression in hippocampus</td>
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<td>Male Sprague–Dawley rats for KA</td>
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<td>• KA-induced seizures; • DM or DX increased seizure latency; decrease seizure activity; decreased mortality; decreased AP-1 DNA binding activity in hippocampus seen at 4 h post-KA; • Pretreatment with Bay K8644 potentiated KA-induced convulsive behavior and increase in AP-1 DNA binding activity; • Pretreatment with Bay K8644 counteracted protective effects of low dose DM or DX Bay K8644-induced seizures; • DM or DX dose-dependently attenuated seizures and increase in AP-1 DNA binding activity seen at 2 h post-Bay K8644; • DM decreased seizure intensity for cocaine or lidocaine individually; • DM decreased seizure incidence for cocaine or lidocaine individually</td>
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<td>Male Sprague–Dawley rats</td>
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<td>Male C57BL/6 mice for locomotor activity</td>
<td>Single administration</td>
<td>• DM dose–dependently attenuated seizures; • attenuated increase in c-fos/c-jun mRNA and protein expression, AP-1 DNA binding activity, and FRA-IR</td>
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<td></td>
<td>Male Fischer 344 rats</td>
<td>• DM: 12.5 or 25 mg/kg, s.c. twice at an interval of 6 h and then once a day for 26 days following TMT; • TMT: 8 mg/kg, i.p. given 30 min before 2nd DM administration and daily for 26 days; • Bay K8644: 1 or 2 mg/kg, i.p.; 15 min before DM; • Ifenprodil: 5 or 10 mg/kg, i.p.; 15 min before DM</td>
<td>• DM inhibited seizure activity; • DM prevented loss of neurons within CA1, CA3 and CA4 of hippocampus; • DM attenuated impairments of spatial reference memory in hidden platform task and impairments of associated memory in passive avoidance task; • DM attenuated decrease in sigma-1-like receptor immunoreactivity in CA1, CA3 and CA4 of hippocampus; • Pretreatment with BD1047, but not ifenprodil, blocked the protective effects of DM</td>
<td>(Shin et al., 2007)</td>
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3-MM, 3-methoxymorphinan; 3-HM, 3-hydroxymorphinan; AP-1, activator protein 1; CPP, conditioned place preference; dB, decibel; DF, dimemorfan; DM, dextromethorphan; DX, dextrophan; ED50, median effective dose; FRA-IR, fos related antigens immunoreactivity; GABA, gamma-aminobutyric acid; i.c.v., intracerebroventricular, i.p., intraperitoneal; i.v., intravenous; NMDA, N-methyl-D-aspartate; PCP, phencyclidine.

Increases in AP-1 DNA binding activity and AP-1 transcription factors (Shin et al., 2004; Kim et al., 2001), suggesting that DM may have anti-convulsant and protective effects in part through L-type VGCCs.

Dysregulation in the gamma-aminobutyric acid (GABA) system, such as altered expression of alpha-1, beta-2, and gamma-2 subunits of GABA-A receptors, has also been associated with epilepsy (Hui Yin et al., 2013). In an animal model of PTZ (a GABA-A receptor antagonist)-induced seizures, prenatal morphine exposure increased seizure susceptibility that was associated with an upregulation of alpha-1 subunits and down-regulation of beta-2/gamma-2 subunits in the hippocampal CA1 region and temporal cortex of rat offspring (Wang et al., 2011). Postnatal administration of DM prevented the prenatal...
morphine-induced alterations (Wang et al., 2011), suggesting that DM may have protective effects in part through alterations in the subunit composition of GABA-A receptors, though the precise mechanisms through which this is achieved remain to be elucidated.

Overall, DM may be facilitating anticonvulsant and neuroprotective effects through three major mechanisms: antagonist activity at NMDA receptors and VGCCs and agonist activity at sigma-1 receptors. Note-worthy, DM has been shown to not only protect against brain damage associated with KA- or TMT-induced seizures, but also attenuate the loss of neurons in the hippocampus (Kim et al., 1996, 2003; Shin et al., 2007). In addition, administration of DM prevented TMT-induced learning and memory deficits (Shin et al., 2007). Pretreatment with the sigma-1 receptor antagonist BD1047 prevented these beneficial effects of DM (Kim et al., 2003; Shin et al., 2007), suggesting that the positive effects on cognition could be related to sigma-1 agonism (Maurice & Lockhart, 1997). This may occur in addition to the neuroprotective effects, which are likely due to a combination of the NMDA and VGCC antagonism and sigma-1 agonism.

In relation to the doses required to achieve anticonvulsant actions, in a pharmacokinetic study of DM and DX in epileptic patients (N = 16), the pharmacokinetic parameters of DM showed wide intersubject variation, possibly attributed to the genetic polymorphism of DM metabolism (Kazis et al., 1996). This study suggested that DM given at dosages of 40 mg every 6 h (treatment period 1) and 50 mg every 6 h (treatment period 2) lasting 8 weeks each can produce plasma and brain concentrations similar to in vitro antiepileptic levels, without causing adverse effects (Kazis et al., 1996). In the follow up paper evaluating the efficacy of DM in these patients, Kimiskidis and colleagues reported that IM and PM subjects appeared to show greater reductions in the Seizure Activity Index than EM subjects (Kimiskidis et al., 1999). These preliminary clinical findings suggest that an increase in bioavailability of DM may result in greater therapeutic efficacy against seizures.

5.5. Pain

The analgesic effects of DM have been extensively studied for the treatment of numerous pain conditions, including cancer-related (Dudgeon et al., 2007; Siu & Drachtman, 2007), post-operative (Weinbroum et al., 2004; Suski et al., 2010), neuropathic (Zhou et al., 2012), and gastrointestinal pain (Zhou et al., 2011). Since it is beyond the scope of this review to fully explore the effects of DM on pain in each of these conditions, we have chosen to emphasize the therapeutic potential of DM in common pain conditions, that is, post-operative and neuropathic pain.

5.5.1. Post-operative pain

Managing post-operative pain can be challenging, especially due to inconsistent antinociception of opioids (Weinbroum et al., 2002). Considering that higher doses of analgesics usually increase unwanted side effects, the objective of pain management is to regulate pain at the lowest, but most effective doses of an analgesic. This intent is especially true with opioids, in view of well-documented side effects which include dizziness, nausea, constipation, and drowsiness (Eisenberg et al., 2006). The post-operative analgesic effect of DM has been explored in several clinical studies and in various types of surgeries. Although there is some inconsistency in the literature, DM administration prior to surgery appears to reduce the amount of other analgesics required to achieve post-surgical analgesia and possibly attenuate post-operative pain (Ilkjaer et al., 2000; Weinbroum et al., 2002; Ehret et al., 2013; Entezary et al., 2013). A combination of analgesics is an attractive therapeutic option because dual administration may allow for lower doses of each drug. This may lessen the unwanted side effects of each drug, while maintaining analgesia (Raffa, 2001).

DM has been examined in combination with opioids in most post-operative pain studies. In a particularly painful surgery for bone and soft tissue malignancies, for example, DM reduced the need for morphine post-operatively (Weinbroum et al., 2002). Patients were administered DM 90 min before surgery and had a patient-controlled analgesia device for morphine self-administration. The group receiving DM pre-operatively required only half of the morphine doses needed by the placebo group immediately after surgery, and this analgesic effect remained stable 3 days after surgery (Weinbroum et al., 2002). DM also significantly attenuated the intensity of self-reported pain scores compared to those of the placebo group. In a similar study in knee surgery patients, pre-emptive DM administration also reduced the need for opioids and attenuated self-reported pain scores, as compared to the placebo treated group, for 8 h post-surgery (Entezary et al., 2013). These results indicate that DM reduces the need for morphine and post-operative pain.

In contrast, in patients scheduled for an elective abdominal hysterectomy, DM produced no differences in pain scores compared to the placebo post-operatively (Ilkjaer et al., 2000). However, DM did reduce morphine consumption for up to 4 h post-operatively, with no differences between the groups at any other time point (Ilkjaer et al., 2000). In another study, DM did not affect morphine consumption in adolescents after a scoliosis operation, but did attenuate pain intensity in the first 4 h after surgery (Suski et al., 2010). These studies used similar anesthetics for the different types of surgeries. Thus, DM-induced reduction in analgesic consumption and pain intensity scores may rely on the type of surgery and age group.

Evidence from preclinical models have suggested that DM increases the serum levels of morphine, possibly by altering the formation of the main morphine metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) (Chen et al., 2005; Suski et al., 2010), thus potentially providing an additional mechanism for post-operative pain attenuation (Chen et al., 2005). However, in humans, DM did not affect the serum levels of morphine or its main metabolites, M3G and M6G (Suski et al., 2010). Baker and colleagues showed in mice that DM can potentiate the antinociceptive effects of mu agonists morphine, fentanyl, and sufentanil, but not delta or kappa agonists (Baker et al., 2002). This suggests that the potentiation of opioid nociceptive by DM arises from its indirect agonist action on mu opioid receptors. How this is achieved and through what other mechanisms reduction of required morphine after surgery is achieved by DM remains to be studied.

5.5.2. Neuropathic pain

Recent studies have provided evidence of DM analgesia also in experimental models of neuropathic pain. Neuropathic pain presents most commonly as hypersensitivity to noxious stimuli (i.e., hyperalgesia) or pain perception to non-noxious stimuli (i.e., allodynia). DM (10 mg/kg, i.p. once a day for 7 days) attenuated tactile allodynia and mechanical hyperalgesia after spinal nerve ligation (SNL) in rats (Morel et al., 2014). In a similar model, rats developed mechanical and thermal hyperalgesia after chronic constrictive injury of the sciatic nerve (Wang et al., 2009). After once a day administration for 7 days, DM (15–30 mg/kg, i.p. once a day for 7 days) attenuated tactile allodynia and mechanical hyperalgesia after spinal nerve ligation (SNL) in rats (Morel et al., 2014). In a similar model, rats developed mechanical and thermal hyperalgesia after chronic constrictive injury of the sciatic nerve (Wang et al., 2009). After once a day administration for 7 days, DM (15–30 mg/kg, i.p. once a day for 7 days) attenuated tactile allodynia and mechanical hyperalgesia after spinal nerve ligation (SNL) in rats (Morel et al., 2014). In a similar model, rats developed mechanical and thermal hyperalgesia after chronic constrictive injury of the sciatic nerve (Wang et al., 2009). After once a day administration for 7 days, DM (15–30 mg/kg, i.p. once a day for 7 days) attenuated tactile allodynia and mechanical hyperalgesia after spinal nerve ligation (SNL) in rats (Morel et al., 2014). In a similar model, rats developed mechanical and thermal hyperalgesia after chronic constrictive injury of the sciatic nerve (Wang et al., 2009). After once a day administration for 7 days, DM (15–30 mg/kg, i.p. once a day for 7 days) attenuated tactile allodynia and mechanical hyperalgesia after spinal nerve ligation (SNL) in rats (Morel et al., 2014).
 unwanted side effects. PDN-induced pain in the lower extremities was significantly reduced after daily administration of DM in a 6-week trial (Nelson et al., 1997). The administration of a high dose DM (averaging 381 mg/day) was accompanied by sedation, dizziness, lightheadedness, and ataxia (Nelson et al., 1997). Due to the negative side effects of repeated, high dose DM administration, a single high dose of DM (270 mg) was administered to PDN patients (Carlsson et al., 2004). Although DM significantly attenuated pain intensity, lightheadedness was still reported (Carlsson et al., 2004), indicating that high doses of DM have limited clinical potential.

One approach to reduce the dose of DM needed and increase bioavailability is to co-administer quinidine. In a recent double-blind, placebo-controlled study in patients undergoing knee ligament surgery, administration of DM in combination with quinidine required fewer analgesics, specifically nonsteroidal anti-inflammatory drugs, after surgery compared with the placebo group (without quinidine) (Ehret et al., 2013). Pharmacokinetic data in this study revealed that quinidine was effective in prolonging the half-life of DM and increasing its systemic availability (Ehret et al., 2013). In another study examining the ability of DM to increase the pain threshold of EMs and PMs in healthy subjects, DM had significant antinociceptive effects in the PMs, but not the EMs (Desmeules et al., 1999). These studies suggest that the CYP2D6 phenotype may play a critical role in mediating the spinal antinociceptive effects of DM. In a 13-week, phase 3, randomized-controlled trial (N = 379), the efficacy of DM combined with quinidine was investigated for PDN, in which two dosages of DM/quinidine, 45 mg/30 mg and 30 mg/30 mg, were compared to placebo for analgesic efficacy (Shaibani et al., 2012). Both DM/quinidine doses significantly attenuated pain scores compared to placebo (Shaibani et al., 2012). The higher dose of DM/quinidine was associated with more side effects such as dizziness, fatigue, and nausea and resulted in more discontinuations due to side effects than the lower dose of DM/quinidine and placebo (Shaibani et al., 2012). Though these side effects were mostly mild or moderate and of expected types, further exploration of different fixed-dose combinations of DM/quinidine may identify other effective doses with even less untoward side effects.

In a recent preclinical study using a rodent neuropathic pain model involving SNL, DM (10 mg/kg, i.p.) administered after the development of allodynia and hyperalgesia reversed these symptoms. It was associated with an increase in the phosphorylation of Tyr1336 residues in NR2B NMDA receptor subunits in the spinal cord (Morel et al., 2014). The molecular targets responsible for this effect on phosphorylation remain to be determined. It may involve DM’s agonist activity at sigma-1 receptors, as activation of these receptors can modulate the function of NMDA receptors (Lobner & Lipton, 1990; Pabba & Sibille, 2015). In addition, DM improved memory in the SNL animals (Morel et al., 2014), an effect likely due to the anti-amnestic effects conferred by sigma-1 activation (Maurice & Lockhart, 1997). With increasing evidence demonstrating that sigma-1 antagonists rather than agonists have great potential for neuropathic pain (Davis, 2015), DM’s agonist activity at sigma-1 receptors is unlikely to be contributing analgesic actions under these conditions. Sigma-1 receptor agonism, however, may have secondary benefit for associated symptoms.

Apart from affecting the phosphorylation state of NMDA subunits, DM is believed to attenuate pain primarily by directly inhibiting NMDA receptors in the dorsal horn of the spinal cord. After tissue injury, nociceptive signals travel via A-delta and C sensory fibers to the dorsal horn of the spinal cord. Once the signal is transmitted to dorsal horn neurons, NMDA receptors are activated by glutamate, leading to an increase in neuronal firing (Siu & Drachman, 2007). The increased neuronal activity caused by NMDA receptor activation raises intracellular calcium levels, causing a “wind-up” phenomenon, leading to longer and more severe pain sensations (Herrero et al., 2000; Siu & Drachman, 2007; Zhou et al., 2012). Prolonged NMDA receptor activation can trigger secondary pain, which increases the probability of acute pain deteriorating into chronic pain (Weinbroom et al., 2004; Iwata et al., 2007). DM inhibits NMDA receptors, thereby reducing the hyper-excitability of spinocephaline neurons by decreasing intracellular calcium levels, which decreases NMDA receptor-mediated increases in neural activity (Zhou et al., 2012). In other words, DM reduces pain by interrupting primary afferent neuronal transmission via the spinothalamic tract to the brain, thereby reducing pain perception.

5.6. Methotrexate neurotoxicity

DM has been shown to improve and/or resolve symptoms associated with MTX neurotoxicity in a few retrospective clinical studies (Drachman et al., 2002; Afshar et al., 2014). MTX is a folate antimetabolite drug with multiple clinical uses. For the treatment of rheumatoid arthritis using oral low doses, MTX affects purine metabolism and increases adenosine levels to eventually produce anti-inflammatory or immunosuppressive effects (Cutolo et al., 2001). For use as a chemotherapeutic, at high doses, inhibition of purine metabolism is not thought to be the main mechanism; rather, MTX competitively inhibits dihydrofolate reductase, a key enzyme that participates in tetrahydrofolate synthesis, resulting in decreased replication of cells (Cutolo et al., 2001). A clinically important side effect of MTX is CNS toxicity, which presents most frequently after high dose and/or intrathecal MTX administration. It is seen most commonly in patients with acute lymphoblastic leukemia, lymphoblastic lymphoma, or osteosarcoma, wherein MTX is often a major component of therapy (Afshar et al., 2014). The CNS toxicity has been categorized as being acute, subacute or chronic (Vezmar et al., 2003). Acute toxicity occurs within a few hours after administration, and patients usually exhibit signs of chemical meningitis: somnolence, confusion, headache, nausea, vomiting, and dizziness; it is usually transient, without permanent damage (Vezmar et al., 2003). Subacute and chronic toxicities occur within days to weeks or months to years after administration and are associated with changes in the brain and/or spinal cord which may be progressive and lead to coma and death in severe cases (Vezmar et al., 2003). A patient may exhibit seizures and stroke-like signs including hemiparesis, hemisensory deficits, aphasia, dysarthria, dysphagia, and diplopia with subacute toxicity, and signs of cognitive dysfunction, behavioral abnormalities, and spasticity with chronic toxicity (Vezmar et al., 2003).

The use of DM in MTX neurotoxicity appears promising, at least in the subacute setting. In five patients with severe subacute toxicity (most with dysarthria and/or hemiplegia) who were treated with 1–2 mg/kg/day oral DM, all five had resolution of symptoms (Drachman et al., 2002). In a larger study involving 18 patients treated with 1–3 mg/kg/day, 16 of the patients fully recovered (Afshar et al., 2014). Of note, earlier administration of DM resulted in faster improvement of impairments and led to prevention of recurrent seizure activity (Afshar et al., 2014). In a rat model of MTX-induced cognitive dysfunction, administration of DM (2 mg/kg, i.p. for 4 doses) at 1 month and later at 2 months after the last intrathecal MTX injection significantly and transiently reversed the cognitive deficits at both time points (Vijayanathan et al., 2011). Moreover, DM had no behavioral effects in the vehicle group, suggesting that its effectiveness at improving cognitive function among the MTX-treated rats results from opposing some pathological biochemical change specifically induced by MTX (Vijayanathan et al., 2011). Though increased excitatory amino acids have been correlated with the cognitive deficits in the rats (Vijayanathan et al., 2011), whether or not DM attenuated this increase to ultimately improve cognition remains to be determined. In addition, whether or not DM may have protective effects against late MTX neurotoxicity in clinical populations is unclear; in the Afshar et al. study, of the two patients who failed to fully recover after DM administration, one continued to have ataxia, speech and learning disabilities 9 years later, and the other had residual left-sided weakness 4 months after his initial event (Afshar et al., 2014). Future prospective, randomized placebo-controlled studies are needed to investigate the role of DM in reversing or preventing subacute MTX
toxicity and whether there is any effect on the more insidious neurocognitive toxicity associated with late/chronic MTX neurotoxicity.

While the pathophysiology of MTX neurotoxicity is not completely understood, one possible mechanism is through dysregulation of CNS folate homeostasis, specifically the disruption of the remethylation of homocysteine to methionine. Elevated levels of homocysteine in the plasma and CSF have been reported in patients who received intrathecal homocysteine and have clinical evidence of CNS neurotoxicity (Drachtman et al., 2002; Kishi et al., 2003; Quinn et al., 2004). Also, CSF studies of animals after four doses of intrathecal MTX given over 2 weeks revealed a significant increase in homocysteine and homocysteic acid concentration in association with recognition and spatial memory deficits persisting at least 3 months after the final injection (Vijayanathan et al., 2011). Homocysteine is an endogenous glutamate receptor agonist that preferentially acts on the NMDA receptor subtype (Obeid & Herrmann, 2006). Homocysteic acid, an oxidative product of homocysteine that can be produced and released by brain cells, also functions as an NMDA receptor agonist (Cuendo et al., 1990). Thus, the NMDA antagonism activity of DM could explain in part the use of DM as a treatment of MTX neurotoxicity. Similar to brain injury induced by trauma or stroke, homocysteine may also induce neurological dysfunction via oxidative stress (Obeid & Herrmann, 2006), providing an additional mechanism that DM could therapeutically target, alleviate, or reverse MTX neurotoxicity.

5.7. Parkinson’s disease

DM administration has yielded mixed clinical results for treating PD or improving side effects of PD medications (Bonuccelli et al., 1992; Saenz et al., 1993; Montastruc et al., 1994; Verhagen Metman et al., 1998a, 1998b). Early studies showed promising improvements at high doses (≥180 mg/day) as measured by the Universal PD Rating Scale (Bonuccelli et al., 1992; Saenz et al., 1993). However, a follow-up study failed to show improvement at a low dose, and documented unfavorable side effects at the previously reported higher doses (Montastruc et al., 1994). The authors noted that the lower dose or difference in average age of patients among studies may have contributed to the differing results (Montastruc et al., 1997). A differential response was also observed in another study, with only one-third of the patients showing beneficial effects from DM (Verhagen Metman et al., 1998a). In addition to treating the symptoms of PD, DM may also help with levodopa-induced dyskinesias without significantly reducing levodopa effectiveness (Verhagen Metman et al., 1998b). Further characterization of patient variables that may affect therapeutic outcomes are needed, including metabolism status, age, gender, and stage of disease progression.

In preclinical studies, DM has shown promise through several mechanisms. DM potentiated the effects of anti-PD drugs in restoring movement in a monoamine-depleted mouse model of PD (Kaur & Starr, 1995). DM blocked microglial activation and the resulting degeneration of dopaminergic neurons in LPS-treated cultures (Li et al., 2005a; Liu et al., 2003). DM was also neuroprotective to dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated cultures and in mice injected with MPTP (Zhang et al., 2004). The DM metabolite 3-HM was even more potent in producing this effect, which appeared to occur through a glia-dependent mechanism (Zhang et al., 2005, 2006). Aside from helping protect the dopaminergic neurons directly, DM has other properties which may prove useful in conjunction with other therapies. DM reduced levodopa-induced dyskinesias in the 6-hydroxydopamine rat model of PD (Paquette et al., 2008) possibly through 5-HT receptor agonism, but not NMDA antagonism (Paquette et al., 2012); however, these results were conflicting with a previous study that found only limited benefits of DM in combination with levodopa (Jimenez et al., 1999). The precise mechanisms that underlie these therapeutic effects have yet to be fully elucidated, but are consistent, at least in part, with NMDA antagonist and sigma-1 agonist actions of DM (Lee et al., 2000; Mishina et al., 2005). Earlier reviews have summarized the ability of these pharmacological actions to mitigate an array of cellular mechanisms that are common to neurodegenerative conditions including excitotoxicity, calcium dysregulation, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction (Atlan et al., 2001; Chen & Lipton, 2006; Lipton, 2006; Maurice & Su, 2009; Nguyen et al., 2015), though their ability to affect these mechanisms of neurodegeneration specific to PD remains to be studied. Future studies to systematically test these interactions in experimental models relevant to PD are thus warranted to gain additional insight into the therapeutic potential of DM for treating PD.

5.8. Autism

Although DM has not been extensively tested for the treatment of autism, a case study of a 10-year-old diagnosed with autism spectrum disorder (ASD), pervasive developmental disorder (PDD), and generalized anxiety disorder documented behavioral improvement while the child was taking DM 30 mg twice a day (Woodard et al., 2005). During this pseudo-experimental ABAB (single-subject design) trial, monitoring of classroom behavior as well as anecdotal reports from parents and teachers indicated less anxiety and tantrum behavior during both treatment phases compared to baseline phases. The investigators found mixed results in a follow-up study of 9- to 17-year-old autistic individuals (N = 7 ASD, N = 1 PDD) with a placebo-controlled, ABAB design, using a dose of 30 or 60 mg DM twice daily depending on age (Woodard et al., 2007). As a group, there was no significant difference between DM vs. placebo in treating problem behaviors or core symptoms. However, three of the autistic individuals responded individually to the treatment, with reductions in various core symptoms and/or problem behaviors. One individual responded particularly strongly, with greater than 25–50% reduction in all five core symptoms (irritability, social withdraw, stereotypy, hyperactivity, and excessive speech) and greater than 50% reduction in problem behaviors. This variability in response may be explained in part by the heterogeneous nature of ASD. Because most of the individuals in this study were severely affected with ASD and all experienced varying levels of mental disability, there are likely to be a multitude of variables related to the children’s ability to respond to the treatment. Carefully-designed studies on a wider population will be needed to determine how often and in which cases DM leads to behavioral improvement for autistic individuals. In addition, the metabolism phenotype of the subjects should be determined in future studies to ensure that therapeutic levels of DM are achieved.

The authors offered NMDA receptor antagonism as a potential mechanism, which is consistent with the finding that memantine can also lead to behavioral improvements in autistic individuals (Erickson & Chambers, 2006; Rossignol, 2009). Autistic individuals typically show reduced GABA to glutamate ratio in the brain (Harada et al., 2011). Moreover, NMDA antagonists such as memantine can enhance or impair hippocampal long-term potentiation (LTP) in a dose-dependent and task-specific manner (Mondadori et al., 1989; Parsons et al., 2007). Perhaps at the doses used in the above studies, DM-induced NMDA antagonism preferentially potentiated LTP. However, it is still unclear whether NMDA antagonism is a viable strategy to combat this imbalance and if DM or memantine exert their beneficial effects through this mechanism. In fact, inhibiting NMDA receptors may theoretically worsen the autism phenotype if parvalbumin-expressing GABAergic neurons are targeted (Saunders et al., 2013). Another theory put forth is that sigma-1 receptor agonists could lead to enhanced cognition in ASD and other neuropsychiatric diseases by increasing NMDA receptor trafficking to the cell surface (Hashimoto, 2015). More evidence that sigma-1 receptors could be targeted to modulate ASD core symptoms is the observation that sigma-1 agonists consistently have cognitive enhancing effects in a variety of preclinical models of cognitive dysfunction (Maurice & Lockhart, 1997). Much more work is clearly necessary to systematically test these interactions in experimental models relevant to ASD.
needed in both the clinical and preclinical side to determine the efficacy and mechanism of action of DM in treating ASD, but promising results in several patients warrant increased investigation of this topic.

6. Other considerations and future directions

6.1. Potential effects of metabolism on efficacy

The recent approval of a DM and quinidine combination medication has encouraged an expanded investigation of DM for new indications related to potential neuroprotective effects. Preclinical models suggest that DM metabolites lacking any significant behavioral effects could still have neuroprotective efficacy; 3-HM, for instance, may be neurotrophic for astroglial cells (Shin et al., 2011). DM and 3-HM have also been shown to inhibit protein kinase C-mediated glutamate release from cerebrocortical synaptosomes by reducing calcium influx through voltage-dependent calcium channels (Lin et al., 2009). Oral DM doses in the range of 10–75 mg/kg have demonstrated neuroprotective effects in preclinical models with animal brain DM levels >10,000 ng/g, but most clinical trials have only tested lower doses (Werling et al., 2007b). One clinical trial, dosing DM <10 mg/kg in neurosurgery patients, found that serum levels were highly correlated with fourfold lower CSF (r = 0.88, p < 0.001) and 68-fold higher brain (r = 0.72, p < 0.001) levels (Steinberg et al., 1996). There were no significant correlations between DM and DX levels and no consistent relationship between levels of DX in serum, brain or CSF (Steinberg et al., 1996). Eleven patients in this study attained brain DM >10,000 ng/g, but ten (92%) of them experienced adverse effects such as nystagmus, ataxia or distorted vision that resolved within 24 h after the last dose (Steinberg et al., 1996). Steinberg and colleagues had previously noted in an experimental model of focal cerebral ischemia that plasma levels of DM appeared predictive of cerebroprotective effects with better protection afforded at the higher plasma levels achieved (Steinberg et al., 1993). The inconsistencies between the many protective effects observed in preclinical studies and limited efficacy seen in clinical studies may in part be due to the fact that CYP2D6 activity was not assessed or controlled for in these studies. Future clinical trials should investigate the relationship between DM levels and significant efficacy or safety endpoints depending on the patient population and genotype/phenotype status.

6.2. Concerns about abuse liability and toxicity with long-term use

The pharmacodynamic effects of DM may lead to abuse liability, and OTC DM abuse has increased during the 2000s (Wilson et al., 2011). An analysis of 44,206 DM-related poison control center calls, registered in the National Poison Data System from 2000–2010, found the prevalence increased to a peak of 17.6 calls/million in 2006 and plateaued at 15.7 calls/million in 2010 (Wilson et al., 2011).

This trend has raised concerns since several preclinical animal models have demonstrated adverse effects on cognitive performance. For example, Krug and colleagues revealed that DM at 40 mg/kg in rats suppressed the potentiation of hippocampal field excitatory postsynaptic potentials and population spikes, which suggests DM may impair hippocampal LTP and learning, at least at this 40 mg/kg dosage (Krug et al., 1993). In another study, DM-induced memory impairments in spatial learning were found to be dose-dependent and to lead to declining performance in the Morris water maze (Bane et al., 1996). These cognitive impairments appeared to become permanent; although the 40 mg/kg dose of DM was only given during postnatal days 28–37 (within the adolescent period in rats), the rats also showed water maze impairments at 18 months (Bane et al., 1996). These cognitive impairments appeared to become permanent; although the 40 mg/kg dose of DM was only given during postnatal days 28–37 (within the adolescent period in rats), the rats also showed water maze impairments at 18 months (Bane et al., 1996). Other NMDA antagonists with similar patterns of suppressed LTP, like MK801, have caused morphological damage to rat cortical neurons that could be prevented by both anticholinergic and benzodiazepine pretreatment (Olney et al., 1991). Compared to the therapeutic doses (0.20–100 mg/kg, i.p.) in other preclinical studies, a dose of 40 mg/kg appears to be in the middle range. There also appear to be differences in lethal doses between the specific breeds of male mice tested since a 100 mg/kg dose was lethal in Swiss Webster mice (unpublished data) and not CF-1 mice, while the 300 mg/kg dose did produce deaths in CF-1 mice (Leander, 1989). Whether a higher dose DM continues to have protective effects or begins to elicit detrimental effects depends in large part on the species and experimental conditions, which may be due to its pleiotropic mechanisms of action and polymorphic CYP-dependent metabolism.

In humans, a one-time dose DM (120 mg, the maximum OTC daily dose) did not demonstrate driving impairment in a driving simulator or increase failures in field sobriety testing compared to the placebo gualafenine (400 mg) in healthy adult subjects (Perry et al., 2015). In contrast, Carter and colleagues found DM 100–300 mg/70 kg produced acute and temporary impairments in working memory, episodic memory, attention and metacognition in adults with histories of hallucinogen use (Carter et al., 2013). At a higher dosage of 400 mg/70 kg, DM produced subjective effects (perceptual changes, end-of-session drug liking and mystical-type experience) similar to the classic hallucinogen psilocybin according to volunteers with a history of prior hallucinogen use (Reissig et al., 2012). Other neurologic toxicity symptoms included nystagmus, slurred speech, light-headedness, and fatigue, which were more commonly reported at higher doses of DM (10 mg/kg/day) and occurred within 1 to 2 h of administration (Hollander et al., 1994). These neurotoxic doses of DM are much higher than the doses (usually 10–60 mg daily) used in PBA (Yang & Deeks, 2015) and several other clinical studies (Woodard et al., 2005; Shaibani et al., 2012; Chen et al., 2014; Kelly & Lieberman, 2014). Higher doses of DM have shown efficacy for some conditions, such as in refractory seizures and chronic neurologic pain, but it will be imperative to weigh the potential risks and benefits of these dosages.

CYP2D6 activity appears to be an important factor in the psychoactive effects of high doses of DM. In a pilot study comparing the subjective and psychomotor effects of 3 mg/kg DM in four EMs and two PMs, the authors found that PMs had greater psychomotor impairment on a manual tracking task and more negative subjective effects (e.g., sedation, dizziness) while EMs reported greater abuse potential (e.g., higher ratings on the visual analog scales of “good” drug effects and drug “liking”) (Zawertailo et al., 1998). In a follow up study, using 100 mg quinidine pretreatment with 3 mg/kg DM, the authors found that DM produced dose-dependent decrements in performance on a manual tracking task and digit symbol substitution test, while increasing the subjective feeling of “unpleasantness” and decreasing the positive subjective effects such as euphoria and drug liking (Zawertailo et al., 2010). These altered psychoactive properties of high dose DM, in which the negative subjective effects of DM became more pronounced and the positives effects were blunted, suggest that pretreatment with CY2D26 inhibitors may reduce abuse liability of DM (Miller, 2011).

While many of the above studies tested high doses of DM acutely and reported some detrimental cognitive effects, few studies have addressed the long-term use or abuse of DM. From case reports of long-term abuse of DM, chronic effects include recurrent mania from daily use of 100–400 mL (500–2000 mg) of DM for up to 8 years (Walker & Yatham, 1993), intermittent euphoria (Fleming, 1986), psychological dependence (Wolfe & Caravati, 1995), and severe cognitive deterioration (Hinsberger et al., 1994). Often, distinctions between acute and chronic overdose cannot be readily made, such as in the case of a 23-year-old man who presented to an emergency room with acute intoxication on top of chronic addiction (36–48 oz, or 2160–2880 mg daily of DM for up to 5 years) (Wolfe & Caravati, 1995). Supportive care measures for cases of DM acute toxicity may include benzodiazepines for seizures, aggressive cooling for hyperthermia, and naloxone for respiratory depression or coma (Antoniou & Juurlink, 2014).

One of the largest clinical trials (N = 553) of long-term DM use found that the most frequently reported treatment-related adverse
drug reactions (≥5% of the subjects) were nausea, dizziness, headache, somnolence, fatigue, diarrhea and dry mouth (Pattee et al., 2014). These side effects occurred early in the treatment course and were largely mild to moderate and transient (Pattee et al., 2014). This study dosed DM at 30 mg and quinidine at 30 mg twice daily. Although longer term efficacy and tolerability data for DM/quinidine would be beneficial, the safety and tolerability profile of DM/quinidine in this 1-year study (Pattee et al., 2014) and in earlier studies (which were 12–24 weeks in duration) (Yang & Deeks, 2015) suggests that at therapeutic doses, DM may not have the significant neurologic toxicity reported with higher doses and chronic abusers.

6.3. Additional novel therapeutic applications

Many other indications besides those summarized herein are being currently investigated with DM as a stand-alone or add-on treatment in clinical trials, including Rett syndrome, rheumatoid arthritis, Gulf War illness, diabetic macular edema, attention deficit hyperactivity disorder, agitation in depression, schizophrenia and AD, and episodic migraine. In addition, in an open-label study involving 10 patients with chorea of mixed etiologies, DM/quinidine at 20/10 mg twice daily has been found to produce mild to marked improvement in chorea in eight of the 10 patients (Ondo, 2012). The authors posited that this is likely due its antagonist activity at NMDA receptors, based on the efficacy of the low-affinity NMDA antagonist amantadine for Huntington's disease chorea symptoms and PD drug-induced dyskinesia (Kunig et al., 2000; O'Suilleabhain & Dewey, 2003). Of note, in a recent 10-week, phase 2 randomized clinical trial, Cummings and colleagues found the combination of DM/quinidine at doses up to 30/10 mg twice daily reduced AD-related agitation and was generally well-tolerated (Cummings et al., 2015). Additional indications that remain to be explored include aggression, other affective disorders, and cognitive impairments in a wide array of neurodegenerative disorders. DM may have effects on aggressive behavior through sigma-1 receptor modulation, as sigma-1 receptors are present in brain areas that have long been linked to the regulation of aggression (e.g., hypothalamus and amygdala) (Gundlach et al., 1986); and a prototypic sigma-1 agonist significantly reduced offensive behaviors in male mice (Beltran et al., 2006). The potential utility of DM in anxiety, post-traumatic stress disorder and obsessive–compulsive disorder may arise partly from its antagonistic activity at NMDA receptors similar to ketamine (Feder et al., 2014; Sayed et al., 2014). DM's hypothesized beneficial effects on cognition may have important implications in MDD, which includes a variety of symptoms consistent with cognitive impairment, and neurodegenerative diseases such as ALS, AD and PD. The improvement in cognition may arise from promotion of neuronal survival or growth (e.g., through induction of neurotrophic factors such as BDNF or glial-derived neurotrophic factor) (Zhang et al., 2006; Chen et al., 2014) or anti-apoptotic genes (Lee et al., 2003). Beneficial cognitive effects may also arise from the prevention or mitigation of further damage (e.g., by reducing glutamate excitotoxicity (Choi, 1987; DeCoster et al., 1995), oxidative stress (Feng et al., 2014), and microglial activation (Liu et al., 2003; Li et al., 2005; Thomas & Kuhn, 2005)). It is important to keep in mind, however, that these proposed beneficial effects on cognition may be dose-limited, because high doses of DM have been shown to produce some acute cognitive impairments (see Section 6.2) (Reissig et al., 2012; Carter et al., 2013).

Based on the data reviewed, the use of DM clinically appears most effective when used adjunctively with other established treatments, which enables the use of lower doses of established medications to increase tolerability. DM as a standalone treatment for neurological diseases appears less promising, because higher doses (in an attempt to increase plasma levels of DM) may be needed, at which point side effects are more likely to become problematic. This is because higher doses will lead to greater exposure of DX and potentially more adverse effects with limited benefit. It is possible that this liability can be addressed by including quinidine to reduce the metabolism of DM. Indeed, several recent clinical trials have reported on the safety as well as efficacy of DM/quinidine. Improved consistency in the clinical response to DM would also be achieved by systematically phenotyping subjects (EM, IM, and PMs) prior to dosing and monitoring levels to ensure that therapeutically relevant drug levels are being achieved.

7. Conclusion

DM is approved for use in the absence and presence of quinidine, making it amenable for repurposing and quick translation into the clinical setting. Another highly valuable feature of DM is that it is well-tolerated and has a wide safety margin when used at therapeutically approved doses. Based on preclinical studies, the uncompetitive, low affinity antagonism of NMDA receptors coupled with the high affinity agonist activity at sigma-1 receptors appear to be the two primary mechanisms through which DM conveys therapeutic benefit for CNS disorders. In contrast to the multitude of beneficial effects observed in preclinical models, the limited efficacy of the use of DM in some clinical trials thus far may be due to its rapid metabolism. Overall, findings to date suggest that DM may be promising in the development of future medical therapies, especially for depression, seizures, pain, and methotrexate neurotoxicity. Additional preclinical studies are needed to clarify the cellular actions of DM and larger, prospective clinical studies with pharmacokinetic data are needed to gain greater insight into the potential therapeutic role of DM in a broad spectrum of neuropsychiatric and neurological disorders.

Conflict of interest statement

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