Chapter 71

Dextromethorphan and Dextrorphan as Heuristic Rapid-Acting, Conventional, and Treatment-Resistant Antidepressants, with Substance Abuse Considerations

Edward C. Lauterbach, Samuel D. Shillcutt, Daniel E. Phillips

Department of Psychiatry and Behavioral Sciences, School of Medicine, Mercer University, Macon, GA, USA

Abbreviations

5HT1b/d Serotonin-1b/d receptor
5HTT Serotonin transporter
AMPA Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
DM Dextromethorphan
DO Dextrorphan
FDA Food and Drug Administration
IC50 Concentration required to produce 50% inhibition
KA Ketamine
kg Kilogram
K_i Inhibitor concentration at which 50% inhibition occurs
mg Milligram
mTOR Mammalian target of rapamycin
NET Norepinephrine transporter NMDA *N*-methyl-D-aspartate
nM Nanomolar
NMDA *N*-methyl-D-aspartate
NMDA-2A NMDA 2A receptor
NMDA-2B NMDA 2B receptor
PCP Phencyclidine
SSRI Selective serotonin reuptake inhibitor
< Less than
≤ Less than or equal to
> Greater than
≥ Greater than or equal to
>> Much greater than
α_2 Alpha-2 adrenergic receptor
β Beta adrenergic receptor
μ Mu opiate receptor
μM Micromolar
σ_1 Sigma-1 receptor

INTRODUCTION

Dextromethorphan (DM) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist and σ_1 receptor agonist used as an antitussive and in the treatment of pseudobulbar affect. DM shares properties with ketamine, an agent with demonstrated antidepressant properties in humans (Lauterbach, 2011, 2012; Zarate et al., 2010). Shared pharmacodynamic properties with ketamine, along with additional actions at other receptors, led to the initial consideration that DM may also possess antidepressant potential (Lauterbach, 2011), and that these properties may extend not only to major depressive disorder but also to *treatment-resistant* depression (Lauterbach, 2011, 2012). Further, a *rapid onset* of antidepressant action that is similar to ketamine and different from conventional antidepressants may also be achieved (Lauterbach, 2011, 2012). These considerations are explored below.

A number of investigations ranging from case series to open-label to crossover placebo-controlled studies have established antidepressant effects of ketamine, especially its *rapid-acting* antidepressant effect in both unipolar and bipolar depressive illnesses as well as its efficacy in *treatment-resistant* depression (Katalinic et al., 2013; Lauterbach, 2011; Zarate et al., 2010). Pharmacodynamic similarities between DM and ketamine include actions on NMDA, σ_1, μ opiate, and muscarinic receptors, calcium channels, and the serotonin transporter (5HTT) (Lauterbach, 2011).

DM is *O*-demethylated by the cytochrome enzyme CYP2D6 to dextrorphan (DO), the species thought to have the main euphoriant and abuse properties. Like ketamine, DM or DO can act as NMDA antagonists (Werling, Lauterbach, & Calef, 2007), σ_1 receptor agonists (Werling, Lauterbach, et al., 2007), calcium channel antagonists (Kamel et al., 2008), and 5HTT inhibitors (Codd, Shank, Schupsky, & Raffa, 1995; Martin et al., 1990; Werling, Keller, Frank, & Nuwayhid, 2007; Werling, Lauterbach, et al., 2007). Ketamine, DM, and DM's metabolite DO act as potentiators of μ opioid receptors (Baker, Hoffmann, & Meert, 2002), DM and DO bind μ receptors, and DM binding correlates with its antinociception (Codd et al., 1995), suggesting μ agonist properties whereas DO does not correlate with antinociception (Codd et al., 1995) and appears to act as a μ antagonist (Goldstein & Naidu, 1990). The seemingly paradoxical simultaneous μ antagonism and

μ potentiation of DO can be explained by non-μ mechanisms such as NMDA antagonism. Like the muscarinic antagonist ketamine (Durieux, 1995), DO is a muscarinic receptor ligand (Werling, Keller, et al., 2007), although it is not yet known whether it acts as a muscarinic antagonist. At least in pain disorders, ketamine response has predicted DM response in fibromyalgia (Cohen, Chang, Larkin, & Mao, 2004; Cohen et al., 2006; Lauterbach, 2011). Preclinical data support roles for NMDA, σ_1, and μ actions in antidepressant effects (Lauterbach, 2011, 2012), and clinical findings indicate the antidepressant efficacy of antagonism at NMDA receptors (see Conventional Antidepressants, below) and muscarinic receptors (Furey, Khanna, Hoffman, & Drevets, 2010; Jaffe, Novakovic, & Peselow, 2013), calcium channels (Pazzaglia, Post, Ketter, George, & Marangell, 1993; Ried et al., 2005; Walden, Fritze, Van Calker, Berger, & Grunze, 1995), and 5HTT (most conventional antidepressants). Consistent with the *rapid-acting* antidepressant effect of ketamine, there is clinical evidence that NMDA (Eby & Eby, 2006, 2010; Enya et al., 2004; Ferguson & Shingleton, 2007) and muscarinic (Jaffe et al., 2013) antagonism produce *rapid-acting* antidepressant effects. Concerning ketamine's *treatment-resistant* antidepressant effect, there is additional clinical evidence implicating NMDA antagonism as an effective antidepressant mechanism in this condition (Eby & Eby, 2010). Thus, the pharmacodynamic similarities of DM to ketamine involving receptors relevant to ketamine's clinical spectrum of antidepressant properties suggests the ability of DM or its metabolites to exhibit a similar antidepressant profile of efficacy to ketamine.

Receptor binding affinities of DM and DO suggest differential antidepressant mechanistic profiles for each drug with respect to receptors considered important in mediating antidepressant effects. As detailed in Table 1, relative binding potencies at different antidepressant mechanistic sites vary between DM, DO, and ketamine, including at the NMDA receptor high affinity site (DO > DM > ketamine), phencyclidine (PCP) receptor site (DO > DM), σ_1 receptor (DO > ketamine ≥ DM), μ receptor (DO > DM), μ receptor potentiation (DM ≥ DO > ketamine), muscarinic receptors (DO > ketamine), calcium channel (DM > DO > ketamine), and 5HTT (DM >> DO >> ketamine), indicating DO to be relatively more potent than DM at NMDA, PCP, σ_1, μ, and muscarinic sites, DM more potent than DO at calcium channel and 5HTT sites, but DO and DM both more potent than ketamine (Lauterbach, 2012). These effects generally occurred at or below micromolar concentrations, although DM and DO calcium channel blockade at 80 and 250 μM, respectively, cannot necessarily be discounted as nonphysiologic since DM and DO are concentrated in the brain up to 30 times plasma levels (Werling, Lauterbach, et al., 2007). These different mechanisms apply differentially to the rapid-acting, conventional, and treatment-resistant activities of antidepressant treatments. In summary then, DM and DO bind to receptors that have been associated with antidepressant response at generally physiological tissue concentrations (Lauterbach, 2011, 2012).

DM PHARMACODYNAMIC SIMILARITIES TO THE RAPID-ACTING ANTIDEPRESSANT KETAMINE

Receptor binding affinities of DM and DO suggest antidepressant mechanistic profiles for each drug with respect to rapid-acting antidepressant effects. As detailed in Table 1, relative binding potencies at different antidepressant mechanistic sites vary between DM, DO, and ketamine, including at the NMDA receptor high affinity site, PCP receptor site, σ_1 receptor, μ receptor, potentiation of μ receptor agonists, muscarinic receptors, and 5HTT (Table 2). DM and DO bind to these sites at or below physiological concentrations as seen in Table 1. These findings suggest that DO may be relatively more potent than DM at NMDA, PCP, σ_1, μ, and muscarinic sites, DM more potent than DO in potentiating μ agonists and at 5HTT, and DO and DM each more potent than ketamine at these sites (Lauterbach, 2012). These differences between DM and DO, however, are not clinically significant at physiological doses in cases other than for perhaps μ action (DM has agonist properties while DO has μ antagonist properties) and muscarinic receptor binding (not yet demonstrated for DM), and it may turn out that the rapid-acting effects of each drug depend more on the individual characteristics of patients undergoing treatment.

Rapid-acting antidepressant effects in particular have been related to NMDA receptor antagonism, σ_1 receptor stimulation, and muscarinic receptor blockade. Clinical evidence reveals that the NMDA antagonists magnesium (Eby & Eby, 2006, 2010; Enya et al., 2004) and memantine (Ferguson & Shingleton, 2007) produce rapid-acting antidepressant effects. Rapid-acting antidepressant NMDA receptor effects have been related in particular to antagonism at the high-affinity NMDA receptor site (Zarate et al., 2010) and NMDA-2A (Zarate et al., 2010) and NMDA-2B (Ibrahim et al., 2012; Preskorn et al., 2008; Zarate et al., 2010) receptors (Lauterbach, 2012). Preclinical evidence indicates σ_1 agonist antidepressant effects occurring quite rapidly (Lauterbach, 2012), and the σ_1 agonist igmesine has shown antidepressant activity in a double-blind clinical trial (Lauterbach, 2012). Ketamine administered in five repetitive doses 3 days apart upregulated forebrain muscarinic receptors and reduced behavioral sensitivity to scopolamine in mice (Morita et al., 1995). Moreover, there is clinical evidence that the muscarinic antagonist scopolamine produces rapid-acting antidepressant effects (Jaffe et al., 2013). DO and DM potencies exceed ketamine for the high-affinity NMDA site, DO exceeds and DM approximates the potency of ketamine for the σ_1 receptor, and DO exceeds the potency of ketamine for muscarinic receptors (Table 2). Furthermore, DM and DO are NMDA-2A antagonists, and DM attenuates NMDA-2B receptor expression at least in the morphine hyperalgesia model (Lauterbach, 2012). Thus, rapid-acting antidepressant effects can be effected by DM and DO through high-affinity NMDA, NMDA-2A, NMDA-2B, σ_1, and muscarinic mechanisms.

Additionally, the rapid-acting antidepressant effects of ketamine have been ascribed to activations of the mammalian target of rapamycin (mTOR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation, AMPA receptor trafficking, dendritic spine formation, and synaptogenesis (Lauterbach, 2012).

mTOR can be activated by stimulating σ_1 (Li, Xu, et al., 2010), μ (Cui et al., 2010), and β-adrenergic (Gelinas et al., 2007) receptors (Lauterbach, 2012), and by inhibiting 5HTT (through increasing synaptic serotonin concentrations) (Lauterbach, 2012). DM and DO are σ_1 agonists (Werling, Lauterbach, et al., 2007), DM is a μ agonist (Codd et al., 1995), DM and DO are twice as potent as ketamine in potentiating μ effects (Table 1), DO binds to β receptors (Werling, Keller, et al., 2007) and potentiates the effects of the

TABLE 1 Receptor Potencies of Dextromethorphan, Dextrorphan, and Ketamine

Receptor	Index	DM	DO	Ketamine	Relative Potencies
NMDA high-affinity site (Berman & Murray, 1996)	IC50 displacement of MK-801 in rat cerebellar granule cells	402 nM	147 nM	1074 nM	DO > DM > KA
PCP site (Werling, Keller, et al., 2007)	IC50 displacement of (+)pentazocine in rat hippocampus	2.1 μM	892 nM		DO > DM
σ_1 Site (Werling, Keller, et al., 2007)	K_i displacement of (+)pentazocine in male rats: Cerebellum Pons	 150 nM 196 nM	 118 nM		DO > KA ≥ DM
Robson, Elliott, Seminerio, and Matsumoto (2012)	K_i displacement of pentazocine in rat liver			140 μM	
μ Receptor (Villiger, Ray, & Taylor, 1983)	IC50 displacement of fentanyl in rat brain		3.9 μM		DO > DM
Bunzow et al. (1995)	K_i displacement of diprenorphine in cloned μ from rat brain in COS-7 cells		4.1 μM		
Codd et al. (1995)	K_i displacement of DAMGO in male rat forebrain	1.28 μM	420 nM		
μ Receptor potentiation (Baker et al., 2002)	μ Receptor agonist given i.p. produced antinociceptive potentiation in mice	DM i.p. was twice as potent as ketamine			DM ≥ DO > KA
		18–45 μM[a,b] (20 mg/kg)		36–90 μM[a] (40 mg/kg)	
Advokat and Rhein (1995)	μ Receptor agonist given *intrathecally* produced antinociceptive potentiation in mice		12–30 μM[a] (15 mg/kg)		
Muscarinic receptors (Werling, Keller, et al., 2007)	K_i displacement of quinuclidinyl benzilate in male rat forebrain	(>1 μM)	<1 μM		DO >> KA
Hirota, Hashimoto, and Lambert (2002)	K_i displacement of scopolamine on cloned muscarinic receptors in CHO cells:				
	M1 receptor			45 μM	
	M2 receptor			294 μM	
	M3 receptor			246 μM	
Calcium channels (Kamel et al., 2008)	Calcium uptake in bovine middle cerebral arteries	80 μM	150 μM	250 μM	DM > DO > KA
Serotonin transporter (Codd et al., 1995)	K_i displacement of serotonin in male rat forebrain	23 nM	401 nM		DM >> DO >> KA
Werling, Keller, et al. (2007)	K_i displacement of paroxetine in male rat hippocampus	40 nM	484 nM		
Nishimura et al. (1998)	K_i displacement of serotonin on cloned serotonin transporters in human embryonic kidney cells			162 μM	
Martin et al. (1990)	K_i displacement of paroxetine in rat brain synaptosomes			18.8 μM	

Potencies based on data in the literature. DM, Dextromethorphan; DO, dextrorphan, IC50, concentration required to produce 50% inhibition ketamine; K_i, inhibitor concentration at which 50% inhibition occurs; DAMGO, [D-Ala2,N- Me-Phe4,Gly-ol]-enkephalin; PCP, phencyclidine.
[a]*Extrapolated from animal data (Lauterbach, 2012).*
[b]*DM was administered systemically such that DM and DO species were not distinguished.*

TABLE 2 Rapid-Acting Antidepressant Actions

Relevant Receptor	Relative Potencies
NMDA high-affinity site	DO > DM > KA
Muscarinic receptors	DO > (?DM) >> KA
Other Possible Actions	**Relative Potencies**
PCP site	DO > DM
σ_1 Receptor	DO > KA ≥ DM
μ Receptor stimulation	DM
μ Receptor potentiation	DM ≥ DO > KA
μ Receptor antagonism	DO
Serotonin transporter	DM >> DO >> KA
β Receptor	DO > (?DM)

Potencies based on data in Table 1. Based upon relative potencies, DO is anticipated to be somewhat more likely to exert a more robust rapid-acting antidepressant effect than DM. Parentheses and question marks indicate a need for confirming data. NMDA, *N*-Methyl-D-aspartate; PCP, phencyclidine; DM, dextromethorphan; DO, dextrorphan, KA, ketamine.

β agonist isoproterenol (Kindman, Kates, & Ginsburg, 1991), and DM and, to a lesser extent, DO inhibit the 5HTT (Werling, Keller, et al., 2007; Werling, Lauterbach, et al., 2007), increasing ambient serotonin levels. Consequently, DM may activate mTOR through its μ, σ_1, and 5HTT effects whereas DO can activate it through σ_1, β, and to a lesser degree μ and 5HTT effects.

Rapid-acting antidepressant effects may be mediated by AMPA receptor trafficking and their activation. Although DM, DO, and ketamine do not directly affect AMPA receptors (Lauterbach, 2012), trafficking of AMPA receptors from intracellular to postsynaptic sites (Wang, Barbaro, & Baraban, 2006) and their subsequent activation (Zarate et al., 2010) are considered to be essential for ketamine's rapid-acting antidepressant effect (Lauterbach, 2012). mTOR is a key regulator of this AMPA receptor trafficking that reverses AMPA subunit deficits observed in human mood disorders (Lauterbach, 2012; Wang et al., 2006). NMDA PCP site antagonism (Katayama et al., 2007; Lauterbach, 2012), σ_1 stimulation (Lauterbach, 2012; Tsai, Hayashi, & Su, 2006), inhibited serotonin reuptake (Chitwood, Li, & Glanzman, 2001; Lauterbach, 2012), μ activation (acute AMPA activation) (Lauterbach, 2012), μ antagonism (chronic AMPA activation) (Lauterbach, 2012), and β stimulation (Tenorio et al., 2010) also activate AMPA transmission, and, as indicated above, DM and DO each affect the former four mechanisms (including through μ potentiation) and DO affects the latter two mechanisms. To the extent that DM or DO can activate mTOR, inhibit the PCP site, stimulate σ_1 and μ, potentiate μ, antagonize μ, or potentiate/activate β receptors, the subsequent induction of AMPA receptor trafficking and their subsequent activation could result in rapid-acting antidepressant effects.

Rapid-acting antidepressant effects may also be mediated by dendritic spine elaboration (Zarate et al., 2010) and synaptogenesis (Li, Lee, et al., 2010). NMDA activation inhibits dendritic spine formation (Sala, Cambianica, & Rossi, 2008) while σ_1 agonists promote their outgrowth and maturation (Lauterbach, 2012; Tsai et al., 2009). Synaptogenesis is dependent on mTOR (Li, Lee, et al., 2010) and σ_1 stimulation (Tsai et al., 2006). Thus, the NMDA antagonist, σ_1 agonist, and mTOR activating effects of DM and DO are consistent with promoting the dendritogenesis and synaptogenesis that are linked to rapid-acting antidepressant effects.

In summary, DM (NMDA, NMDA-2A, NMDA-2B, PCP site, σ_1, μ, 5HTT, mTOR, AMPA, dendritogenesis, synaptogenesis) and DO (NMDA, NMDA-2A, PCP site, σ_1, μ, 5HTT, muscarinic, β, mTOR, AMPA, dendritogenesis, synaptogenesis) can potentially exert rapid-acting antidepressant effects through a variety of mediating mechanisms (Lauterbach, 2011, 2012). Considering the differential effects of DM and DO on these mechanisms, it seems somewhat more likely that DO will exert a more robust rapid-activating antidepressant effect than DM.

Conventional Antidepressants

Traditional antidepressant mechanisms include inhibition of the 5HTT and norepinephrine transporter (NET), muscarinic antagonism, α_2 and β receptor downregulation, and serotonin-1b/d (5HT1b/d) stimulation (Lauterbach, 2012). DM and DO exhibit pharmacodynamic similarities to conventional antidepressants and 5HTT has been discussed above in the rapid-acting antidepressant section. Although neither DM nor DO displaced the NET ligand nisoxetine in male rat cortical neurons at 1 μM concentrations (Werling, Keller, et al., 2007), they did so in rat vas deferens at 6 and 6.2 μM IC50s, respectively (Pubill et al., 1998), and each displaced NET binding with respective K_is of 240 and 340 nM in male rat forebrain (Codd et al., 1995). Pharmacodynamic comparison of DM and DO to the antidepressant drugs amitriptyline and fluoxetine in rat brain showed similar binding profiles for muscarinic (detailed in the rapid-acting antidepressant section), β, α_2, and 5HT1b/d receptors (Werling, Keller, et al., 2007). At 1 μM concentrations, 60% DM and 0% DO binding occurred at α_2 receptors in male rat hippocampus, 0% DM and 35% DO binding was present at β receptors in male rat cortex, and 61% DM and 54% DO binding was evidenced at 5HT1b/d receptors in male rat cortex (Werling, Keller, et al., 2007), although whether DO binds as a muscarinic antagonist, DM binds α_2 either as a presynaptic antagonist or postsynaptic agonist, or either DM or DO binds 5HT1b/d as an agonist have apparently not yet been studied. Thus, DM and DO have the potential to act as conventional antidepressants.

Additionally, NMDA, PCP, and σ_1 receptors, bound by both DM and DO, may also play roles in conventional antidepressant response. Conventional antidepressant mechanisms that may be engaged by DM and DO are summarized in Table 3.

Magnesium is an NMDA receptor antagonist, and magnesium ions guard the ion pore of the NMDA receptor. Depression is a manifestation of hypomagnesemia (Berkelhammer & Bear, 1985). In erythrocytes of patients with major depression, decreased magnesium concentrations correlated with depressive severity, and both amitriptyline and sertraline, conventional antidepressants, have been documented to reverse this reduction (Nechifor, 2009). Indeed, magnesium proved to be as effective an antidepressant as the tricyclic antidepressant imipramine in 23 hypomagnesemic

TABLE 3 Conventional Antidepressant Actions

Relevant Receptor	Relative Potencies
Muscarinic receptors	DO > (?DM) >> KA
Serotonin transporter	DM >> DO >> KA
Norepinephrine transporter	DM ≥ DO
α_2 Receptor	DM > (?DO)
β Receptor	DO > (?DM)
Serotonin-1b/d receptor	DM ≥ DO
Other Possible Actions	**Relative Potencies**
NMDA high affinity site	DO > DM > KA
PCP site	DO > DM
σ_1 Receptor	DO > KA ≥ DM
μ Receptor antagonism	DO
Calcium channels	DM > DO > KA

Potencies based on data in Table 1. Based upon relative potencies, DM may be slightly more likely to exert conventional antidepressant effects than DM. Parentheses and question marks indicate a need for confirming data. NMDA, *N*-Methyl-D-aspartate; PCP, phencyclidine; DM, dextromethorphan; DO, dextrorphan, KA, ketamine.

patients with diabetes mellitus type II (Barragán-Rodríguez, Rodríguez-Morán, & Guerrero-Romero, 2008). It is interesting to note that NMDA-2A, NMDA-2B, and mTOR perturbations have been demonstrated in the prefrontal cortex of depressed subjects relative to healthy controls (Jernigan et al., 2011). Desipramine, amitriptyline, and imipramine appear to antagonize NMDA receptors in long-term potentiation paradigms (Watanabe, Saito, & Abe, 1993) while chronic administration of imipramine, clomipramine, citalopram, and electroconvulsive therapy appear to downregulate NMDA receptor density and function (Harvey, Jonker, Brand, Heenop, & Stein, 2002; Pallotta, Segieth, & Whitton, 1999; Popik, Wróbel, & Nowak, 2000). Imipramine and citalopram also reduce NMDA receptor subunit transcription, an action that may be critical to antidepressant activity (Boyer, Skolnick, & Fossom, 1998). It is interesting to note that NMDA-2A, NMDA-2B, and mTOR perturbations have been demonstrated in the prefrontal cortex of depressed subjects relative to healthy controls (Jernigan et al., 2011), and the actions of DM and DO on these mediators has been detailed above (in the section on rapid-acting antidepressants).

The tricyclic antidepressant desipramine acts like the PCP receptor polyamine site antagonist MK-801 (Sernagor, Kuhn, Vyklicky, & Mayer, 1989), and the tricyclics amitriptyline, imipramine, fluoxetine, and citalopram increase MK-801-induced locomotor hyperactivity (Maj, Rogóz, Skuza, & Sowińska, 1992). DM has a similar NMDA PCP receptor site binding affinity to memantine (Werling, Keller, et al., 2007), another NMDA receptor antagonist, and memantine has demonstrated antidepressant activity in major depression in both an open-label flexible-dose study of memantine (Ferguson & Shingleton, 2007) and a double-blind randomized controlled trial of memantine and escitalopram in the context of alcohol dependence (Muhonen, Lönnqvist, Juva, & Alho, 2008).

A number of antidepressants including imipramine and several selective serotonin reuptake inhibitors (SSRIs) have moderate to high affinities for the σ_1 receptor (Bermack & Debonnel, 2005), σ_1 agonists such as cutamesine have shown antidepressant activity including increased dorsal raphe firing rates in preclinical models like the forced swim test (Lauterbach, 2012), and σ_1 receptor activation has been related to SSRI antidepressant efficacy in particular (Stahl, 2005). A number of antidepressants including imipramine, fluoxetine, paroxetine, and reboxetine upregulate μ receptors (Lauterbach, 2012), and the μ antagonist properties of DO suggest the possibility that it could similarly upregulate μ receptors. Finally, clinical observations of calcium channel blocker antidepressant efficacy implicate calcium channels as a mechanism of antidepressant action. These have included observations of a mild antidepressant effect in a large hypertensive population treated with verapamil (Ried et al., 2005), remission of depressive disorders in a case series treated with nimodipine and assessed with the Hamilton depression rating scale (Walden et al., 1995), and prevention of depressive relapse in a double-blind trial of nimodipine in a series of patients with ultra-rapid cycling bipolar disorder (Pazzaglia et al., 1993).

These transporters and receptors, bound by DM (5HTT, NET, α_2, 5HT1b/d, NMDA, NMDA-2A, NMDA-2B, PCP, σ_1, calcium channels) and DO (5HTT, NET, muscarinic, β, 5HT1b/d, NMDA, NMDA-2A, PCP, σ_1, μ, and perhaps calcium channels), support the idea that DM and DO may engage mechanisms involved in a conventional antidepressant response in addition to effecting rapid-acting antidepressant mechanisms (Lauterbach 2011, 2012). However, whether or not DM and DO bind as an agonist or antagonist to α_2, muscarinic, and 5HT1b/d receptors awaits determination.

Treatment-Resistant Depression Rationale

Approaches to treatment-resistant depression have included ketamine (Rao & Andrade, 2010; Stefanczyk-Sapieha, Oneschuk, & Demas, 2008), NMDA-2B antagonists (Ibrahim et al., 2012; Preskorn et al., 2008; Zarate et al., 2010), increased serotonin and norepinephrine release (Carpenter, Jocic, Hall, Rasmussen, & Price, 1999), α_2 antagonists (Carpenter et al., 1999), and a general tendency to use combinations of agents that maximize the involvement of multiple receptor mechanisms linked to antidepressant response (Carpenter et al., 1999). A number of investigations document the antidepressant efficacy of ketamine in treatment-resistant depression (Lauterbach, 2011; Zarate et al., 2010). Low levels of the NMDA antagonist magnesium in cerebrospinal fluid and in brain have been documented in treatment-resistant depression (Eby & Eby, 2010). Magnesium has furthermore been demonstrated to have antidepressant efficacy in treatment-resistant depression (Eby & Eby, 2010). Additionally, σ_1 (Noda, Kamei, & Nabeshima, 1999) and μ (Berrocoso & Mico, 2009; Kabli, Nguyen, Balboni, O'Dowd, & George, 2013; Schreiber, Bleich, & Pick, 2002) agonists have been considered for treatment-resistant depression. The multiple receptor actions of DM (NMDA, NMDA-2B, PCP, σ_1, μ, 5HTT, NET, α_2, 5HT1b/d, calcium channels) and DO (NMDA,

TABLE 4 Treatment-Resistant Depression Antidepressant Actions

Relevant Receptor	Relative Potencies
NMDA high-affinity site	DO > DM > KA
σ1 Receptor	DO > KA ≥ DM
μ Receptor stimulation	DM
μ Receptor potentiation	DM ≥ DO > KA
α_2 Receptor	DM > (?DO)
Multiple receptor mechanisms including calcium channels, 5HTT, NET, and 5HT1b/d receptor	DM > DO
Multiple receptor mechanisms including the PCP site and muscarinic and β receptors	DO > DM
	DO > (?DM)

Potencies based on data in Table 1. Based upon relative potencies, it is difficult to judge whether DM or DO will exert a more robust treatment-resistant antidepressant effect, and it may turn out that each species might be preferentially effective in differential subpopulations. Parentheses and question marks indicate a need for confirming data. NMDA, *N*-Methyl-D-aspartate; PCP, phencyclidine; 5HT1b/d, serotonin-1b/d receptor; 5HTT, serotonin transporter; β, beta adrenergic receptor; DM, dextromethorphan; DO, dextrorphan; KA, ketamine; NET, norepinephrine transporter.

PCP, σ_1, μ, 5HTT, NET, muscarinic, β, 5HT1b/d, and possibly calcium channels) offer the tantalizing possibility of their utility in treatment-resistant depression (Lauterbach, 2011, 2012) and are summarized in Table 4.

DM and DO, or DM Alone?

Given the overlapping and complementary receptor profiles of DM and DO (Table 5), the use of DM alone allows brain exposure to both DM and DO and may offer greater potential for antidepressant activity across rapid-acting, conventional, and treatment-resistant domains. On the other hand, from a safety perspective, psychotomimetic and abuse potential has been associated with DO (Schadel, Wu, Otton, Kalow, & Sellers, 1995), and side effects, plasma and brain concentration variability (Lauterbach, 2012), and logistical complexity are more likely with this approach (Lauterbach, 2012), suggesting an advantage of coadministering a CYP450 inhibitor to block the conversion of DM to DO. The Food and Drug Administration (FDA)-approved Nuedexta® constitutes one such approach to blocking this conversion, allowing the functional administration of DM alone. Moreover, the quinidine component can afford additional antimuscarinic antidepressant effects that DM is not known to provide, and that remain to be proven for DO. In any event, we have detailed elsewhere specific considerations for a clinical trial of either agent, and these detailed considerations should be scrutinized (Lauterbach, 2012).

Although no studies of DM or DO have yet been published, an open-label study of Nuedexta in treatment-resistant depression (NCT1882829) is currently enrolling. Several case reports indicate that DM can induce mania and improve treatment-resistant depression (Table 6). These reports support the possibility of antidepressant potential, since antidepressants are also associated with inducing mania. They further document that mania can also be induced by the μ receptor ligands propoxyphene and hydrocodone. A single case report indicates DM efficacy in improving treatment-resistant depression, although it is not clear which specific major depressive symptoms other than mood, crying, and function improved (Table 6).

Until study results are published, DM dosing has involved 5 mg/kg administered beginning at 90 mg and escalating every 6 h for five doses up to 210–400 mg over 30 h and continued for several weeks, with patients assessed by clinical depression ratings (Lauterbach, 2012). Since DM has a short half-life, patients will be predominantly exposed to DO by this method, and patients who are CYP2D6 poor metabolizers are unlikely to derive benefit from metabolism of DM to DO (Lauterbach, 2012). Patients who are hypersensitive to DM or any of its metabolites, taking monoamine oxidase inhibitors, or taking CYPD2D6 inhibitors (most antidepressants) should be excluded, and caution is advised in patients with cardiac disease or otherwise at risk for dysrhythmias (Lauterbach, 2012). Side effects, risks, and tolerability are detailed elsewhere (Lauterbach, 2012). For DM with quinidine, the best advice is to follow the FDA-approved treatment guidelines, exclusions, and caveats for Nuedexta, with some of these highlighted elsewhere (Lauterbach, 2012). It is anticipated that a single 20 mg DM–10 mg quinidine dose every 24 h for a period of 7 days may be suitable to engage most of the mechanisms indicated in Table 5. Patients should be followed on this dose for 4 weeks by means of clinical ratings (Lauterbach, 2012).

Applications to Other Addictions and Substance Misuse

Although DM itself has abuse potential, it is possible that abuse potential of DM itself *may* be reduced by CYP2D6 inhibition to prevent its conversion to DO. It still remains uncertain if DM is effective in major depression, let alone depressive syndromes that complicate substance abuse. If treatment is effective, amelioration of a depressive syndrome may or may not reduce the likelihood of a relapse in underlying substance use disorders. Case reports of DM induction of mania (Table 6) have been noted in those with a history of alcohol and opiate abuse. Of interest, a family history of alcohol dependence has been observed to predict an antidepressant response to a single dose of ketamine (Luckenbaugh et al., 2012; Phelps et al., 2009). Moreover, DM NMDA antagonist effects appear to be particularly salient in major depression that attends alcohol dependence since the NMDA antagonist memantine has been found to be effective in a double-blind controlled trial in these patients (Muhonen et al., 2008). These findings further suggest that certain substance use disorders may confer factors that select for a positive DM antidepressant response, suggesting a direction for future research inquiry. DM conjoined with CYP2D6 inhibition by quinidine has also been helpful in reducing the symptoms of heroin withdrawal (Akerele et al., 2008). In summary, to the extent that DM proves to be similar to ketamine in its clinical antidepressant efficacy, it is expected that DM may be particularly useful in treating major depression in alcoholism, and perhaps in opiate dependence.

TABLE 5 DM and DO Heuristic Antidepressant Mechanisms

	Type of Antidepressant Action					
	Rapid-Acting		Conventional		Treatment- Resistant	
Mechanism	DM	DO	DM	DO	DM	DO
NMDA Receptor Sites						
NMDA	+	+	+	+	+	+
High-affinity	+	+			+	+
PCP site	+	+	+	+	+	+
NMDA-2A	+	+	+	+		
NMDA-2B	+		+		+	
σ1	+	+	+	+	+	+
μ Agonist[a]	+				+	
μ Potentiation	+	+			+	+
μ Antagonist		+		+		
Muscarinic		+		+		+
α_2			+		+	
β		+		+		+
Serotonin-1b/d			+	+	+	+
5HTT	+	+	+	+	+	+
NET			+	+	+	+
Calcium channels			+	+	+	+
mTOR	+	+				
AMPA	+	+				
Dendritogenesis	+	+				
Synaptogenesis	+	+				

Mechanisms that are possibly engaged by DM and DO to mediate rapid-acting, conventional, and treatment-resistant antidepressant effects. 5HTT, Serotonin transporter; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DM, dextromethorphan; DO, dextrorphan; mTOR, mammalian target of rapamycin; NET, norepinephrine transporter; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine.
[a]*μ Agonist activity is suggested by μ receptor binding correlating with antinociceptive activity (Codd et al., 1995) but remain to be more definitively demonstrated.*

KEY FACTS ON DEXTROMETHORPHAN AND DEXTRORPHAN

- Not all cases of depression respond to conventional antidepressants, and new antidepressants are needed.
- Ketamine is one such new antidepressant, possessing the capacity to rapidly improve depression within days, contrasting with conventional antidepressants that take months to exert their full response.
- DM and its metabolite DO share a number of pharmacodynamic actions with ketamine that are relevant to ketamine's antidepressant activity and occur at similar physiological doses.
- In addition to the possibility that DM and DO can produce rapid-acting antidepressant effects like ketamine, DM and DO may also harbor conventional antidepressant activity, and may be further effective in cases of treatment-resistant depression that is unresponsive to conventional antidepressants.
- DM and DO possess some unique pharmacodynamic properties that distinguish them from each other in their potential to produce rapid-acting, conventional, and treatment-resistant antidepressant effects.
- Clinical trials are under way to determine these antidepressant effects, but results have not yet been published.
- DM has been abused, but abuse potential seems to be related to its metabolite DO, rather than to DM itself, which has a short half-life.
- Strategies to selectively functionally administer DM or DO are discussed.

TABLE 6 Clinical Reports of Dextromethorphan Effects on Mania and Depression

Mendez (1992)	29-year-old man with mania after ingesting 180–480 ml of DM 2 mg/ml, phenylpropanolamine 2.5 mg/ml, and chlorphenhydramine 0.4 mg/ml for a cough and finding it resolved his depression; three such episodes related to the cough syrup; history of a right parietal porencephalic cyst from a head injury at 1 year of age; apparently no previous history of mania, but an aunt had bipolar disorder
Walker and Yatham (1993)	40-year-old man with recurrent mania on pure DM (without other ingredients) in cough syrup on at least three separate occasions, with response to "small doses" of haloperidol, resulting in return to premorbid level of functioning each time; two episodes were observed while he was in the hospital after abuse of DM in response to craving; at least one manic episode had occurred previously after ingestion of DM with diphenhydramine
Polles and Griffith (1996)	43-year-old man with euphoria, increased energy, reduced need for sleep (3 h per night), spending sprees, flight of ideas, and, eventually, paranoid delusions and auditory hallucinations after abusing DM and gradually increasing his dose; urine toxicology screen on admission showed DM, nor-DM, levorphanol, and norlevorphanol, and a false positive screen for PCP, which was later shown to be related to DM; the mania responded to a single injection of haloperidol (dose unknown) and the discontinuation of the cough syrup, improving to baseline functioning within 4 days; two subsequent hypomanic relapses after renewed use of the DM cough syrup; two previous manic episodes 20 years earlier after abusing propoxyphene and hydrocodone, without spontaneous manic episodes in the interval; father and brother had alcoholism; sister took lithium for an unknown affective disorder
	28-year-old man with persistent cough and taking DM with pseudoephedrine cough syrup, leading to subsequent abuse to improve mood and energy; developed manic mood, irritable and elated affect, reduced need for sleep, increased activity, distractibility, flight of ideas, and restlessness, without previous history of mania or clear bipolar features; previous history of alcohol, diazepam, and hydrocodone abuse and abstinent for 7 months prior to current episode; toxicology screen showed DM, benzodiazepine, pseudoephedrine, and a false-positive PCP screen later found to be related to DM; returned to baseline functioning within 48 h after clorazepate and clonidine detoxification
Bostwick (1996)	35-year-old woman with personal and family history of bipolar disorder with therapeutic lithium level (1.0 mEq/L) developed manic symptoms during euthymia after taking prescribed doses of DM with guaifenesin (twice), DM with guaifenesin and phenylpropanolamine, and DM with pseudoephedrine, chlorpheniramine, and acetaminophen, without abuse, and discontinuing each within 2 days due to manic symptoms
Lee et al. (2012)	A double-blind study of DM vs. placebo added to valproate in the treatment of bipolar disorder showed no statistically different improvements in mania or depressive rating scales with active DM over 12 weeks' treatment
Messias and Everett (2012)	32-year-old woman with recurrent DSM-IV major depressive disorder and borderline personality disorder; depression had failed to respond to paroxetine, citalopram, escitalopram, duloxetine, venlafaxine, desvenlafaxine, mirtazapine, selegiline, bupropion–escitalopram combination, bupropion–fluoxetine–levothyroxine combination, and ECT; she began dextromethorphan and quinidine 20 mg/10 mg daily for emotional lability (other treatment regimen and then-current depressive symptoms unspecified), with "significant improvement in her mood lability and crying spells" and the ability to stay out of the hospital and to work daily for 1 year

Clinical reports indicating that DM can induce mania and improve treatment-resistant depression. DM, Dextromethorphan; PCP, phencyclidine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

- In addition to abuse considerations, there are some data to suggest that DM or DO may be particularly effective antidepressants in alcohol use disorders and in reducing the severity of heroin withdrawal.

SUMMARY POINTS

- While we await the results of clinical trials, DM and DO possess a spectrum of pharmacodynamic actions that are consistent with antidepressant effects, including rapid-acting, conventional, and treatment-resistant depression antidepressant efficacy.
- Rapid-acting antidepressant properties shared by DM and DO include NMDA, NMDA-2A, and PCP site antagonism, σ_1 stimulation, μ potentiation, 5HTT inhibition, mTOR activation, AMPA activation, dendritogenesis, and synaptogenesis; DM also downregulates NMDA-2B and DO binds muscarinic and β receptors.
- Conventional antidepressant properties shared by DM and DO include 5HTT and NET inhibition, NMDA, NMDA-2A, and PCP antagonism, σ_1 stimulation, calcium channel antagonism, and 5HT1b/d binding, while DM also downregulates NMDA-2B and DO can antagonize μ receptors.
- Treatment-resistant antidepressant properties of DM and DO may be mediated by these NMDA, PCP, σ_1, μ, 5HTT, NET, 5HT1b/d receptors, and calcium channel effects and additionally through NMDA-2B (DM).
- Clinical evidence suggests that abuse potential can be limited by coadministration of CYP2D6 inhibitors such as quinidine, alcohol use populations may be especially sensitive to DM and DO antidepressant effects, and DM may reduce heroin withdrawal severity.

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