Research paper

Dextromethorphan/quinidine pharmacotherapy in patients with treatment resistant depression: A proof of concept clinical trial

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A R T I C L E   I N F O

A B S T R A C T

Background: At least one-third of patients with major depressive disorder (MDD) have treatment-resistant depression (TRD), defined as lack of response to two or more adequate antidepressant trials. For these patients, novel antidepressant treatments are urgently needed.

Methods: The current study is a phase IIa open label clinical trial examining the efficacy and tolerability of a combination of dextromethorphan (DM) and the CYP2D6 enzyme inhibitor quinidine (Q) in patients with TRD. Dextromethorphan acts as an antagonist at the glutamate N-methyl-d-aspartate (NMDA) receptor, in addition to other pharmacodynamics properties that include activity at sigma-1 receptors. Twenty patients with unipolar TRD who completed informed consent and met all eligibility criteria we enrolled in an open-label study of DM/Q up to 45/10 mg by mouth administered every 12 h over the course of a 10-week period, and constitute the intention to treat (ITT) sample. Six patients discontinued prior to study completion.

Results: There was no treatment-emergent suicidal ideation, psychotomimetic or dissociative symptoms. Montgomery-Asberg Depression Rating Scale (MADRS) score was reduced from baseline to the 10-week primary outcome (mean change: -13.0 ± 11.5, $t_{19} = 5.0$, $p < 0.001$), as was QIDS-SR score (mean change: -5.9 ± 6.6, $t_{19} = 4.0$, $p < 0.001$). The response and remission rates in the ITT sample were 45% and 35%, respectively.

Limitations: Open-label, proof-of-concept design.

Conclusions: Herein we report acceptable tolerability and preliminary efficacy of DM/Q up to 45/10 mg administered every 12 h in patients with TRD. Future larger placebo controlled randomized trials in this population are warranted.

1. Introduction

Major depressive disorder (MDD) represents one of the major sources of disease related disability worldwide, accounting for more than 40% of the 184 million disability-adjusted life years (DALYs) attributed to all mental and substance use disorders in 2010 (Whiteford et al., 2013). It is estimated that only one out of three patients with MDD treated with a first-line antidepressant medication will achieve full symptom remission (Rush et al., 2006), and up to one-third of patients will remain symptomatic despite multiple optimized treatment

steps (Trivedi et al., 2006a, 2006b). Patients who have failed to respond to two or more antidepressant medication trials of adequate dose and duration may be classified as experiencing treatment-resistant depression (TRD), and as a group these patients suffer a more chronic and severe disease course and account for up to half of the total economic cost of the illness (Mathew, 2008; Shelton et al., 2010). All antidepressant medications currently marketed in the United States (U.S.) act mechanistically by enhancing monoamine signaling in the brain, for example via serotonin or norepinephrine transporter blockade. This mechanistic homogeneity likely contributes substantially to the pre-

valence of TRD by limiting the pharmacotherapeutic options available to treatment providers.

A critical need in neuropharmacology research is to identify safe and more effective treatments for depression by targeting neural receptors and signaling pathways outside of the monoamine system (Berton and Nestler, 2006; Mathew et al., 2008; Papakostas and Ionescu, 2015). In this context, the discovery of a rapid antidepressant effect of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine now more than a decade ago, has provided a major impetus for drug discovery research focused on the NMDA receptor and other targets linked to glutamate signaling (Sanacora et al., 2008, 2014). One potentially fruitful research strategy involves the conduct of proof-of-concept (POC) clinical trials of agents with known effects at the NMDAR receptor or other novel molecular targets in patients with TRD, taking advantage of the availability of marketed drugs as tool compounds. This strategy essentially 're-purposes' existing compounds as pharmacological probes in order to gain information concerning the viability of a given target for a new indication (e.g., TRD).

Dextromethorphan (DM) is an antitussive medication with a complex pharmacology that includes inhibition of NMDA receptors, as well as interactions with serotonin and norepinephrine transporters, nicotinic acetylcholine receptors, and sigma-1 (σ_1) receptors (reviewed in Taylor et al. (2016)). A fixed-dose combination product of DM and the cytochrome P450 (CYP) 2D6 enzyme inhibitor quinidine (Q) gained approval for the treatment of pseudobulbar affect (PBA) in the U.S. in 2010 [DM 20 mg/Q 10 mg every 12 h (Nuedexta®, Avanir Pharmaceuticals, Inc.)]. Although early clinical trial experience with DM in neurological disorders showed minimal efficacy, low plasma levels of DM owing in part to substantial first-pass metabolism may have largely limited brain exposure (Pope et al., 2004; Werling et al., 2007). The concurrent administration of Q with DM, in contrast, substantially increases DM plasma levels by reducing the first-pass metabolism of DM by CYP2D6 (Yang and Deeks, 2015). Given the unique pharmacology of DM that includes NMDA receptor antagonism, we took advantage of the availability of DM/Q to conduct a phase IIa open-label POC study of DM/Q dosed up to 45 mg/10 mg every 12 h in patients with TRD. Our goal was to examine initial feasibility, tolerability, and open-label antidepressant efficacy of this approach.

2. Materials and methods

2.1. Participants

Study participants were recruited from hospital outpatient clinics, physician referrals, and internet and newspaper advertising. Participants were between ages 18 and 65 and had a primary diagnosis of MDD currently in a major depressive episode (MDE) of at least moderate severity, without psychotic features, as assessed by a trained rater using the Structured Clinical Interview for DSM-IV-TR axis I disorders (SCID) (First et al., 2002) and confirmed by a diagnostic interview with a study psychiatrist. To be eligible, participants must have failed to respond to two or more adequate trials of an FDA approved antidepressant according to the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Allowed comorbid disorders included anxiety disorders and posttraumatic stress disorder (PTSD) as long as MDD was the primary presenting problem. Exclusionary diagnoses included substance use disorder in the past year or lifetime history of schizophrenia or other psychotic disorder, bipolar disorder, pervasive developmental disorders or mental retardation. Lifetime history of abuse of ketamine or dextromethorphan was exclusionary. All patients underwent a medical clearance process that included a medical history, measurement of vital signs, measurement of height and weight, a physical examination, electrocardiogram (ECG), complete blood count, complete metabolic panel with liver function tests, thyroid stimulating hormone, urinalysis, and urine toxicology. Medical exclusion criteria included a urine toxicology positive for illicit drugs,

prolonged QT interval or other clinically significant ECG findings, history of congenital long QT syndrome, history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions, history of heart failure, history of complete atrioventricular (AV) block, known hypersensitivity to dextromethorphan or quinidine, or any other medical condition that was judged to be unstable. Prohibited medications included quinidine, quinine, mefloquine, or digoxin, inhibitors of the CYP3A4 pathway, and medications that both prolonged the QT interval and are metabolized by the CYP2D6 pathway (including the antidepressant medications paroxetine and duloxetine). Current use of a monoamine oxidase inhibitor (MAOI) or beginning study drug within 14 days of stopping an MAOI was prohibited. Participants were allowed to stay on a stable dose of an U.S. Food and Drug Administration (FDA)-approved antidepressant medication during the trial, as long as it was not prohibited according to the study protocol.

Participants were required to have at least moderate depression severity, as defined by a score of ≥ 32 on the Inventory of Depressive Symptomatology – Clinician Rated (IDS-C) (Rush et al., 1996) at screening, and stable symptoms, as defined by no more than a 20% fluctuation in IDS-C$_{30}$ score between screening and baseline.

The Program for the Protection of Human Subjects at Mount Sinai approved the protocol and study procedures, and written informed consent was obtained from all subjects after the nature of the procedures had been fully explained prior to any study procedures being performed. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study is registered at http://ClinicalTrials.gov (NCT01882829).

2.2. Study Procedures and Rating Instruments

Eligible participants meeting all inclusion and no exclusion criteria were entered into an open-label trial of DM/Q dosed up to 45/10 mg every 12 h. We selected the dose of 45/10 mg every 12 h, which is higher than the dose FDA-approved for PBA, in an effort to minimize the likelihood of a false negative finding resulting from under dosing, and based on preliminary safety and tolerability data on file at Avanir. Following screening (−2 weeks) and baseline (week 0), patients were started on DM/Q 20/10 mg daily for one week (week 1), and then titrated to DM/Q 20/10 mg every 12 h for one week (week 2). Patients then underwent an ECG for measurement of QTc to monitor for QT prolongation (defined in the current study as a QTc interval of > 470 ms for men and > 480 ms for women). If tolerated and in the absence of QTc prolongation, patients were titrated to the experimental dose of 45/10 mg every 12 h beginning at week 2 and continuing through the end of an 8-week treatment period (week 10). Following the treatment period, patients were tapered down to 45/10 mg daily for one week, and then discontinued from the study drug. Patients returned for a final study exit visit (week 12), which included a medical history, measurement of vital signs, physical examine, clinical laboratory tests, urinalysis, urine toxicology, and ECG. Patients were evaluated in the clinic at: weeks 0, 1, 2, 4, 6, 8, 10, and 12 (see Fig. 1).

At each visit, participants completed self-report questionnaires, underwent clinician administered rating scales performed by trained raters, and met with the study psychiatrist who assessed suicidal thinking or behavior, adverse events and concomitant medications. Safety and tolerability were assessed by discontinuation rate, frequency of adverse events, and score change on the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007), the Brief Psychiatric Rating Scale-Positive Subscale (BPRS+), and the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998).

The primary efficacy outcome was change in depression severity from baseline to end of treatment (week 10) using the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Secondary outcomes included global illness severity measured using the Clinical Global Impression – Improvement/Severity (CGI-I/S)
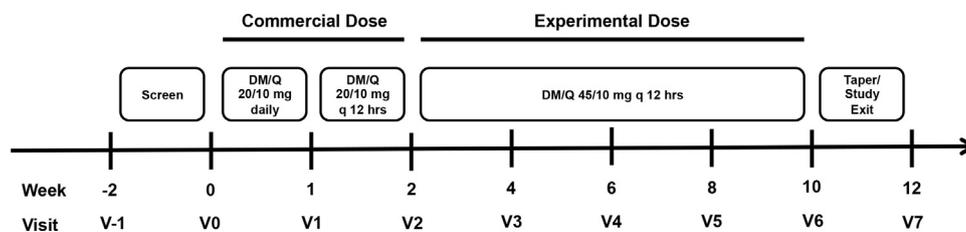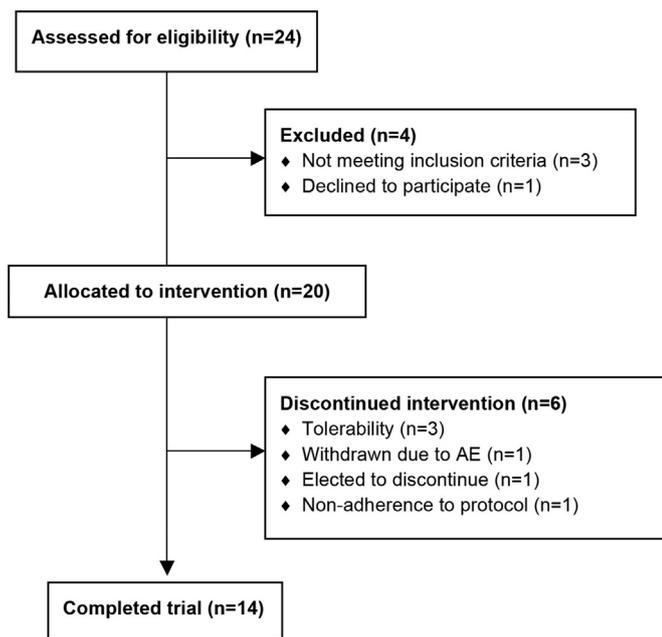
Fig. 1. Study flow diagram.

Fig. 2. CONSORT diagram.

(Guy, 1976), self-reports of depression measured using the Quick Inventory of Depressive Symptomatology (QIDS-SR) (Rush et al., 2003), anxiety measured using the Hamilton Anxiety Scale (HAM-A) (HAMILTON, 1959), and suicidal thinking measured using the Beck Scale for Suicidal Ideation (BSI) (Beck et al., 1988). To evaluate cognitive dysfunction, quality of life, functional impairment, and illness-related disability, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al., 2009), Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) (Stevanovic, 2011), Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 1999), and Sheehan Disability Scale (SDS) (Leon et al., 1992) were used, respectively.

The MADRS, QIDS-SR, CGI-I/S, and C-SSRS were administered at every study visit. The BPRS + and CADSS were administered at week 0, 1, 2, 6, and 10. All other secondary outcomes were performed only at baseline (week 0), and primary outcome (week 10).

2.3. Statistical methods

Patient demographic and clinical characteristics were described using summary statistics. The primary efficacy analysis was conducted on the intention to treat (ITT) sample, defined as patients who were administered at least one dose of study drug. For patients with incomplete data, last observation carried forward (LOCF) was used to impute missing data. This single imputation method was selected as a conservative approach based on the assumptions that subjects, on average, would tend to improve over time in the trial, and that data may not be missing at random since subjects exhibiting a poor response may be more likely to dropout prior to the end of the study. Per-protocol analyses including only trial completers were conducted

secondarily. Safety analyses included the full ITT sample.

Change in MADRS score from baseline to week 10 represented the primary efficacy outcome. Paired *t*-tests were used to compare baseline and week 10 scores. Secondary outcomes were analyzed in a similar manner. For instruments with more than two time points available for analysis repeated measures analysis of variance (ANOVA) was also performed. A p value of < 0.05 was considered statistically significant; repeated measures analyses utilized Bonferroni correction. Response rate defined as a reduction in MADRS score from baseline to week 10 of 50% or more, and remission rate defined as an absolute MADRS score at week 10 less than or equal to 10, is also reported.

Safety and tolerability were assessed by discontinuation rate, frequency of adverse events (AEs), occurrence of treatment-emergent suicidal ideation as captured by the C-SSRS, and occurrence of psychotomimetic or dissociative effects as measured by the BPRS + and CADSS, respectively. For analysis of AEs, the number of patients experiencing adverse events by term was tabulated and AEs were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Treatment-emergent suicidal ideation was defined as any increase on the suicidal ideation sub-scale of the C-SSRS, or any occurrence of suicidal behavior. Any increase from baseline in BPRS + or CADSS score assessed by a paired *t*-test with an alpha level of 0.20 was considered significant.

3. Results

Twenty-four individuals were assessed for eligibility; 20 individuals meeting all inclusion and no exclusion criteria were enrolled and constitute the ITT sample (see Fig. 2 for CONSORT Diagram). On average study participants were 49 years old, in their current MDE for more than 2 years, experienced recurrent MDD, and had failed to respond to a median of 2.5 lifetime adequate antidepressant trials (range: 2–10). Half the sample (n = 10) was on a concomitant anti-depressant medication at the time of screening and remained on a stable dose of the medication for the duration of the study. Additional clinical and demographic details of the sample are provided in Table 1. See Supplementary material Table S1 for a summary of concomitant psychotropic medication in the study sample.

Of the n = 20 individuals who received at least one dose of study drug, n = 14 completed all study visits, yielding a completer sample of 14 patients and a retention rate of 70%. Of the six individuals who discontinued from the study, three elected to discontinue due to poor tolerability of study drug, one elected to discontinue for unspecified reasons, one was withdrawn due to psychiatric hospitalization (see AE section below), and one was withdrawn due to non-adherence to the study protocol.

4. Efficacy

MADRS score significantly decreased from study baseline to week 10 (mean change: −13.0 ± 11.5, t_{19} = 5.0, p < 0.001). MADRS score decreased during the study as a function of time ($F_{6,14}$ = 5.39, p = 0.005); pairwise comparison showed significant difference from baseline starting at week 4 and continuing through week 10 (all

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Table 1
Characteristics of study sample (n = 20).

Characteristic	Total sample (n=20)	Responders (n=9)	Non-Responders (n=11)	Test statistic[a]
Age at enrollment, yrs (mean ± SD)	49.4 ± 7.7	50.9 ± 7.5	48.1 ± 8.0	$t_{18} = 0.80$, $p = 0.43$
Male (no., %)	11 (55%)	7 (78%)	4 (36%)	χ^2 (1, $n = 20$) = 3.4, $p = 0.064$
White (no., %)	14 (70%)	6 (67%)	8 (73%)	χ^2 (2, $n = 20$) = 1.3, $p = 0.522$
College education (no., %)	18 (90%)	9 (100%)	9 (91%)	χ^2 (6, $n = 20$) = 5.2, $p = 0.520$
Current employment (no., %)	8 (40%)	4 (44%)	4 (36%)	χ^2 (3, $n = 20$) = 6.5, $p = 0.090$
Age of onset of first MDE, yrs (mean ± SD)	25.3 ± 15.8	26.3 ± 18.9	24.5 ± 13.7	$t_{18} = 0.26$, $p = 0.80$
Duration of current MDE, months (mean ± SD)	39.1 ± 33.9	40.6 ± 37.9	37.8 ± 32.0	$t_{18} = 0.18$, $p = 0.86$
Chronic MDE (no., %)	13 (65%)	6 (67%)	7 (64%)	χ^2 (1, $n = 20$) = 0.020, $p = 0.888$
Recurrent MDD (no., %)	16 (80%)	7 (78%)	9 (82%)	χ^2 (1, $n = 20$) = 0.051, $p = 0.822$
No. of lifetime episodes (median, min-max)	3 (1–10)	3 (1–10)	3 (1–8)	$t_{18} = 0.052$, $p = 0.61$
First-degree relative with mood disorder (no., %)	12 (60%)	5 (56%)	7 (64%)	χ^2 (1, $n = 20$) = 0.135, $p = 0.714$
No. of failed antidepressants in current MDE (median, min-max)	2.0 (0–10)	2.0 (0–5)	2.0 (0–10)	$t_{18} = -0.65$, $p = 0.52$
No. of failed antidepressants, lifetime (median, min-max)	2.5 (2–10)	2.0 (2–5)	3.0 (2–10)	$t_{18} = -0.073$, $p = 0.48$
Past substance use disorder (no., %)	2 (10%)	1 (11%)	1 (9%)	χ^2 (1, $n = 20$) = 0.022, $p = 0.881$
Current anxiety disorder or PTSD (no., %)	3 (15%)	2 (22%)	1 (9%)	χ^2 (1, $n = 20$) = 0.669, $p = 0.413$
Baseline CGI-S score (mean ± SD)	4.5 ± 0.5	4.2 ± 0.4	4.6 ± 0.5	$t_{18} = -1.93$, $p = 0.07$
Baseline MADRS score (mean ± SD)	32.5 ± 3.9	31.4 ± 3.3	33.4 ± 4.2	$t_{18} = -1.11$, $p = 0.28$
Baseline IDS-C$_{30}$ score (mean ± SD)	40.9 ± 6.1	39.9 ± 5.2	41.6 ± 7.0	$t_{18} = -0.62$, $p = 0.54$
Concomitant antidepressant medication (no., %)	10 (50%)	5 (56%)	5 (45%)	χ^2 (1, $n = 20$) = 0.202, $p = 0.653$

CGI-S, Clinical Global Impression Scale–Severity; IDS-C$_{30}$, Inventory of Depressive Symptomatology–Clinician Rated, 30-item; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major depressive disorder; MDE, major depressive episode; PTSD, posttraumatic stress disorder.

[a] Test statistic compared responder and non-responder subgroups.

p's < 0.01, Bonferroni adjusted; Fig. 3). There was no interaction with time when concomitant antidepressant therapy (i.e., monotherapy yes/no) was included in the model. We explored the influence of treatment-resistance severity on MADRS score change over time by including a treatment-resistance term (high/low; low = 2 lifetime failures, n = 10; high = > 2 failures, n = 10) in the model and found no interaction between time and treatment-resistance ($F_{6,13} = 0.68$, p = 0.67). The response and remission rates in the ITT sample were 45% and 35%, respectively. In the completer sample, the response and remission rates were 64% and 50%, respectively.

Consistent with the observed change in MADRS, QIDS-SR score significantly decreased from study baseline to week 10 (mean change: −5.9 ± 6.6, $t_{19} = 4.0$, $p < 0.001$). Anxiety was also significantly reduced from study baseline to week 10, as reflected by a reduction in HAM-A score (−5.7 ± 5.9, $t_{19} = 4.36$, $p < 0.001$). At end of treatment, 50% of patients were classified as 'improved' or 'very much improved,' 20% of patients were classified as 'minimally improved,' and 30% of patients were classified as 'no change' in improvement according to the GCI-I. Change in additional measures, including suicidal thinking, cognition, disability, and quality of life are reported in Table 2.

4.1. Safety and tolerability

The most common AE was constipation, which occurred in 3 participants; dry mouth, nausea, dizziness, and sedation occurred in 2 participants. One serious adverse event (SAE) occurred: a participant was hospitalized for worsening insomnia in the context of depression 3 days after initiating study drug. Altogether, 4 patients discontinued the study in association with an AE (3 patients due to a non-SAE, 1 patient due to an SAE): 3 of the 4 discontinuations occurred at a dose lower than 45/10 mg. See Table 3 for a summary of study AEs.

There were no significant changes in BPRS+ or CADSS score from baseline to primary outcome. There was no treatment-emergent serious suicidal ideation compared to baseline, as defined by an increase in the maximum suicidal ideation score to 3 or greater on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0–3) at baseline. No patients experienced emergence of suicidal behavior during the study.

5. Discussion

Herein we report on the feasibility, tolerability, and initial antidepressant efficacy of DM/Q dosed up to 45/10 mg every 12 h in patients with TRD in a current MDE. Study patients had failed a median of 2 adequate antidepressant trials in the current episode. We observed acceptable tolerability in this TRD group, with AE frequencies similar to what has been observed previously in studies of PBA (Doody et al., 2015; Pioro et al., 2010). Patients showed a large mean reduction in MADRS score of −13.0 at study end and 50% of patients were classified as 'improved' or 'very much improved.' Response and remission rates were 45% and 35%, respectively in the ITT sample. The magnitude of improvement was similar between individuals who were taking a concomitant antidepressant medication and those who were not, and between patients with a moderate level of treatment-resistance and those with a higher level. Although direct comparisons between studies are difficult to make, the observed remission rate of 35% in the current study compares to remission rates of 25–39% in level 2% and 8–25% in level 3 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Warden et al., 2007). Remission rates following acute treatment with repetitive transcranial magnetic stimulation (rTMS) in patients with moderate levels of treatment resistance are reported to be 15–33% (Perera et al., 2016). Taken together, the current POC study supports the hypothesis that DM/Q represents a promising pharmacotherapeutic strategy in patients with TRD. Future randomized, controlled trials will be required to further examine the antidepressant potential of this approach.

As noted in the introduction, DM possesses a complex pharmacology that features NMDA receptor antagonism, σ_1 receptor agonism, and effects on serotonin and norepinephrine signaling, among others (Taylor et al., 2016). NMDA receptor antagonism in particular may be an important aspect of DM's putative antidepressant mechanism of action given the growing evidence that ketamine, a non-competitive high-affinity NMDA receptor antagonist, possess rapid and robust antidepressant effects in patients with TRD (Caddy et al., 2015; Murrough et al., 2013; Newport et al., 2015; Singh et al., 2016; Zarate et al., 2006). More broadly, glutamate signaling via NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and metabotropic glutamate receptors (mGluRs) has been implicated in the pathophysiology and treatment of MDD and other mood disorders
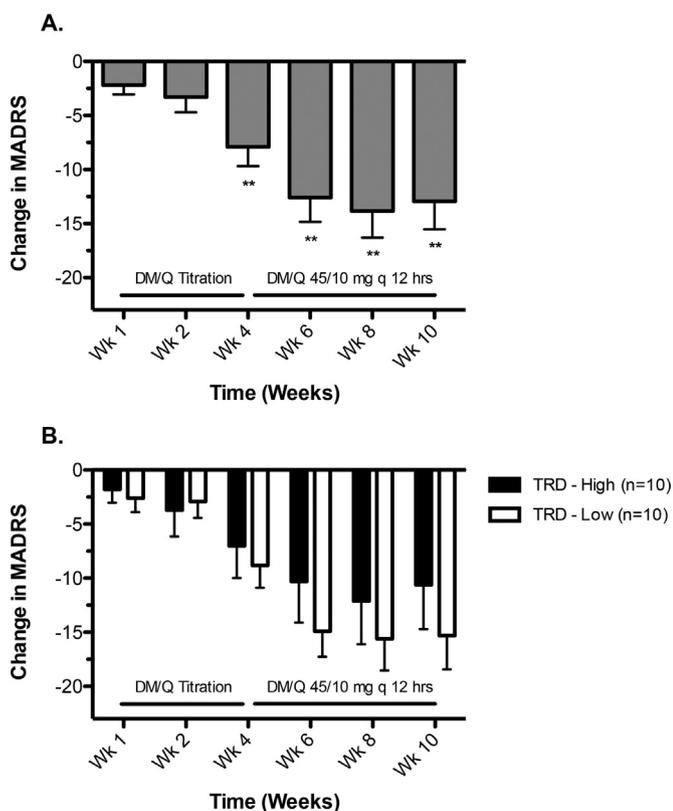
A.

B.

Fig. 3. Change in MADRS score during clinical trial of dexomethorphan/quinidine in patients with treatment-resistant depression (n = 20 ITT sample, LOCF). Panel A. Graph depicts mean change from week 0 baseline at each time point (error bars are standard error of the mean). There was a main effect of time on MADRS score ($F_{6,14}=5.39$, p = 0.005). "**" Indicates pairwise comparison between time point and baseline is significant at p < 0.01, with Bonferroni adjustment for multiple comparisons. Panel B. Graph depicts mean change from week 0 baseline at each time point for high and low treatment-resistant depression classification subgroups. Low treatment-resistance classification indicates 2 historic antidepressant medication treatment failures; high treatment-resistance classification indicates 3 for more historic antidepressant medication treatment failures (range 3–10). There was no significant interaction between time and treatment-resistance level ($F_{6,13}=0.68$, p = 0.67). DM/Q, dextromethorphan/quinidine; MADRS, Montgomery-Asberg Depression Rating Scale; TRD, treatment-resistant depression.

(Abdallah et al., 2015; Manji et al., 2003; Sanacora et al., 2008). Electrophysiological studies show that DM exerts voltage-dependent blockade of the NMDA receptor, likely binding to a site within the channel pore, similar to ketamine and other channel blockers such as MK-801 (Ferrer-Montiel et al., 1998). DM shows a somewhat lower affinity for the NMDA receptor channel compared to ketamine ($K_i = 780$ and 200, respectively), but similar to memantine ($K_i = 700$) (Taylor et al., 2016). Interestingly, a recent study showed that DM exerted an antidepressant-like behavioral effects in the tail suspension test (TST) that were blocked by administration of AMPA receptor antagonist NBQX, similar to ketamine and other glutamate-based antidepressant candidates (Nguyen and Matsumoto, 2015).

Sigma-1 receptors are transmembrane proteins located in the endoplasmic reticulum (ER), and constitute a class of receptors distinct from ligand-gated ion channels and G-protein coupled receptors (Hayashi, 2015). These receptors were first characterized in the 1990's and their potential role in neuropsychiatric disease mechanisms and as potential novel treatments is only beginning to be explored. Several lines of evidence suggest that DM acts as an agonist at σ_1 receptors. For example, the antitussive, anticonvulsant, and neuroprotective effects of DM can be blocked in model systems by administration of a selective σ_1 receptor antagonist (Shin et al., 2005, 2007). More recently, pretreatment with the σ_1 receptor antagonist BD1063 was shown to attenuate the antidepressant behavioral effects of DM in the

Table 2
Secondary efficacy outcomes (n = 20).

Measure[a]	Mean change[b]	Standard deviation	Statistic	P-value[c]
BSI (total)	−2.5	5.1	$t_{19}=-2.19$	0.041*
BSI (responders)	−4.6	6.0		
BSI (non-responders)	−0.8	3.8		
CGI-I (total)	−1.6	1.2	$t_{19}=-5.87$	< 0.001**
CGI-I (responders)	−2.4	0.7		
CGI-I (responders)	−0.9	1.1		
CGI-S (total)	−1.3	1.3	$t_{19}=-4.48$	< 0.001**
CGI-S (responders)	−2.7	0.9		
CGI-S (non-responders)	−0.5	0.5		
CPFQ (total)	−4.1	6.5	$t_{19}=-2.83$	0.011*
CPFQ (responders)	−8.7	6.9		
CPFQ (non-responders)	−0.4	2.7		
HAM-A (total)	−5.7	5.9	$t_{19}=-4.36$	< 0.001**
HAM-A (responders)	−9.7	6.2		
HAM-A (non-responders)	−2.5	3.0		
LIFE-RIFT[d] (total)	−3.7	4.1	$t_{17}=-3.83$	0.001**
LIFE-RIFT (responders)	−7.8	2.1		
LIFE-RIFT (non-responders)	−0.4	1.0		
QIDS-SR (total)	−5.9	6.6	$t_{19}=-4.0$	0.001**
QIDS-SR (responders)	−11.0	5.4		
QIDS-SR (non-responders)	−1.7	4.1		
Q-LES-Q-SF (total)	0.14	0.22	$t_{19}=2.91$	0.009*
Q-LES-Q-SF (responders)	0.28	0.24		
Q-LES-Q-SF (non-responders)	0.04	0.13		
SDS (total)	−4.3	7.3	$t_{19}=-2.62$	0.017*
SDS (responders)	−8.4	7.9		
SDS (non-responders)	−0.9	4.9		

Abbreviations: BSI, Beck Scale for Suicidal Ideation; CGI-I/S, Clinical Global Impression – Improvement/Severity; CPFQ, Cognitive and Physical Functioning Questionnaire; HAM-A, Hamilton Anxiety Scale; LIFE-RIFT, Range of Impaired Functioning Tool; QIDS-SR, Quick Inventory of Depressive Symptomatology; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS, Sheehan Disability Scale
[a] Measures are listed in alphabetical order.
[b] Value represents mean week 10 score minus baseline.
[c] "*" Indicates p-value is significant at alpha = 0.05, "**" indicates that p-value is significant at alpha = 0.05 after Bonferroni adjustment for multiple comparisons (adjusted alpha = 0.0056).
[d] n = 18 due to missing data.

forced swim test (FST) (Nguyen et al., 2014). Sigma-1 receptors appear to function as chaperone proteins, and may have a role in regulating the cellular effects of oxidative stress and free radical generation, among other functions (see (Hayashi, 2015) for a recent review).

In addition to PBA, prior clinical trials have examined DM or DM/Q for the treatment of pain, seizure, and traumatic brain injury (TBI), among other neuropsychiatric conditions (Nguyen et al., 2016). In the area of mood disorders, two studies are reported in the literature, both of which involved patients with bipolar disorder (Chen et al., 2014; Kelly and Lieberman, 2014). One prior study conducted in patients with bipolar II disorder or bipolar disorder not otherwise specified consisted of a retrospective chart review of the efficacy of augmentation treatment with DM/Q 20/10 mg either once or twice daily (Kelly and Lieberman, 2014). Patients in this study had a predominance of depressive symptoms, and had high levels of treatment-resistance and chronicity. Of the 77 patients met the study eligibility criteria, 19 patients discontinued due to adverse effects attributed to treatment with DM/Q; this discontinuation rate of ~25% compares to a discontinuation rate observed in the current study of 30%. Among the remaining 58 patients, state of illness showed on average between 'slightly improved' and 'much improved' on a clinical global impression

Table 3
Adverse events (n = 20).

Organ class	Preferred term	Patient count	Causality (2 = possibly, 3 = probably, 4 = definitely)	Intensity (1 = mild, 2 = moderate, 3 = severe)
Cardiac disorders	Palpitations	1 (5%)	2	1
Eye disorders	Vision blurred	1 (5%)	2	1
Gastrointestinal disorders	Constipation	3 (15%)	3	2
	Dry mouth	2 (10%)	3	1
	Flatulence	1 (5%)	2	2
	Nausea	2 (10%)	2	2
General disorders	Fatigue	1 (5%)	2	2
	Malaise	1 (5%)	2	1
Metabolism and nutrition disorders	Decreased appetite	1 (5%)	2	1
Nervous system disorder	Headache	1 (5%)	2	1
	Dizziness	2 (10%)	2	1
	Sedation	2 (10%)	4	2
	Somnolence	1 (5%)	2	1
Psychiatric disorders	Anxiety	1 (5%)	2	1
	Depression	1 (5%)	2	3
	Insomnia	1 (5%)	2	2
	Libido decreased	1 (5%)	2	1
	Mental status changes	1 (5%)	2	2
	Restlessness	1 (5%)	3	1

Table summarizes occurrence of adverse events in the trial that occurred subsequent to at least one dose of study medication and were associated with a causality rating of at least "possibly." If a patient experienced more than one event with the same term, the highest causality and severity ratings are listed.

scale. The effect of treatment on depression or other symptoms specifically, however, was not reported. In the second study, patients with bipolar disorder on a stable dose of valproic acid were randomized to adjunctive treatment with DM at a dose of 30 or 60 mg per day (no concurrent Q) or placebo for 12 weeks (Chen et al., 2014). Both depression and mania symptoms improved in both groups to a similar degree.

6. Limitations

The current study had several limitations. Chiefly, in the absence of a control group no firm conclusions can be drawn concerning efficacy. The observed response rate of 45% is relatively modest and is within the range observed under placebo conditions in large clinical trials of antidepressants, which can be 40% or higher (Furukawa et al., 2016). This fact underscores the need for future large, controlled trials. Another potential limitation is that the study sample contained a mix of patients with and without concurrent treatment with an antidepressant. Although we did not find evidence for a differential effect of DM/Q on these subgroups, the study was not powered to detect such effects. The study did not collect blood samples for pharmacokinetic analysis, precluding an evaluation of the relationship between peripheral drug level and clinical outcome. While good brain exposure at the drug doses administered is expected based pharmacokinetic models (Lutz and Isoherranen, 2012; Steinberg et al., 1996), we did not evaluate target engagement in the current study.

7. Conclusion

In this first prospective study of DM/Q in patients with unipolar TRD, we found that the study drug was well tolerated up to doses of 45/10 mg every 12 h and was associated with a preliminary efficacy signal in the context of this open-label design. Future larger randomized controlled trials are warranted.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.04.072.

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