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Research paper

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

James W. Murrough[a,b,c,*], Elizabeth Wade[a], Sehrish Sayed[a], Gabriella Ahle[d], Drew D. Kiraly[a,b], Alison Welch[e], Katherine A. Collins[a], Laili Soleimani[e], Dan V. Iosifescu[a,b,c], Dennis S. Charney[a,b,f]

[a] Mood and Anxiety Disorders Program, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[b] Fishberg Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[d] Thomas Jefferson University, Jefferson College of Biomedical Sciences, Philadelphia, PA, United States
[e] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[f] Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY, United States

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ABSTRACT

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-

Abbreviations: ATHF, Antidepressant Treatment History Form; CYP, cytochrome P450; DALYs, disability-adjusted life years; DM, Dextromethorphan; POC, proof-of-concept; Q, quinidine; TRD, treatment-resistant depression

* Corresponding author at: Mood and Anxiety Disorders Program Department of Psychiatry Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1230, New York, NY 10029, United States.
E-mail address: james.murrough@mssm.edu (J.W. Murrough).

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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)