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Treatment Resistant Depression with Loss of Antidepressant Response: Rapid—Acting Antidepressant Action of Dextromethorphan, A Possible Treatment Bridging Molecule

By Edward C. Lauterbach

ABSTRACT ~ Dextromethorphan (DM) may have ketamine—like rapid—acting, treatment—resistant, and conventional antidepressant effects.^{1,2} This reports our initial experience with DM in unipolar Major Depressive Disorder (MDD). A patient with treatment—resistant MDD (failing adequate trials of citalopram and vortioxetine) with loss of antidepressant response (to fluoxetine and bupropion) twice experienced a rapid—acting antidepressant effect within 48 hours of DM administration and lasting 7 days, sustained up to 20 days with daily administration, then gradually developing labile loss of antidepressant response over the ensuing 7 days. Upon full relapse in DSM-5 MDD while taking 600 mg/day of the strong CYP2D6 inhibitor bupropion XL, a 300 mg oral loading dose of DM was given, followed by 60 mg po bid after an additional dose—finding period, without side effects. DM exhibited a ketamine—like rapid—acting antidepressant effect, thought to be mediated by mTOR activation (related to NMDA PCP site antagonism, sigma-1 and beta adrenergic receptor stimulation) and 5HTT inhibition, resulting in AMPA receptor trafficking, and dendritogenesis, spinogenesis, synaptogenesis, and increased neuronal survival (related to NMDA antagonism and sigma-1 and mTOR signaling). This report appears to be the first report of a rapid—acting effect in unipolar MDD and adds to antidepressant effects observed in the retrospective chart review of 77 patients with Bipolar II Disorder (Kelly and Lieberman 2014). If replicated, there is some reason to think that the administration of other agents with DM, such as lithium or D-cycloserine, might prolong the duration of the rapid-antidepressant effect. *Psychopharmacology Bulletin*. 2016;46(2):53–58.

INTRODUCTION

Dextromethorphan (DM) resembles ketamine in its rapid—acting antidepressant properties including sigma-1 and mu receptor agonist, NMDA high affinity

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PCP site, NMDR2A, NMDR-2B, serotonin transporter (5HTT), and calcium channels antagonist, and likely activation of mTOR, AMPA receptor trafficking, dendritogenesis, spinogenesis, synaptogenesis, and neuronal survival.^{1,2} *Treatment—resistant antidepressant properties* include increased synaptic serotonin (5HT) and norepinephrine (NE) availability, NMDA PCP site, NMDR-2B, and presynaptic alpha-2 antagonism, and its multiple other receptor mechanisms.^{1,2} *Conventional antidepressant properties* include 5HTT and NE transporter inhibition, sigma-1 agonist, NMDA and PCP site antagonism,² alpha-2 adrenergic and serotonin 1b/d receptors binding profiles,³ and case reports of DM—induced mania.⁴ In bipolar disorder, adding DM 60 mg/d to extant valproate in 250 patients failed to improve depression after 12 weeks in a double—blind placebo—controlled investigation⁵ although the dose may have been 5-fold too low to observe a response, however, a retrospective case series of 58 patients with *treatment—resistant* Bipolar II Disorder and and Bipolar Disorder NOS with continuous or near—continuous bipolar depressive symptoms over at least 2 years treated with DM plus the CYP2D6 inhibitor quinidine (Q) 20 mg/10 mg q d or bid for 90 days found moderate improvement on the Clinical Global Impression—Improvement scale, with some improving within 1–2 days of starting DM/Q.⁶ In unipolar depression, reports are lacking. This case reports our initial experience with DM in this condition.

CASE HISTORY

Symptomatology and Diagnosis

A 51 year—old employed married white male presented with DSM-V Major Depressive Disorder (MDD), recurrent, severe, non-psychotic and Generalized Anxiety Disorder (GAD), each with the full range of symptoms (insomnia, weight loss, psychomotor retardation, and *all* other MDD and GAD symptoms except for suicide plan or attempt), and a history of hypothyroidism, GERD, BPH, hyperlipidemia, and recurrent depressive relapses. There was no history of nicotine, alcohol, or substance use ever. He was treated with levothyroxine 0.150 mg per day and esomeprazole. At each depressive relapse, thyroid function tests were checked and found to be within normal limits. His family history was remarkable for a depressive disorder in his mother and maternal half—sister, anxiety in his mother, alcohol dependence in a paternal uncle, alcohol abuse vs. dependence in the maternal half—sister, and an absence of bipolar disorder or suicide.

Treatment

Fluoxetine 20 mg po q AM plus psychotherapy was prescribed for his first episode of Major Depressive Disorder (MDD), nonpsychotic occurring at age 27 in 1991, leading to remission for 6–7 months and then relapse despite compliance, eventually experiencing spontaneous remission. In 2014, his primary care physician treated his second episode of MDD with citalopram 20 mg q AM, without response despite sexual adverse events (AEs). Bupropion XL 300 mg q AM was added, leading to remission but he suddenly relapsed over several days after 6 months on this regimen despite compliance and euthyroid status by thyroid function tests (TFTs).

Vortioxetine And Second Bupropion Trials. He was subsequently switched to vortioxetine 10 mg q day in August of 2014. He continued without improvement and was referred to us and diagnosed with MDD and GAD as above. TFTs indicated euthyroid status in early September 2014, so vortioxetine was increased to 20 mg po q AM and lorazepam 2 mg po q HS was added for insomnia. There was no improvement after 5 weeks so, in mid-October, vortioxetine was discontinued, bupropion XL 300 mg q AM was started, TFTs were again euthyroid, and lorazepam 1 mg po TID was added for GAD. In mid—January 2015, MDD and GAD were each fully remitted, and lorazepam was reduced to 0.5–0.75 mg po TID and 2 mg HS. In mid—February, he experienced a partial relapse of MDD symptoms (BDI score 25) despite an absence of psychosocial stressors or worsened anxiety so the bupropion XL was increased to 450 mg po q AM on March 4, 2015, with both MDD and GAD in complete remission (BDI 10) three weeks later. In mid—April 2015, he experienced full and sudden relapse in MDD symptomatology that evolved within 48 hours with continued remission of GAD. TFTs were again euthyroid and there were no contributory psychosocial stressors. Bupropion XL was increased to 600 mg q AM without improvement one week later (BDI 32).

Dextromethorphan Add-On Trial. On April 29, after two weeks of bupropion XL 600 mg q AM, there was no improvement, with a full range of MDD symptoms (BDI 32). CBC/DIFF, basic metabolic profile, ESR, and CRP were normal. Assuming tolerance to bupropion, including to CYP2D6 inhibition, after informed consent, we initiated dextromethorphan at 300 mg po BID (Delsym 30 mg/5 ml) added to the bupropion XL 600 mg q AM, lorazepam 0.5–0.75 mg TID and 2 mg HS, which remained unchanged throughout the DM treatment course in order to minimize treatment variables. TFTs were again fully euthyroid. After his first DM 300 mg dose on DM treatment day one (DMTD 1), the patient reported euthymia with

complete remission of MDD (BDI 9), apparent somewhere between 3–6 hours post—dose.

After the second dose on DMTD 1 however, he developed AEs of nausea, dizziness, blurred vision, and lethargy. We hypothesized lack of tolerance to bupropion 2D6 inhibition and reduced the DM dose to 30 mg po BID. AEs resolved by mid—afternoon of DMTD 2 and he denied any noticeable MDD symptoms. He continued on DM 30 mg BID from DMTD 2–9.

On DMTD 9, he reported feeling as though he might be relapsing. No psychosocial or other precipitating circumstances were discoverable and so the DM dose was increased to 60 mg BID on DMTD10. On DMTD 12, he reported remission of all MDD symptoms within 48 hours of commencing 60 mg BID and no AEs. On DMTD 14 there were no symptoms of MDD (BDI 10), GAD, or AEs. On DMTD 21, MDD (BDI 6), GAD, and AEs continued remitted. Liver function tests (LFTs) were without change and unremarkable. He continued to do well from DMTD 12 through DMTD 32 for 20 days. Throughout the DM treatment trial, he was followed by frequent phone calls with the patient and his wife, who each independently verified the time courses of DM response and MDD relapse. He and his wife had consistently denied that he had experienced euphoria on DM, and he had never developed any manic symptoms. On DMTD 32 he noticed the onset of labile intra-day variability in fatigue and irritability that gradually worsened over 8 days until he was in full MDD relapse with afternoon diurnal worsening (BDI 27) by DMTD 39. Psychosocial stressors were not evident and TFTs and LFTs drawn that day were unremarkable. After discontinuing DM and bupropion, he subsequently remitted on an adequate trial of mirtazapine and then lost the response several months later, but then remitted again on aripiprazole 10 mg po q AM without loss of response over 6 months, each trial conducted while maintaining the previous lorazepam regimen.

DISCUSSION

The observed DM antidepressant effect with onset over 3–48 hours and lasting 7 days after a single administration and 20 days with daily administration is strikingly consistent with the *rapid—acting antidepressant effects* seen with ketamine, which has provided a sustained antidepressant response for less than one week after a single dose and about 18 days with 6 consecutive ketamine infusions.⁷ DM also evidenced a *treatment—resistant antidepressant response* (this patient failed adequate trials of citalopram and vortioxetine). Ketamine response has been predicted by a family history of alcohol dependence;⁸ the patient's family

history was mildly positive for alcohol use disorders. The duration of DM response was not consistent with a *conventional antidepressant response* although this might be obtainable in a different dose range.

Sudden relapses in this case remain cryptic since bipolar disorders, atypical depression, and medical causations were excluded. Fast remission with DM within 3 hours after the initial 300 mg dose and within 48 hours after dose increase from 30 mg bid to 60 mg bid may be related to the number of doses required to re-establish an adequate antidepressant DM plasma level after a 90% dose reduction, with antidepressant effects again occurring within a few hours after reaching this concentration. Viewed as two different exposures (300 mg and then 60 mg bid) and adapting the Naranjo Scale⁹ to this case, the likelihood of attribution of therapeutic effects to DM would be considered as “definite” with a score of 10 (effect appeared after DM administration +2, effect resolved on a sub-therapeutic dose +1, effect re-appeared on therapeutic re-administration +2, absence of alternative causation +2, presence of a dose—related effect +1, similar response on previous administration +1, confirmation by objective evidence +1). Although 60 mg bid proved therapeutic in this case, there will likely be between—patient variability, as seen in bipolar cases.⁶ Unknown is whether escalation of DM dose to 90 mg po BID would have recovered the antidepressant effect and whether DM had anything to do with his first onset of diurnally—varying MDD symptoms. The duration of response was significantly shorter (20 days) than the 90 days observed in bipolar disorders.⁶ Lithium⁷ and D-cycloserine^{7,10} may prolong ketamine’s duration of antidepressant action by synergistic inhibition of glycogen synthase kinase 3, promoting the antidepressant and neuroplasticity effects of both drugs (Iosifescu 2015), with lithium possibly accounting for the response duration difference.

While the brief duration of response is consistent with ketamine, a placebo response cannot be fully excluded in this case. If the treatment—resistant and rapid—acting antidepressant properties of DM can be robustly confirmed, placebo controlled studies and blood and CSF therapeutic levels should be investigated. Otherwise, this case report provides initial evidence of a rapid—acting antidepressant response in treatment—resistant non—bipolar Major Depression. ❀

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