Efficacy and Tolerability of Esketamine Augmented With Dextromethorphan/Bupropion for Treatment-Resistant Depression:

A Case Series

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In recent years, esketamine and dextromethorphan combined with bupropion have gained US Food and Drug Administration approval for treatment-resistant depression (TRD) and major depressive disorder (MDD), respectively.[1–6] Unlike most other monoaminergic oral antidepressants, dextromethorphan/bupropion and esketamine both antagonize the *N*-methyl-D-aspartate (NMDA) receptor, with dextromethorphan having stronger affinity for the NMDA receptor.[7] Thus, there is an urgent need to identify the efficacy and tolerability of coadministration of these two rapidly acting antidepressants.

The following is a case series of 3 patients with TRD who had no or partial response to 4 weeks of biweekly esketamine 84 mg monotherapy as part of their participation in an open-label (OL) clinical trial (NCT04599855[8]) who then received augmentation with dextromethorphan/bupropion 45 mg/105 mg daily for 3 days, which was then increased to twice a day. All participants provided informed consent as part of their participation in this clinical trial, and their information has been deidentified for this case series.

Case 1

Patient A is 30-year-old male with MDD, single episode; social anxiety disorder; and generalized anxiety disorder whose current depressive episode had lasted 21 years. During this episode, he had failed to respond to adequate trials of escitalopram, venlafaxine, and bupropion. His Montgomery-Asberg Depression Rating Scale (MADRS) score prior to OL esketamine treatment was 37, which decreased to 31 after 4 weeks and then decreased to 2 after 6 weeks of augmentation with dextromethorphan/bupropion (Figure 1). He reported no adverse events during the duration of treatment.

Case 2

Patient B is a 35-year-old female with MDD, recurrent; generalized anxiety disorder; and attention-deficit/hyperactivity disorder whose depressive episode had lasted 22 months. During this episode, she had failed to respond to adequate trials of paroxetine, bupropion, and duloxetine. Her MADRS score prior to OL esketamine treatment was 36, which decreased to 28 after 4 weeks and then decreased to 14 after 9 weeks of augmentation with dextromethorphan/bupropion (Figure 1). She reported no adverse events during the duration of treatment.

Case 3

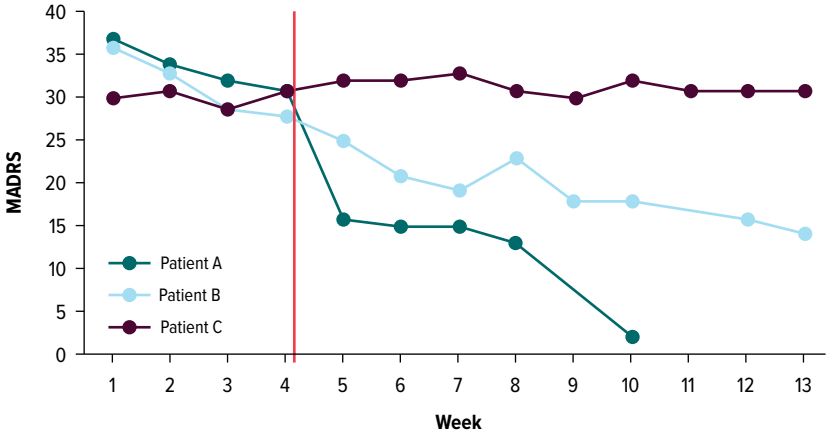
Patient C is a 27-year-old male with MDD, recurrent; social anxiety disorder; and generalized anxiety disorder whose current depressive episode had lasted 4 years. During this episode, he had failed to respond to adequate trials of venlafaxine, bupropion, imipramine augmented with aripiprazole, tranylcypromine, sertraline, and vortioxetine. His MADRS score prior to OL esketamine treatment was 30, which increased to 31 after 4 weeks and remained the same after 9 weeks of augmentation with dextromethorphan/bupropion. He reported no adverse events during the duration of treatment.

Discussion

To our knowledge, this is the first report of efficacy and tolerability of esketamine and dextromethorphan/bupropion coadministration. Caution is warranted regarding any conclusions, as this case series included only 3 patients; however, 2 of the 3 patients had a clinical improvement with coadministration. In addition, among these 3 patients, no adverse events were reported, including no significant changes in blood pressure or somnolence.

Figure 1.

Depression Severity in 3 Patients With TRD Treated With 4 Weeks of Esketamine Monotherapy Followed by Weekly Esketamine and Coadministration of Dextromethorphan/Bupropion[a]



[a]The red line represents the time dextromethorphan/bupropion was started.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, TRD = treatment-resistant depression.

The decrease in MADRS scores for Patient A is consistent with the potential of rapid-acting antidepressants, as MADRS scores dropped rapidly after augmentation with dextromethorphan/bupropion. Patient B's response to augmentation was less dramatic, and, considering the slope of down-trending MADRS scores prior to augmentation that appears consistent after augmentation, it is unclear to what degree dextromethorphan/bupropion contributed to clinical improvement. Patient C had no response to esketamine monotherapy or augmentation with dextromethorphan/bupropion, which may be due to his level of treatment resistance, as he failed more antidepressants during the current depressive episode, including a monoamine oxidase inhibitor.

This case series provides the first step in understanding the safety and potential efficacy of antidepressant medications that interact with the NMDA receptor. Further studies are warranted to examine the tolerability and efficacy of esketamine and dextromethorphan/bupropion coadministration.

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Patient Consent: Informed consent to participate in this clinical trial was obtained from each patient. Their information has been de-identified to protect anonymity.

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