A Case of Electroconvulsive Therapy–Resistant Depression Responding to Multiple Dopaminergic Medications

To the Editor: Treatment-resistant depression is common, challenging, and difficult to treat. In this case report, we discuss the role of using multiple dopaminergic medications to achieve remission of depression. To our knowledge, this is the first case report on the use of combination therapy (clomipramine, dextroamphetamine, pramipexole, and aripiprazole) for electroconvulsive therapy–resistant unipolar depression.

Case report. Mr A is a 51-year-old Hispanic man with treatment-resistant depression stage V. According to treatment-resistant depression staging,[1] stage V is failure to a course of electroconvulsive therapy (ECT), which is defined as 12 ECTs, of which 8 have to be bilateral. Mr A had received 10 ECTs, and the last one was 2 weeks prior to the first visit (week 0). He had comorbid anxiety and no illicit substance use disorder. The following medications did not help Mr A in the past: fluoxetine, sertraline, paroxetine, trazodone as a hypnotic, bupropion, imipramine, phenelzine, aripiprazole 20 mg, and buspirone. Dose and duration for some medications were not available in the chart. The 9-item Patient Health Questionnaire (PHQ-9) for measurement-based care has been used in psychiatric clinics.[2,3] Medication titrations are summarized in Table 1.

As shown in Table 1, Mr A attained near remission only after treatment with multiple dopaminergic medications, showing a decrease in PHQ-9 severity score as each medication was added. The final regimen at week 29 was clomipramine 300 mg at bedtime; dextroamphetamine 20 mg AM, 10 mg noon, and 10 mg 4 PM; pramipexole 3 mg at bedtime, and aripiprazole 15 mg AM. Mr A declined a blood test to check clomipramine levels. His corrected QT interval was 429 ms on clomipramine 300 mg and other medications. His functioning improved in the following areas: submitted thesis for his master's degree, had more contact with his family, and had more energy to take care of household chores. Mr A was followed for 6 more months without relapse.

There is evidence to support the use of stimulants for treatment-resistant depression.[4] Dextroamphetamine releases both dopamine and norepinephrine, causing a surge of monoamines. Pramipexole, a presynaptic dopamine agonist, has affinity for D_2, but higher affinity for D_3, resulting in higher dopamine tone, which is a different mechanism.[5] The D_3 receptor is involved in the motoric and anhedonic symptoms.[5] Large effect sizes (0.6–1.1) have been reported for both unipolar and bipolar depression.[5] Eleven of 14 depressed patients responded to aripiprazole augmentation on the basis of the cerebral utilization of 6-[(18)F]-fluoro-3,4-dihydroxy-l-phenylalanine (FDOPA) in a positron emission tomography study.[6] Whole-brain, voxel-wise comparisons of pre- and postaripiprazole scans revealed increased FDOPA trapping in the right medial caudate of augmentation responders. This finding suggests that augmentation of antidepressant response by aripiprazole may be associated with potentiation of dopaminergic activity.[6] Pramipexole has been combined with antipsychotic treatment in people with schizophrenia with good response.[7]

There is evidence to support the use of the combination of clomipramine 300 mg, dextroamphetamine 30 mg, pramipexole 3 mg, lithium 900 mg, and quetiapine 200 mg daily in a patient with treatment-resistant bipolar depression.[8] To our knowledge, this is the first case report on the use of combination therapy (clomipramine, dextroamphetamine, pramipexole, and aripiprazole) for ECT-resistant unipolar depression. Mr A responded only to multiple dopaminergic medications. This combination was safe, effective, and tolerable. The neurotransmitter dopamine is not frequently targeted in the management of treatment-resistant depression. Dopamine is involved in anhedonia, anergia, motor retardation, motivation, wakefulness, alertness, reward, and pleasure-seeking neuronal circuits. We emphasize the importance of targeting dopamine in the difficult-to-treat treatment-resistant depression patients with dopamine depleted brain.[9,10] This combination may be used more often by clinicians in their practices when dealing with difficult-to-treat treatment-resistant depression patients.

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Table 1. Medication Titration During Each Visit

Timeline	PHQ-9 Score	Medications	Intervention
Week 0	14 (moderate depression)	Mirtazapine 45 mg Venlafaxine 375 mg Methylphenidate 10 mg 4 times daily Propranolol 10–20 mg when necessary for anxiety	Stopped methylphenidate, mirtazapine, and venlafaxine Clomipramine 75 mg at bedtime Dextroamphetamine 20 mg AM and 10 mg noon
Week 5	15	Clomipramine 150 mg at bedtime Dextroamphetamine 20 mg AM and 10 mg noon	Increase clomipramine 300 mg at bedtime Pramipexole 0.5 mg twice a day (patient stopped due to side effects)
Week 12	24	Clomipramine 250 mg	Increase clomipramine 300 mg at bedtime Pramipexole 0.25 mg at bedtime Dextroamphetamine 20 mg AM, 10 mg noon, and 10 mg 4 PM
Week 19	11	Clomipramine 300 mg at bedtime Pramipexole 3 mg at bedtime Dextroamphetamine 20 mg AM,10 mg noon, and 10 mg 4 PM	Aripiprazole 2.5 mg AM
Week 25	11	Clomipramine 300 mg at bedtime Pramipexole 3 mg at bedtime Dextroamphetamine 20 mg AM, 10 mg noon, and 10 mg 4 PM Aripiprazole 15 mg AM	Clomipramine 300 mg at bedtime Pramipexole 3 mg at bedtime Dextroamphetamine 40 mg AM, 10 mg noon, and 10 mg 4 PM
Week 29	7	Clomipramine 300 mg at bedtime Pramipexole 3 mg at bedtime Dextroamphetamine 40 mg AM, 10 mg noon, and 10 mg 4 PM Aripiprazole 15 mg AM	This regimen was continued because PHQ-9 score of 7 was close to remission

Abbreviation: PHQ-9 = 9-item Patient Health Questionnaire.

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