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Pramipexole in Treatment Resistant Depression: A Case Review

Nada Abdallah[1*], Jeffrey Kahn[2]

[1]Weill Cornell Medicine, New York, NY, USA
[2]Department of Psychiatry, Weill Cornell Medicine, New York, NY, USA
Email: *nat4005@med.cornell.edu

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Abstract

Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease and Restless legs syndrome. Although off-label, the use of Pramipexole as an adjunct therapy in treatment resistant depression has recently been documented in the literature with promising results. We present a 75-year-old male with MDD who has failed trials of SSRIs, SNRIs, TCAs, SGA, TMS, Ketamine, and ECT who was initiated on Pramipexole. We discuss, based on existing literature, the probability of a favorable long-term response to Pramipexole and the potential side effects for our patient. We also highlight the need for future studies designed to test the efficacy of Pramipexole in geriatric patients with TRD.

Keywords

Pramipexole, Treatment Resistant Depression, Augmentation, Dopamine Agonism, Geriatric Psychiatry

1. Introduction

Pramipexole is a dopamine promoter primarily known for its use in the treatment of Parkinson's disease and Restless legs syndrome (FDA approved in 1997 and 2006 respectively). It is a selective D2-D3-D4 receptor agonist with preferential affinity for D3 receptors primarily located in the reward associated mesolimbic system [1]. By potentiating dopamine receptors within this pathway, Pramipexole is especially useful in alleviating Parkinson's disease's anhedonia, defined by a reduced ability to experience pleasure, or a diminished interest in engaging in pleasurable activities.

In the past decade, studies have shown anhedonia to be the single biggest predictor of poor outcomes in antidepressant treatment [2]. While traditional anti-

depressants and stimulants fail to target the inflammatory cytokines underlying anhedonia [3], Pramipexole is believed to be capable of controlling this type of dopamine pathway specific pathogenic cellular immunity [4]. We present the case of a geriatric patient with Major Depressive Disorder who was prescribed Pramipexole as an adjuvant to Sertraline and ECT, after failed trials of SSRIs, SNRIs, TCAs, MAOIs, TMS and Ketamine infusions. The purpose of this case is to explore the role of new dopaminergic adjuvants in Treatment Resistant Depression and illustrate the need to expand existing treatment paradigms for these populations.

2. Case Presentation

Our patient, Mr. Z, is a 75-year-old albino man with a history of adjustment disorder secondary to vision loss that progressed to treatment resistant major depressive disorder. His medical comorbidities include coronary artery disease (CAD) and a 5-year history of hereditary retinal degeneration that resulted in complete legal blindness diagnosed in the past year. The patient was brought for evaluation on transfer from another location of our hospital, where he was hospitalized for Altered Mental Status (AMS) after he collapsed onto the floor at home. While at NYP, his labs showed elevated erythrocytosis with a hematocrit of 56% and hypercalcemia with a blood gas calcium level of 1.46 mmol/L which were corrected with IV fluids. His worsening AMS was attributed to depression following neurological imaging and infection work-up, which showed no abnormalities. He had a similar presentation of AMS one month prior to his collapse which led to a three-week psychiatric inpatient stay at a different hospital. During that hospitalization, he was started on aripiprazole 10 mg daily and Lithium 300 mg daily.

On mental status exam in our Evaluation Center, the patient presented as a thin man with disheveled hair, appearing older than his stated age, with evidence of psychomotor slowing and unsteady gait for which he was given a wheelchair to ambulate. The patient's speech was quiet, with slow rate and hesitant rhythm. He needed to be prompted several times to answer questions. The patient described his mood as "depressed" and his affect was dysphoric, nonlabile, constricted and congruent. His thought process was linear and goal-oriented. He denied delusions as well as auditory and visual hallucinations. He endorsed passive suicidal ideation but had no intent, means or plan. He was alert and oriented to self, time and place. He was able to recite the days of a full week. A urinalysis, basic metabolic panel, complete blood count, chest radiograph, and head CT scan were unremarkable. He was continued on the medication regimen of Aripirazole and Lithium, and admitted to the inpatient unit for further management.

Collateral information obtained from Ms. Z indicated that Mr. Z had been depressed for many 1-month periods of time over the course of their past 30 years of marriage. She believed that these episodes have been in response to var-

ious stressors such as unemployment, debt, and a hernia. His psychiatrist at the time had put him on Doxepin, Paroxetine and Venlafaxine to which he partially responded and later discontinued. She described the past 5 years as being different as he was unable to cope with the idea of losing his vision. His current psychiatrist had tried several medication regimens, including the following treatments at varying doses since the onset of his worsening vision and severe depression: Zoloft, Wellbutrin, Paxil, Lexapro, ECT, Pristiq dTMS, Rexulti, Doxepin, Trintellix, Intranasal ketamine, Desipramine, Strattera, Cytomel, Parnate, Dexedrine. When he presented at our Evaluation Center, the only medications he was taking were Abilify and Lithium, started at the previous hospital as previously discussed.

In our inpatient unit, Mr. Z continued to suffer from low mood, low energy and general hopelessness. He was tapered off Abilify and Lithium, started on Sertraline up-titrated gradually to 200 mg and underwent 15 bilateral ECT sessions. There were no improvements in his presenting symptoms of low mood, low energy and passive suicidal ideation which led to the initiation of Pramipexole 1.25 mg that was up titrated to 3 mg. One month the initiation of this new regimen, there have been mild symptomatic improvements that can be quantified by a decrease in his HAM-D score from 24 to 22, which demonstrate a general upward trajectory. Staff and family thought it was the largest improvement over the course of the present illness. No side effects were noted by his medical team or reported by the patient.

3. Differential Diagnosis

The patient's presentation is highly suggestive of treatment resistant melancholic major depressive disorder, satisfying the DSM5 criteria of depressed mood with low energy, decreased appetite, decreased interests, psychomotor retardation and suicidal ideation for the past year. Given Mr. Z's collateral, the diagnosis of major depressive disorder is also supported by his history of MDD episodes triggered by various stressors. His mood disorder can be characterized as treatment resistant given the extensive trials of antidepressants of different classes (SSRIs, SNRIs, TCAs, Atypical Antipsychotics, Mood stabilizers, SGA, ECT, Ketamine, TMS) that have failed to elicit a clinical response.

It is also important to consider the diagnosis of Depression with Psychotic features as it is one of the most serious types of depression in the geriatric population and is overlooked 27% of the time, according to the National Institute of Mental Health's STOP-PD study. This diagnosis maintains the criteria of MDD while also allowing for the presence of delusions or hallucinations. Delusions are more common e.g. "I am dying", "I have cancer") which can be easily confused with symptoms of depression. While Mr. Z met the criteria for depression, he never exhibited any delusions of guilt or nihilism, thoroughly explored by interview. The presence of psychotic features would likely have prohibited the addition of Pramipexole to his treatment as its dopamine agonism could have ex-

acerbated these delusions.

Finally, other mood disorders such as Bipolar disorder, which could also present with periods of recurrent depression episodes, should always be considered. However, after extensive questioning of Mr. Z and his wife, all signs of episodes of hypomania or mania were ruled out as he had never experienced periods of euphoria, impulsivity, grandiosity, talkativeness, or flight of ideas.

4. Discussion

Although off label, several reports of the addition of Pramipexole to the medication regimen of treatment resistant depression patients have been documented. A summary of these findings will be followed by a discussion of the unique features of this case and its implications for the use of Pramipexole in TRD.

In a 2012 study by Hori and Kunugi, 17 MDD (5 bipolar and 12 unipolar MDD) patients who had failed to respond to SSRIs were administered Pramipexole (1.6 mg max dose) in addition to existing medication [5]. The study found that 12 patients (71%) were responders based on the definition of 50% or more reduction in the HDRS-21 score. Ten patients (59%) remitted (HDRS-21 total score at endpoint < 8). These results were almost unchanged when the sample was confined to patients with MDD.

In a 2016 study, Fawcett *et al.* tested Pramipexole in 42 patients between the ages of 25 - 81 (24 had MDD and 18 had bipolar depression). All were considered to have treatment resistant depression as they had failed to respond to 4 antidepressant trials. The study found that 76% of 42 patients showed a meaningful response: 20 remitted and 12 responded with a mean effective dose of 2.46 mg/day. In the remaining group, 2 did not respond and 8 could not tolerate the drug due to extreme nausea with SE occurring 3 - 10 days after drug initiation [6]. The main limitation of this study was the fact that these remittances and responses were based on clinical judgment rather than objective criteria.

In 2019, Tundo *et al.* conducted a systematic review and meta-analysis that evaluated 3 open label trials and 5 observational studies including 504 patients with a median age of 45.3 years [7]. The study found a superior Pramipexole response as compared to placebo (RR 1.77) but a similar response compared to SSRIs (RR 0.93). The study also found that the common side effects experienced by Parkinson's patients being treated with Pramipexole of gambling, impulsivity, hypersexuality were not reported with MDD patients treated with Pramipexole.

Similar to these reports, since the initiation of Pramipexole, the patient in this case has shown promising improvements in the symptoms of depressed mood, low energy and passive suicidal ideation as reflected in the reduction of HDRS scores. Many of the former studies measure outcomes in terms of response (MDRS decrease by 50%) and remittances (MDRS < 7) 15+ weeks after therapy, which are too early to assess in our patient who has only been on this medication for 4 weeks. Additionally, these studies provide better insight into the timeframe of Pramipexole side effects (first 2 weeks) which gives us a degree of certainty in

predicting no future adverse effects or intolerance of the drug in our case. It is also important to note that many of the studies have included patients that failed 1 - 4 different MDD depression treatments, while Mr. Z has been on far more medication trials including dTMS, Ketamine and ECT. This makes this case especially pertinent to those who have exhausted every step of the MDD treatment paradigm algorithm.

What makes this report unique, unlike many of the studies in the literature, is the patient's advanced age. Most trials and reviews studied patients with median ages of 30 - 40, with few outliers above the age of 65. Our case presents a geriatric patient with several comorbidities including CAD and blindness, making him especially sensitive to new medications, dosage changes and side effects. This case shows promise in the use of Pramipexole at higher doses (3 mg) and in an elderly population, and invites future studies to substantiate these results and elaborate its role in TRD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Aiken, C.B. (2007) Pramipexole in Psychiatry. *The Journal of Clinical Psychiatry*, **68**, 1230-1236. https://doi.org/10.4088/JCP.v68n0810

[2] Uher, R., *et al.* (2012) Depression Symptom Dimensions as Predictors of Antidepressant Treatment Outcome: Replicable Evidence for Interest-Activity Symptoms. *Psychological Medicine*, **42**, 967-980. https://doi.org/10.1017/S0033291711001905

[3] Hannestad, J., DellaGioia, N. and Bloch, M. (2011) The Effect of Antidepressant Medication Treatment on Serum Levels of Inflammatory Cytokines: A Meta-Analysis. *Neuropsychopharmacology*, **36**, 2452-2459. https://doi.org/10.1038/npp.2011.132

[4] Escalona, R. and Fawcett, J. (2017) Pramipexole in Treatment Resistant-Depression, Possible Role of Inflammatory Cytokines. *Neuropsychopharmacology*: *Official Publication of the American College of Neuropsychopharmacology*, **42**, 363. https://doi.org/10.1038/npp.2016.217

[5] Hori, H. and Kunugi, H. (2012) The Efficacy of Pramipexole, a Dopamine Receptor Agonist, as an Adjunctive Treatment in Treatment-Resistant Depression: An Open-Label Trial. *Scientific World Journal*, **2012**, Article ID: 372474. https://doi.org/10.1100/2012/372474

[6] Jan Fawcett, A., Rush, J., Vukelich, J., Diaz, S.H., Dunklee, L., Romo, P., Yarns, B.C. and Escalona, R. (2016) Clinical Experience with High-Dosage Pramipexole in Patients with Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression. *American Journal of Psychiatry*, **173**, 107-111. https://doi.org/10.1176/appi.ajp.2015.15060788

[7] Tundo, A., Filippis, R. and De Crescenzo, F. (2019) Pramipexole in the Treatment of Unipolar and Bipolar Depression. A Systematic Review and Meta-Analysis. *Acta Psychiatrica Scandinavica*, **140**, 116-125. https://doi.org/10.1111/acps.13055