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CASE SERIES

Aripiprazole, a Novel Option in the Management of Restless Legs Syndrome (RLS) Patients with Augmentation and/or Severe RLS Symptoms: A Report of 4 Cases

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Purpose: Restless Legs Syndrome (RLS) is a sensorimotor disorder associated with an unpleasant urge to move the limbs, relieved with movement, occurring in the evenings and with prolonged rest/inactivity. Treatment with dopamine agonists is effective for up to 60–90% of affected individuals. However, augmentation, ie, the paradoxical worsening of RLS symptoms after prolonged RLS treatment, is frequently reported, typically after 3–10 years of treatment. Here, we present 4 patients with RLS who were successfully treated with dopamine agonists but later developed augmentation. A trial of aripiprazole, a dopamine receptor partial agonist (DRPA), was initiated for treatment of augmentation symptoms.

Patients and Methods: Four patients treated for RLS with dopamine agonists developed augmentation. In each instance, augmentation symptoms did not respond adequately to a variety of medications including α2δ drugs, opioids or other agents. A trial of aripiprazole was initiated for each patient, and effects were evaluated.

Results: All four patients with severe RLS and augmentation with dopamine agonists achieved symptom control with aripiprazole. Patients endorsed 90–100% efficacy with aripiprazole by subjective self-report after failures with other agents. Further evaluation with the International Restless Legs Syndrome Study Group RLS Rating Scale (IRLS-SGRS) showed that benefits (from moderate to very severe, to mild to moderate severity) were largely maintained for 1–2 years. Aripiprazole doses to control augmentation symptoms were low (1–4 mg). No significant side effects were reported.

Conclusion: Aripiprazole may have utility for augmentation in RLS. We speculate that the partial agonist and antagonist properties of aripiprazole may limit potential for dopamine hyposensitization to progress to cause augmentation. Further research is needed to see if aripiprazole and/or other DRPAs are a viable long-term treatment option for patients experiencing augmentation and/or severe RLS with dopamine agonist therapy.

Keywords: partial dopamine agonist, Willis Ekbom disease, dopamine treatment, dopamine receptor partial agonist, augmentation, restless legs syndrome, aripiprazole

Introduction

Restless Legs Syndrome (RLS) is a sensorimotor disorder associated with an unpleasant urge to move the limbs. The urge to move is worse during periods of inactivity and is partially or totally relieved by movement. The urge to move is worse in the evenings than the day. RLS prevalence is estimated to be between 5 and 10% of the population in the United States.[1] Untreated RLS has several associated morbidities, including poor sleep, depression, anxiety, cardiovascular disease, cerebrovascular disease, and decreased quality of life.[2,3] Primary treatments include dopamine agonists, α2δ drugs, benzodiazepines, and opioids, with dopamine agonists generally being effective for up to 60–90% of affected individuals.[4–6] Augmentation is the paradoxical worsening of RLS symptoms after prolonged RLS treatment that

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typically occurs in 10–68% of patients who underwent sustained treatment with dopamine agonists, usually after 3–10 years of effective management.[6] Augmentation risks are thought to be lower with use of smaller doses of longer acting dopaminergic agonists such as pramipexole and ropinirole, with rotigotine being the longest acting and having the lowest augmentation risk among these agonists.[6] Shorter acting dopaminergic agonists, such as levodopa, have the highest potential for augmentation developing with persistent use.[6] Although the mechanism for augmentation is unclear, it is thought to occur due to excess postsynaptic desensitization of dopamine 2 (D2) receptors in the substantia nigra and putamen with chronic intermittent dopaminergic stimulation.[7] Augmentation is very challenging to manage clinically, with at least one-third of patients who experience augmentation continuing to suffer significant symptoms despite current algorithms for available management options.[8] Current management recommendations include discontinuing the offending agent, optimizing sleep and sleep habits, or adding α2δ drugs or opioid therapy, but these latter options have significant potential side effects.[6,8] Additionally, avoiding dopamine agonist use will prevent augmentation from occurring.

Aripiprazole is a dopamine partial receptor agonist (DRPA) with intrinsic D2 and D3 activity in various parts of the brain acting as agonist or antagonist. Aripiprazole has been described in some case reports to be helpful for RLS, though worsening of RLS has also been reported.[9–13] Here we report the outcome of four patients who developed augmentation following successful treatment of RLS with a dopamine agonist. In each case, augmentation was treated with aripiprazole.

Materials and Methods

RLS was diagnosed in all patients by a board certified sleep medicine specialist (EKL). All patients provided written informed consent to have their anonymized data reported and case details published, and review with the Royal Ottawa Mental Health Center Clinical Records department and Royal Ottawa Health Care Group (ROHCG) Research Ethics Board voiced no objections. No external sources of funding were used for this study. Patients completed an assessment of their sleep and were followed by a board certified sleep specialist (EKL) including clinical evaluation and polysomnography. Patients were asked to fill out the International Restless Legs Syndrome Study Group Restless Legs Syndrome Rating Scale (IRLS-SGRS) to describe the severity of their RLS symptoms after aripiprazole use in 2023, 1–2 years after they had started aripiprazole (permission provided by Mapi Research Trust). This scale is a validated scale to describe the severity of RLS symptoms, consisting of a 10-question survey that has been shown to have high internal consistency, test–retest reliability and convergent validity.[14] Patients were also asked to retrospectively fill out this scale prior to aripiprazole use to describe the severity of their symptoms before aripiprazole therapy was initiated to the best of their recollection.

Results

All patients completed overnight polysomnography prior to starting aripiprazole and had sleep disordered breathing diagnosed and treated, with objective validation of adequate treatment (with positive airway pressure) before RLS symptoms/augmentation was treated. All RLS patients had some form of RLS treatment prior to polysomnography except subject 3. Patient 4 had severe RLS symptoms despite RLS treatment with gabapentin 900 mg qhs, medical cannabis 1 g/day, and clonazepam 0.5 mg daily, such that total sleep time was very low on polysomnography. Each patient had ferritin levels above 75 ug/L and/or were prescribed iron supplements to reach these levels. Potential causes of secondary RLS symptoms, such as vitamin B12 deficiency, were ruled out for all patients. Each patient had a documented period of symptom relief and stability with dopaminergic agonists prior to the use of aripiprazole. No psychiatric medication dosages or classes were changed while augmentation developed. In each instance, augmentation developed after there was symptom control achieved with dopaminergic agonists, sometimes with additional pharmacologic agents. Augmentation symptoms included paradoxical worsening severity RLS symptoms after symptom stability (all patients), and symptoms occurring earlier in the day (patient 1). In two cases (patient 2 and 3), impulse control problems developed with prolonged pramipexole use, including binge eating and gambling impulses. Various combinations and/or altered timing of medications were used in an attempt to control augmentation symptoms, see Table 1 for summary of patient profiles and attempted augmentation control treatments. After discontinuation of the dopaminergic

Table 1 Patients with RLS – Demographics, Polysomnography Results, Treatment Summary

Patient Number	Current age/ Gender (M/F)	Medical/Psychiatric Diagnoses	PSG findings (Year, Summary) and Medications Used During PSG	RLS Disease Duration (Years)	Estimated Period of Control of Symptoms with Dopamine Agonist Before Augmentation Developed (Years)	Previous RLS Treatments	Aripiprazole Year, Dose, Subjective Response (mg, % Response)
1	76 (F)	Atrial fibrillation, GERD, OSA, Osteoarthritis, MDD	(2016) AHI = 20.8, RDI = 51.2 TST = 3 hr21 min, PLMI = 55.7; PLMA = 42.6 gabapentin, pantoprazole, sertraline, metoprolol, pramipexole, vitamin D, atorvastatin	16	12 (2007–19)	Pramipexole, gabapentin, pregabalin clonazepam, codeine, •nabilone	2022 1 mg 95%
2	61 (F)	OSA, Vitamin B12 deficiency, hypothyroidism, metabolic syndrome, BPD	(2010) AHI = 9.8, RDI = 45.8 TST = 4 hrs, PLMI=2.9, PLMA = 2.9 Duloxetine*, pramipexole, lamotrigine*, quetiapine*, l-thyroxine, trazodone, iron *medications for BPD	13	11 (2010–21)	Pramipexole, pregabalin, iron, codeine, gabapentin,	2022 4 mg 100%
3	53 (M)	Osteoarthritis, chronic tonsillitis, OSA	(2019) AHI = 5.7, RDI = 18.3 TST = 5hr18 min, PLMI=0, PLMA = 0 no prescription meds	12	1 (2020–21)	Gabapentin, pregabalin, pramipexole, ropinirole, clonazepam, •nabilone	2021 2 mg 90–100%
4	64 (M)	OSA, DM II, GERD, HTN, COPD, hypercholesterolemia, low testosterone, Peyronie's disease, Back injury, anger issues, cocaine use in past, MDD	(2018) AHI = 0, RDI = 33 TST = 9 min, PLMI= 106.7, PLMA = 53.3 pantoprazole, perindopril, escitalopram**, atorvastatin, ezetimibe, clonazepam, bupropion**, sitagliptin and metformin, gabapentin, testosterone, marijuana	6	2 (2019–21)	Clonazepam, gabapentin, pramipexole, iron, codeine •marijuana	2022 4 mg 95–100%

Notes: *Indicates medications used for BPD. **Indicates medications used for MDD. •Indicates off label treatment for RLS.

Abbreviations: M, male; F, Female; tx, treatment; RLS, restless legs syndrome; PSG, polysomnography; OSA, obstructive sleep apnea; BPD, bipolar disorder; MDD, major depressive disorder; DM II, diabetes mellitus type II; GERD, gastroesophageal reflux disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; AHI, apnea hypopnea index; RDI, respiratory disturbance index; TST, total sleep time; hr(s), hour(s); PLMI, periodic limb movement index; PLMA, periodic limb movement arousal index.

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agonist and multiple trials of medications and/or combinations with varying effects, aripiprazole was initiated, starting at 1 mg 30 minutes before bedtime, and was increased by 1 mg every week until RLS symptoms were relieved. One mg dosage increments were achieved by splitting 2 mg tabs in half. In each case, aripiprazole was initiated specifically to control RLS augmentation symptoms and not for any other psychiatric symptoms. Importantly, patients had very positive comments about aripiprazole use for RLS symptoms, after years of persistent RLS/augmentation symptoms and some control with dopaminergic agonists. Some patients referred to aripiprazole "a miracle drug" (patient 1 and 2), the "medication that did it" (patient 2), "took care of my leg issues" (patient 3) and "incredible success with those pills" (patient 4). Doses needed for RLS symptom control were ≤4 mg. No side effects were described by any patients, though patient 1 wondered about possible mild weight gain. Results of their IRLS-SGRS scores after their trial of aripiprazole, as well as their retrospective recollection, along with their prescribed medications with specific doses are shown in Table 2. Patients 1, 2 and 4 have largely maintained significant benefits with aripiprazole use, while patient 3 may be having some return of symptoms. Note that in cases where a dopamine agonist was still being used for intermittent management of RLS symptoms, patients were instructed to taper then discontinue the dopamine agonist, before initiating their trial of aripiprazole.

Table 2 Medications of Patients Prior to Aripiprazole Initiation and IRLS-SGRS Scores Pre-Post Aripiprazole Use

Patient	Medications Before Starting Aripiprazole (Year)	IRLS-SGRS Prior to Starting Aripiprazole (Year)	IRLS-SGRS After Aripiprazole Use (June 2023)
1 (76 year old female)	Pramipexole 0.25 mg po qhs, 2 hrs before bedtime, with weekly holidays to minimize augmentation symptoms, Apixaban 5 mg po bid, Atorvastatin 40 mg po qhs, Metoprolol 25 mg po bid, Patanol eye drops, Pantoprazole 40 mg po bid, Feramax 150 mg po qd, Sertraline 75 mg po qhs, Codeine phosphate 35–75 mg po qhs prn, using as rescue medication for RLS symptoms with holidays from pramipexole (2022)	33 - very severe (2022)	13 (moderate)
2 (61 year old female)	Vitamin B12 1000 mcg po qdaily, Escitalopram 20 mg po qdaily, Gabapentin 600 mg po qhs, Lamotrigine 200 mg po qhs, Levothyroxine 100 mcg po qdaily, Methylphenidate 36 mg po qdaily, Rosuvastatin 20 mg po qdaily, Semaglutide 0.25 mg subcutaneous weekly, Trazodone 50 mg po qhs (2022)	36 - very severe (2022)	7 (mild)
3 (53 year old male)	Nabilone 0.5 mg po qhs (could not tolerate because of excess sedation, though reported it was effective for RLS symptoms), Ropinirole 0.25 mg po qhs prn, uses as rescue medication (2021)	26 – severe (2021)	20 (moderate)
4 (64 year old male)	Atorvastatin 20 mg po qdaily, Budesonide/Formoterol-200 2 inhalations daily, Bupropion XL 300 mg po qdaily, Medical Marijuana 1 g daily, Clonazepam 0.25–0.5 mg po qhs, Codeine phosphate 45–60 mg po qhs, Empagliflozin 10 mg po qdaily, Escitalopram 20 mg po qdaily, Gabapentin 600 mg po qam, 900 mg po afternoon, 1200 mg po qhs, Ipratropium bromide inhaler 2 puffs q6hrs prn, Perindopril erbumine 4 mg po qdaily, Pramipexole 0.5 mg po qhs 2 hours before bedtime, using in spite of augmentation, Salbutamol 2 puffs 4 times per day prn, Metformin/sitagliptin 1 tab po qdaily, Tiotropium 1 inhalation daily, Trazodone 25–50 mg po qhs (2022)	34 - very severe (2022)	3 (mild)

Notes: IRLS-SGRS Scoring: 0= none; 1–10 = mild, 11–20 = moderate, 21–30 = severe, 31–40 = very severe.
Abbreviation: IRLS-SGRS, International Restless Legs Syndrome Restless Legs Syndrome Study Group Rating Scale.

Discussion

To our knowledge, this is the first report of aripiprazole being effective for treatment of augmentation in RLS, with doses under or equal to 4 mg being necessary for symptom control. These doses are generally lower than doses used as a primary medication for schizophrenia (10–30 mg)[15] or adjunctive strategies used to treat major depressive disorders (2–15 mg).[16] Although aripiprazole is generally well tolerated, common side effects that can occur with aripiprazole can include akathisia, disturbing dreams, weight gain and parkinsonism. Once aripiprazole was added, patients 1 and 3 were maintained exclusively on aripiprazole for RLS, while patient 2 maintained gabapentin (600 mg qhs) with aripiprazole, and patient 4 remains on gabapentin (1200 mg qhs), codeine (45 mg qhs) and medical cannabis due to concomitant chronic pain. Follow-up data available for these patients is limited to 1–2 years for each patient, thus restricting assessment on possible duration of efficacy of aripiprazole treatment for augmentation. One limitation of this report is that follow-up data available were limited to subjective estimation. We had patients fill out the IRLS-SGRS retrospectively, which clearly could be subject to recall bias, though the current IRLS-SGRS scores do reflect the RLS symptom control these patients currently experience with aripiprazole. Additional follow-up objective assessments, such as polysomnography, were not performed in these patients, though conventional sleep study findings including presence/absence of periodic limb movements have not been found to be useful to identify augmentation.[6] The significant psychiatric and medical comorbidities of these patients, as well as the number of medications patients were using prior to initiation of aripiprazole treatment limit the conclusions that can be drawn for the use of this medication in these clinical contexts.

We speculate that, because augmentation in RLS is related to excess desensitization from chronic stimulation with dopaminergic agonists, aripiprazole may be effective for RLS augmentation because of its partial agonism activity, which has a self-limiting agonist capacity and acts as an antagonist at higher doses. This medication has the capacity to block postsynaptic D2 receptors with high dopaminergic tone but activate postsynaptic receptors with low dopaminergic tone.[17] Alterations in dopamine receptor sensitivity are thought to underlie the development of augmentation. Consequently, these properties of aripiprazole may make it a "goldilocks" drug for patients with RLS and augmentation, where the clinical challenge may emerge from excessive or inadequate dopamine stimulation and subsequent sensitization and desensitization effects on D2 receptors. Additionally, aripiprazole has been shown to have a slow dissociation profile from the D2 receptor, which may further limit hyposensitization from occurring.[18]

While aripiprazole may not be potent enough to treat RLS in its original presentation and even exacerbate RLS in some circumstances, this medication may be better suited to treat augmentation, where the D2 receptor profile might be distinct from treatment naïve RLS patients. The partial agonist and slow dissociation properties of aripiprazole may limit its capacity to trigger further desensitization in dopaminergic receptors and thereby limit progression to augmentation symptoms in patients who specifically responded to dopamine agonist therapy and achieve initial symptom control, though further research is needed to evaluate this hypothesis. Although there are other current medications and/or combinations or medications (including α2δ drugs, opioids) that have been shown to be beneficial for augmentation, the majority of these options have significant drawbacks such as sedation and potentially addictive properties. Other off-label drugs, including cannabis products, may have potential for symptom relief, but preliminary observations suggest that efficacy may be variable and that sedation and other side effects can be problematic for some people.[19]

Conclusion

Augmentation in RLS is challenging to manage, and results in significant suffering for patients. Aripiprazole, a DRPA, may represent another option for management of augmentation in RLS given its unique pharmacological profile, but caution is warranted in interpreting these results given the significant medical and psychiatric complexities presented, as well as the number of medications these patients were using. Additional research is needed to confirm these initial results for patients with RLS who specifically have experienced augmentation after a history of treatment response to dopamine agonists. Furthermore, it may be worthwhile to consider use of other dopamine partial agonists such as brexpiprazole and cariprazine to determine if these drugs may also have potential benefits for augmentation and/or rebound RLS symptoms.

Disclosure

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