Case Report

Psychosis Following the Addition of Pramipexole in an Intellectually Disabled Adult

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Abstract

A fifty-six-year old verbal male with moderate mental retardation (IQ range of 35-40 to 50-55) residing in a state-run facility developed psychosis following the addition and titration of pramipexole for Parkinson's disease. No evidence of psychosis was noted at the time of admission or prior to the addition and titration of pramipexole with good response. When titrated to 0.375 mg three times daily, psychosis presented and escalated. Pramipexole was tapered to extinction and behavior rates returned to baseline. This increase may represent a separation of risk-benefits where a partial positive response is achieved and no adverse effects are noted.

Key Words: Pramipexole, Psychosis, Developmentally Disabled, Aging, Side Effects

Introduction

Parkinson's disease (PD) represents a progressive neurological disorder arising from loss of dopaminergic neurons in the substantia nigra (1). The location of these changes in neuron density resulted in the use of dopamine receptor agonists. In 1993, the American Academy of Neurology reviewed the use of a number of medication classes in the treatment of Parkinson's disease. At that time, the Academy concluded that levodopa was the most effective medication for PD symptoms, particularly bradykinesia or rigidity, and that dopamine agonists, while effective for all symptoms, were not considered as effective (2).

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Submitted: Feb 16, 2007; Revised: June 19, 2007; Accepted: June 20, 2007

The literature was recently reexamined to help identify the role of non-ergot dopamine agonists in therapy (2). Medications in this class have demonstrated safety and efficacy as initial therapy for mild to moderate stages of PD (3). Consistent with these findings, there has been increased interest in the use of the dopamine-2 and -3 agonist pramipexole in the treatment of Parkinson's-associated depression, unipolar depression, and treatment-resistant depression (4-6); yet, there has been limited reporting of treatment-associated increases in thought-processing disorders. In one report, therapy with pramipexole was associated with a higher risk for hallucinations compared to another newer dopamine agonist and placebo (7). Two recent cases of delusional jealousy developing secondary to the addition of pramipexole to the treatment regimen were also reported (8, 9). The diagnosis of psychopathologies in persons with intellectual disabilities who may have experienced adverse medication effects has not been widely reported. In this paper, we report a case of increased physical and verbal aggression, self injury, and hallucinations/delusions in a man with an intellectual disability following the addition of pramipexole.

Case Report

The patient is a fifty-six-year old verbal male with moderate mental retardation (IQ range of 35-40 to 50-55) residing in a state-run facility. He has a history of problematic behaviors which includes physical aggression toward others, noncompliance, invasion of personal space, and inappropriate sexual behavior. Prior to admission to the present facility, he experienced multiple placements, including inpatient admissions secondary to these behaviors. Paranoid schizophrenia and dementia were diagnosed during the course of these admissions. Behaviors consistent with schizophrenia were not noted at the time of this admission. There were no reports or evidence of delusions, hallucinations, or responding to internal stimuli characterized by statements inconsistent with past events, bizarre story-telling, talking or yelling at self or others not present, or environmental stimulation just prior to hitting himself. No antecedents were identified for these events or thinking others were taking his belongings. The diagnosis of dementia was not supported by documentation of decline in executive function or activities of daily living.

When evaluated by the neurologist following admission, significant bilateral rigidity and a bilateral resting tremor were noted. A combination of primary Parkinsonism with a secondary parkinsonian syndrome due to high-dose, long-term neuroleptic use was considered. At the time of admission, the medication regimen included benztropine 2 mg, divalproex 2,000 mg, memantine 20 mg, quetiapine 400 mg, olanzapine 20 mg, and estradiol. Medication adjustments were made following admission with benztropine, memantine, quetiapine, and depo-estradiol discontinued or tapered to extinction. Divalproex and olanzapine were continued. Nonpharmacologic behavioral interventions were implemented. One month following admission, the patient remained psychiatrically stable. A gross tremor was noted during the course of psychiatric clinic and consideration was given to withdrawal dyskinesia. In the first quarter following admission, medication adjustments included increasing the doses of divalproex and olanzapine secondary to increased rates of aggression. Topiramate 50 mg was added to the medication regimen for mood lability. No additional medication adjustments were made. Environmental factors, including participation at the sheltered worksite on campus and staffing changes, were not considered contributing factors to increased aggression rates.

Approximately fifteen months later, increased resting tremors, increased rigidity, a markedly stooped posture, and slow gait were noted, left side greater than right. Resting tremor was significant and interfered with activities of daily living. The total daily dose of divalproex was 2,500 mg and olanzapine 25 mg. Pramipexole was initiated at 0.125 mg twice daily and titrated slowly to the goal of 0.25 mg three times daily. The patient responded positively with fewer tremors, and rigidity was improved. Neuropsychiatric symptoms were negative. The pramipexole dose was then slowly titrated to 0.375 mg three times daily. Following this increase, noncompliance and aggression, both verbal and physical, increased. Episodes of yelling at persons not present occurred. Topiramate was discontinued. The following month, refusals, aggression, including to self, and noncompliance continued to escalate. Episodes of hallucinations and delusions tripled from the prior month.

The tapering of pramipexole was initiated following this exacerbation. The Naranjo ADR Probability Scale (10) was used to help evaluate the relationship between the adverse effect of increased psychosis and the addition of pramipexole therapy in this patient. A score of "8" was obtained, indicating the treatment effects resulted in a probable relationship. Following discontinuation, behavior rates returned to baseline by the second month.

Discussion

Rush and colleagues reported the risk of developing mental health problems in people with intellectual disabilities may be up to four times greater than occurs in the general population (11). The potential for underdiagnosis may be the result of a combination of influencing factors including the absence of appropriate assessment measures, the lack of appropriate diagnostic criteria for special populations, and diagnostic overshadowing (11). In the case of diagnostic overshadowing, the level of intellectual impairment is often compared with the emotional disturbance. If the level of cognitive impairment is more severe, the impact of the mental health problem may be under appreciated. There may also be the perception that symptomatology demonstrated by a person with an intellectual disability is a component of normally occurring behavior. This same behavior may be fully recognized as an indicator of a mental health problem in the general population (11).

Additional problems accurately identifying psychiatric disorders include the inability of a person with an intellectual disability to self-report complex concepts, such as psychosis or akathisia, and service providers who are unfamiliar with differences in receptive and expressive language skills. During the course of the interview, the patient may appear to answer interviewer questions but cannot explain the concept when asked. Assessment tools may also present challenges to accurate information capture, particularly if the evaluation relies on caregiver recall (11).

Parkinson's disease (PD), a progressive neurological disorder, is characterized by classic symptoms of postural instability, bradykinesia, rigidity, and resting tremor. Recent research in the literature has focused on the use of non-

ergot dopamine agonists. Use of the newer non-ergot agents sought to address concerns that early use of levodopa would increase the potential for long-term motor complications (2). In addition, when compared to levodopa, dopamine agonist monotherapy was associated with decreased effectiveness and delayed onset. The longer duration of action with the newer agents may decrease the stimulation of the dopamine receptors (2). The initiation of dopaminergic treatment is always a concern for the clinician, particularly with regard to whether levodopa or a dopamine agonist would afford the most favorable long-term benefit. The review of the literature found PD patients receiving the newer non-ergot dopamine agonists experienced fewer motor complications compared to the levodopa group (2).

Complications are not limited to movement disorders. Neuropsychiatric changes are also reported and may include alterations in mood and cognition, the etiology of which is not fully elucidated. Contributing causes may be disease progression, both pathophysiological and the emotional consequences of a progressive disorder, or treatment-related side effects (12). The evidence-based review of the literature comparing pramipexole and levodopa found more patients in the pramipexole groups experienced somnolence and hallucinations during the dose escalation phase of the trials, and edema during the maintenance phase, than those in the levodopa groups (2).

The combination of an intellectual disability and PD complicates the diagnosis. Persons with intellectual disabilities are significantly more at risk for developing mental health problems. The prevalence of psychopathology is estimated to be four times greater than that of the general population (11). The diagnosis of PD has been complicated by confounding variables of age and comorbidities and presentation heterogeneity (1). Non-motor symptoms may be more prevalent as the disease progresses. One fifteen-year follow-up evaluation found 48% of the participants experienced dementia and 50% experienced hallucinations (1). Overall, more than 60% of patients diagnosed with PD report at least one psychiatric symptom during the progression of the disease (12).

Pramipexole is a non-ergoline aminobenzothiazole-type dopamine agonist with selective D_2, D_3, and D_4 activity and has been approved for monotherapy in early Parkinson's disease (13). A review of the literature was performed comparing the risk of adverse events between non-ergoline dopamine agonists. Compared to placebo, pramipexole demonstrated a significantly higher risk for hallucinations (7). The patient in this case report tolerated increased doses to a threshold of 0.25 mg three times daily. This may represent a separation of risk benefits where at this point a partial positive response is achieved, and no adverse effects are noted.

The impact of concomitant medications cannot be neglected. Additional medications included divalproex and olanzapine. Evidence-based treatment recommendations for persons with PD with psychosis found olanzapine use was not associated with improvement in PD patients and also worsened motor symptoms (14). Clozapine and quetiapine have been reported to improve psychosis without impacting motor function (14, 15). A prior trial of quetiapine was unsuccessful in this patient and, due to the prominence of mood lability, a trial of olanzapine was initiated. Clozapine was not considered due to concerns the patient would not tolerate the Food and Drug Administration-required weekly white blood cell monitoring.

Divalproex, too, can worsen parkinsonian symptoms. The neurological side effect of tremor is well-known. Parkinsonian syndromes and cognitive impairment have been rarely reported with this drug. As with PD, these symptoms had an insidious and progressive onset with clinical features mimicking Parkinson's disease (16). The patient in this case report was monitored with regular lab work, including a comprehensive metabolic panel with fasting lipids, complete blood count, and valproic acid level every four months. Findings were reviewed by the primary care physician, psychiatrist, and neurologist. The results were noncontributory.

Conclusion

We report the development of psychosis following initiation and titration of pramipexole in a man with an intellectual disability. Medication adverse effects may be under reported in this population secondary to diagnostic overshadowing, intellectual impairment limiting self-reporting, a lack of assessment instruments available for special needs populations, and healthcare providers and care givers unfamiliar with mental health presentation which may be different than what is demonstrated in the general population. In this patient, rates for psychosis returned to baseline following medication discontinuation. Individuals with intellectual disabilities represent an often under served population significantly more at risk for psychopathology compared to the general population. Recognizing treatment-emergent psychosis and intervening may facilitate better community integration.

References

1. Poewe W. The natural history of Parkinson's disease. J Neurol 2006;253(Suppl 7):vii2-vii6.
2. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2002;58(1):11-17.
3. Holloway RG, Shoulson I, Fahn S, Kieburtz K, Lang A, Marek K, et al. Pramipexole vs levodopa as initial treatment for

Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 2004;61(7):1044-1053.

4. Lemke MR, Brecht HM, Koester J, Kraus PH, Reichmann H. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci 2005;17(2):214-220.
5. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161(3):564-566.
6. Cassano P, Lattanzi L, Soldani F, Navari S, Battistini G, Gemignani A, et al. Pramipexole in treatment-resistant depression: an extended follow-up. Depress Anxiety 2004;20(3):131-138.
7. Etminan M, Gill S, Samii A. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. Drug Saf 2003;26(6):439-444.
8. Singh A, Althoff R, Martineau RJ, Jacobson J. Pramipexole, ropinirole, and mania in Parkinson's disease. Am J Psychiatry 2005;162(4):814-815.
9. Almeida S, Ranjith G. Using pramipexole in neuropsychiatry: a cautionary note. J Neuropsychiatry Clin Neurosci 2006;18(4):556-557.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-245.
11. Rush KS, Bowman LG, Eidman SL, Toole LM, Mortenson BP. Assessing psychopathology in individuals with developmental disabilities. Behav Modif 2004;28(5):621-637.
12. Ferreri F, Agbokou C, Gauthier S. Recognition and management of neuropsychiatric complications in Parkinson's disease. CMAJ 2006;175(12):1545-1552.
13. Dooley M, Markham A. Pramipexole. A review of its use in the management of early and advanced Parkinson's disease. Drugs Aging 1998;12(6):495-514.
14. Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66(7):996-1002.
15. Rongve A, Aarsland D. Management of Parkinson's disease dementia: practical considerations. Drugs Aging 2006;23(10):807-822.
16. Masmoudi K, Gras-Champel V, Masson H, Andrejak M. Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. Pharmacopsychiatry 2006;39(1):9-12.