Pramipexole Augmentation of Buprenorphine Improves Pain and Depression in Opioid Use Disorder: A Case Report

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Opioid use disorder is often complicated by chronic pain and depression. These comorbidities are challenging to manage and often lead to ongoing disability and greater risk of suicide.[1] Buprenorphine is commonly used with antidepressants in this patient population, but many patients continue to experience debilitating pain and depression. A case is reported in which pramipexole was used to augment buprenorphine and antidepressant medications, leading to a remarkable reduction in pain and depressive symptoms.

Case Report

Mr A is a 48-year-old man with a 6-year history of opioid use disorder (*DSM-5*; prescription pain medications), major depressive disorder (*DSM-5*), and severe chronic back pain admitted to our inpatient psychiatry unit with worsening depression, poorly controlled pain, and suicidal ideation with plans to walk into traffic to end his suffering. He was on a complex medication regimen including buprenorphine 2 mg/naloxone 0.5 mg 3 times a day, venlafaxine 300 mg/d, methylphenidate 10 mg/d, clonazepam 2 mg/d, gabapentin 2,400 mg/d, and baclofen 30 mg/d. During hospitalization, we reduced the venlafaxine dose to 150 mg/d and discontinued methylphenidate and clonazepam. We added mirtazapine 15 mg per night to improve sleep and to avoid possible nausea from pramipexole.

After 3 days of these initial changes and with the patient already showing improved sleep and having no known history of restless leg syndrome, we started pramipexole 0.5 mg per night and increased it the next day to 0.5 mg twice a day. Two days later, we increased the dose to 0.75 mg twice a day with excellent tolerability. On reaching pramipexole 1.5 mg/d, Mr A noticed remarkable improvement in mood, but most interestingly a great reduction in pain—in fact, to the lowest pain levels he had experienced in years. After this hospitalization, he has been followed in a pain clinic for more than 2 years, and he continues to report good pain control, no evidence of opioid misuse, and well-controlled depression.

Discussion

Our case illustrates the complexity of treating depression in opioid use disorder patients with chronic pain. Depression in this population is difficult to treat, and standard treatments do not work well.[2] The initial and longer-term results of our case suggest that pramipexole, a US Food and Drug Administration–approved dopamine receptor agonist for Parkinson's disease and restless leg syndrome, may be useful as an adjunctive treatment in patients with depression and opioid use disorder with pain who are receiving opioid agonist therapy. The relief of depression is not surprising given recent reports of pramipexole augmentation of antidepressants in severe treatment-refractory depression.[3,4] However, the effects on pain are novel and very interesting. The only limited clinical evidence of pramipexole treatment of pain is in fibromyalgia,[5] but no clinical data exist for other types of chronic pain. We have recently argued that pramipexole may work better than antidepressants and even stimulants in depression with high levels of inflammation because of pramipexole's unique effects on reducing proinflammatory cytokines.[6] We hypothesize that pramipexole blocks the activation of the toll-like receptor 4 to nucleotide-binding oligomerization domain–like receptor protein 3 pathway, resulting in a significant reduction of the production of interleukin 1β. This proinflammatory cytokine is involved in mediating pathologic chronic pain, especially when there is chronic opiate use and abuse.[7] Studies using pramipexole to treat animals with an inflammatory model of depression suggest that the reduction of proinflammatory cytokines is independent of dopamine receptor activation.[8] It is also possible that this anti-inflammatory effect in addition to the direct dopamine receptor agonism of pramipexole on reward processing may explain the remarkable relief in anhedonia across diagnostic categories, such as depression, neuropathic pain, and addiction. Further evaluation of the use of pramipexole in patients with depression in opioid use disorder with chronic pain is warranted.

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Potential conflicts of interest: **Dr Escalona** has received consulting and speaking fees from Alkermes and is named co-inventor on patent application No. US 2020/0121651 A1: Pramipexole for Use in the Treatment of Pain; Inventors: Milligan ED, Escalona PR. **Dr Rush** has received consulting fees from Compass Inc, Curbstone Consultant LLC, Emmes Corp, Holmusk, Johnson & Johnson (Janssen), Liva-Nova, Neurocrine Biosciences, Otsuka-US, and Sunovion; speaking fees from Liva-Nova and Johnson & Johnson (Janssen); and royalties from Guilford Press and the University of Texas Southwestern Medical Center, Dallas, Texas (for the Inventory of Depressive Symptoms and its derivatives). He is also named co-inventor on two patents: US Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication; Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS; and US Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication; Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S. **Dr Fawcett** declares no conflicts of interest.

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