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Propranolol for mirtazapine-induced akathisia: Single case report

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Abstract

Despite psychomotor restlessness and akathisia being an occasionally reported side effect of antidepressants as a class, and mirtazapine specifically, there is no general consensus on the best treatment approach. Propranolol may prove to be an effective treatment approach in patients who are not candidates for alternative therapies.

Keywords: mirtazapine, akathisia, propranolol

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Background

While akathisia and psychomotor restlessness are listed as "warnings and precautions" occurring in less than 1% of the population prescribed mirtazapine,[1] you can find more research citing mirtazapine as a treatment for antipsychotic-induced akathisia than case reports establishing it as the culprit.[2-5] In fact, a head-to-head trial[6] comparing the efficacy of mirtazapine to propranolol for antipsychotic-induced akathisia found mirtazapine to be as effective, if not better, and a well-tolerated treatment approach. A separate study[7] found evidence supporting the use of mirtazapine for aripiprazole-induced akathisia as well. At this time there is no general consensus on the appropriate treatment approach for the few subjects who experience the drug-induced akathisia caused by mirtazapine.

Case

A patient was admitted to a 90-day psychosocial rehabilitation residential program with diagnoses of dysthymia and substance use disorder involving multiple substances including: marijuana, until the time of admission; alcohol, last use 2 weeks prior; heroin, last use 5 or 6 years prior; opioid "pills," last use 4 to 5 months prior; benzodiazepines, last use 3 years prior; and various stimulants, last use greater than 1 year prior. Three weeks after his admission he reported a worsening of his depression symptoms and requested to initiate an antidepressant. This 30-year-old white male has a long history of treatment with psychotropic medications, starting in childhood, including alprazolam, amphetamine/dextroamphetamine, bupropion, citalopram, divalproex, lamotrigine, lithium, paroxetine, sertraline, venlafaxine, and zolpidem; however, he was not prescribed any psychotropic medications at the time of his admission. The patient reported poor adherence and misuse of previously prescribed medications. This patient also reports using a variety of illicit substances at the time of his prior medication trials, so the efficacy of past prescriptions is unknown; however, he did endorse sexual side effects with prior antidepressant trials. Patient endorsed symptoms at this time including a depressed mood, poor sleep with difficulty falling and staying asleep, nightmares, lack of interest, and poor appetite. This patient reports feeling hopeless and helpless, with a Patient Health Questionnaire-9 score of 26.[8]

Patient agreed to a trial of mirtazapine for depression, initiated at 7.5 mg for 1 week then titrated to 15 mg at bedtime. After 12 days of therapy patient reported that for "at least the past week" he had a sensation of "uncomfortable tightness" in his legs lasting for several hours after each mirtazapine dose. The patient likened this experience to a previous withdrawal from heroin. The sensation causes him to want to move his legs in an effort

to alleviate it; for this reason he has been taking the mirtazapine earlier in the evening, so the side effect could wear off before bedtime. This restlessness occurred while at rest as well as while active, and for 2 to 3 hours following each mirtazapine dose, rather than just at bedtime, ruling out restless leg syndrome. The patient attempted to exercise to alleviate the symptoms, but this was ineffective. As this symptom was occurring primarily in the evening, staff was unable to observe this patient during the occurrence. Patient also shared that he had forgotten to take his mirtazapine on 2 occasions and did not feel restlessness on those days, but it did recur when he resumed the medication as prescribed. A Naranjo Adverse Drug Reaction Probability Scale total score was determined to be 6, which is indicative of probable causality.

This patient also reported a significant improvement in his depressive symptoms, and as such requested to continue mirtazapine and treat this side effect, which was determined by the treatment team to be probably akathisia. Initially a trial of benztropine 0.5 mg at bedtime was initiated, which was increased to 1 mg 3 days later. Patient reported no improvement in akathisia at either dose but endorsed anticholinergic side effects, and as a result after a 1-week trial the benztropine was discontinued and propranolol immediate release 10 mg initiated. This was titrated to 20 mg to be taken at 6:00 PM with mirtazapine. Patient reported a significant reduction in the restlessness previously reported, and the combination was continued. After 3 weeks of continuous use of mirtazapine with propranolol, patient reportedly missed a dose of propranolol and discovered his symptoms of akathisia had improved significantly. Propranolol was continued on an as-needed basis.

Discussion

Given this report is based on a single case, several limitations exist. In this particular case, the patient was unable to be directly observed by staff at the time of his reported side effects, so there are no objective findings to report. Other factors could have contributed to these findings, however the risk of substance use or withdrawal is low, given sobriety in a controlled environment for 1 month prior to this presentation. Akathisia has been reported as a side effect to mirtazapine in several cases, with hypothesized mechanism by Raveendranathan and Swaminath[2] being related to alpha 2 receptors. While the exact mechanism is still unknown it seems clear the mechanism is different than that of antipsychotic-induced akathisia, given the body of evidence supporting the efficacy of mirtazapine can be an effective treatment in those cases.

The existing recommendations for treatment of akathisia are based off evidence in antipsychotic-induced akathisia. The suggested first-line approach is to decrease or discontinue the offending agent whenever possible. There is evidence to support the use of beta blockers, mirtazapine, benztropine, and benzodiazepines from small clinical trials of subjects with antipsychotic-induced akathisia,[6,7,9] but no trials regarding the treatment of antidepressant-induced symptoms. The majority of existing publications regarding the treatment of mirtazapine-induced akathisia found the most efficacy with discontinuation of the mirtazapine[2] or initiation of diazepam[4] or other benzodiazepines.[5] In this unique case, given the patient's history of substance use disorder, benzodiazepines were not considered. The patient also requested to maintain his current mirtazapine prescription. While it cannot be said with certainty that benztropine would not have been effective, in this 30-year-old patient that anticholinergic side effects limited the dosing range to the point of inefficacy. Propranolol provided effective treatment of akathisia and improved tolerability without hampering the efficacy of mirtazapine on depression. Also with continued time on mirtazapine it appears tolerability to akathisia symptoms has begun to develop, suggesting that this may not be a long-term side effect as we seen with other psychotropic medications.

Conclusion

In patients with mirtazapine-induced akathisia requesting to continue their mirtazapine prescription, propranolol should be considered as a potentially effective treatment option for either long- or short-term use.

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