

Case Reports

Steroid-Induced Mania Treated with Aripiprazole

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Brown and Chandler reviewed the literature on significant psychiatric side effects of corticosteroids, noting presentations of depression, mania, psychosis, and memory deficits.¹ Naber et al. followed a prospective, uncontrolled cohort of 50 patients on methylprednisolone or flucortolone, at initial doses of 119 ± 41 mg/d, and tapered to 75 ± 22 mg/d over 8 days. They found that “manic-type” symptoms were reported by 26% of the participants, most of which began in the first 3 days of treatment and continued, despite the taper, over the 8 days of the study.²

If possible, removing the offending steroid is desirable when patients present with psychiatric side effects. However, if the steroid-induced behavior puts the patient at significant risk of morbidity and mortality, adjunctive use of an anti-manic medication may also be warranted. The data for pharmacologic intervention in steroid-induced mania is limited in scope and study design. Among the classic mood stabilizers, lithium has the most evidence in steroid-induced mania, with a 71-patient, retrospective report.³ There is a positive case report regarding the use of valproic acid.⁴ Amongst the antipsychotics, the use of phenothiazines is supported by a 14-patient case series.⁵ Haloperidol⁶ and quetiapine⁷ have positive case reports. Olanzapine use is supported by an open-label trial in 12 patients.⁸ Risperidone has recent pediatric case reports.⁹

Case Report

Ms. A, a 55-year-old woman with breast cancer and brain metastases was brought to the emergency department (ED) by her family for 4 weeks of psychomotor agitation, tangential thought processes, decreased need for sleep, and irritability. Ms. A’s paranoia had worsened to the point that she thought her cancer was the result of family members poisoning her food and she had waved a knife at her family.

One month prior to her ED presentation, Ms. A was treated with whole brain radiotherapy (WBRT) and a dexamethasone taper was initiated at 4 mg PO BID. Per her family, her psychiatric symptoms began in the first few days after the dexamethasone was started. At time of her ED presentation, Ms. A was down to 2 mg of dexamethasone every other day. Her other medications had been stable, but included a chemotherapy regimen of weekly vinorelbine and trastuzumab. Her most recent brain MRI, done 1 week prior to the ED presentation, showed numerous bilateral lesions throughout her cerebral hemispheres, cerebellum, and brainstem. The largest lesion in this right-handed woman was in the left medial temporal lobe and measured $1.7 \times 2.2 \times 1.5$ cm.

Ms. A’s family noted that she had mild insomnia and racing thoughts during a prior chemotherapy regimen that had included prednisone. Otherwise, her family noted that Ms. A had no lifetime psychiatric symptoms or treatment. Ms. A, on longer-term follow-up, subsequently confirmed this history.

In the ED, blood work and urine toxicology were normal. A head CT showed no acute changes. She was admitted for two nights to psychiatry, wherein dexamethasone was discontinued. Olanzapine 5 mg daily and lorazepam 1 mg PRN were initiated. Her behavior was still manic, but her paranoia had improved when she left against medical advice (AMA) with her family. At home that night, she refused olanzapine. On the day after discharge, she was brought to an outpatient psychiatrist at her cancer clinic. At this appointment, she was loud, pres-

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sured, expansive, tangential, stood for most of the appointment, and refused to eat at home. She was promptly sent back to the ED where labs were again unremarkable and an MRI showed no acute changes. She was hospitalized, involuntarily this time, on the psychiatric unit. On this admission, Ms. A refused olanzapine, citing the side effect of sedation. However, she agreed to try a different antipsychotic, so long as it was less likely to cause sedation. The treating team agreed to prescribe aripiprazole 10 mg PO daily. Clonazepam 0.5 mg PO BID was also initiated.

On the first evening of psychiatric admission, Ms. A was described as grandiose, euphoric, refusing food, and too disorganized to answer questions. By the third day of admission, she was eating and sleeping better, but still disorganized and paranoid regarding her family. By the fifth day of admission, her mental status was normal, save some mild disorganization. She was then transferred to the oncology service for inpatient chemotherapy. She was discharged from the hospital after a total of 12 days.

Three weeks after hospital discharge, and 5 weeks after her last dexamethasone dose, she tapered off aripiprazole. Until the time of her death, 1 year after psychiatric hospitalization, Ms. A was not on psychiatric medication, was not given steroids, and had no mood or psychotic symptoms.

Discussion

Ms. A's paranoia was causing her to refuse to eat and to physically threaten her family. This behavior motivated the treating team to consider not only stopping the dexamethasone, but the addition of an antipsychotic to hasten her improvement. When she was admitted involuntarily, Washington state law would have allowed the treating team, with the consent of two attendings, to pursue a compel order to give intramuscular olanzapine when she refused oral olanzapine. Unlike olanzapine and quetiapine, aripiprazole has no prior case reports for steroid-induced mania. However, aripiprazole does not bind the H₁ receptor (associated with sedation) as strongly as olanzapine or quetiapine.¹⁰ Aripiprazole can cause akathisia, which would increase agitation, but the medication is FDA-approved for bipolar mania and continues to demonstrate efficacy in meta-analyses.¹¹ Thus, the treatment team felt that a compromise with Ms. A wherein she would be given oral aripiprazole in order to preclude the need for compelled IM medications, was appropriate.

Given the significant renal risks associated with her chemotherapy regimen, the treating team did not wish to introduce lithium. Similarly, her chemotherapy regimen can cause myelosuppression, and we did not want to introduce a confounder by using valproic acid. A phenothiazine, such as chlorpromazine, would have been sedating.

Ours is a single case report and there are significant potential confounders that stand in the way of a conclusion regarding the diagnosis and treatment. Evidence arguing for a steroid component to her presentation includes her history of mild insomnia and racing thoughts when on prednisone. The onset of her symptoms were shortly after dexamethasone initiation, though the psychiatric symptoms continued during dexamethasone dose reduction and for a week after complete cessation. A large review of the case reports of steroid-induced psychiatric symptoms suggested that 8% of patients did not respond to steroid taper alone.¹² None of her other medications, including the chemotherapy agents, have been reported to be associated with mania, and their dosing did not correlate with the onset or resolution of her symptoms.

It is possible that Ms. A's manic symptoms would have improved after a week by virtue of being completely off dexamethasone, though a taper had not shown rapid benefit and the severity of the psychotic symptoms necessitated more pro-active treatment. The treating team included a benzodiazepine as an augmentation strategy to target her physical agitation. The benzodiazepine could have hastened her improvement, but her refusal to eat due to active psychosis merited, in our mind, the use of an antipsychotic.

It is also possible that the etiology behind her psychiatric symptoms was not the steroid, but rather related to her metastases, transient cerebral edema, or structural damage caused by WBRT. Ms. A's metastatic lesions worsened during her last year of life and she had no further psychiatric symptoms, despite being off aripiprazole. Though her metastases may have contributed to vulnerability, her durable euthymia argues against the lesions being the primary etiology behind her mania.

Steroid-withdrawal mania is also a possible explanation for her presentation, and this has been previously reported.¹³ However, Ms. A did not have any other symptoms of steroid withdrawal, such as body aches, weakness, fatigue, or low blood-pressure.

An agitated, psychotic delirium from another etiology could have resulted in a similar presentation and cannot be wholly ruled out. However, Ms. A's symptoms did not wax and wane, and she was oriented. Her blood work,

toxicology screen, brain imaging, lumbar puncture, clinical course, and vitals did not suggest other acute delirium etiologies. An EEG was not done in the setting of her initial, significant agitation, and her symptomatology improved steadily after admission.

Further research is indicated, but when circumstances and side effects warrant, aripiprazole may prove

to be a useful medication for steroid-induced psychosis and mania.

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