Clonazepam to the Rescue?

Post-Steroid Mania and a Paradoxical Response to an Atypical Antipsychotic

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The incidence of corticosteroid-induced psychiatric disorders (CIPD) may exceed 18% in patients treated with at least 80 mg/day of prednisone or its equivalent.[1] Lupus patients are at even greater risk compared to other corticosteroid-treated autoimmune patients.[2] While CIPD can mimic the neuropsychiatric manifestations of lupus, it is more commonly associated with affective symptomatology, especially hypomania and mania.[3] No consensus exists on an optimal treatment protocol for acute CIPD, but antipsychotics have been suggested for rapid management.[4] Here, we report the case of a patient exhibiting post-steroid mania with agitation, for whom olanzapine resulted in a paradoxically increased number and intensity of manic symptoms, whereas further treatment with clonazepam and haloperidol was rapidly successful.

Case Report

A 20-year-old man with no history of psychiatric disorders was hospitalized for diffuse joint pain. Lupus nephritis with hypoalbuminemia was identified on laboratory analysis, and the patient was treated with a daily methylprednisolone pulse of 1,000 mg for 3 days followed by an intravenous push of 120 mg split into twice-daily doses. The patient quickly exhibited acute agitation and manic symptoms, including aggression and disinhibited behavior. He was switched to prednisone oral therapy tapered down to 60 mg/day, which was temporarily successful in alleviating his psychiatric disturbance. One week later, manic symptoms gradually recurred including decreased need for sleep, flight of ideas, overfamiliarity with staff, and distractibility. It was medically necessary to maintain a significant prednisone dose, and lithium was avoided given the persistence of lupus nephritis. Olanzapine 5 mg twice daily was initiated as monotherapy. Over the next 3 days, symptoms of mania paradoxically increased in intensity, compounded by newly evident delusions of grandeur. Olanzapine was discontinued, and clonazepam 1 mg administered orally every 8 hours was initiated based on evidence of antimanic properties.[5] Haloperidol 5 mg twice daily was added for further management of agitation. Over 3 more days, symptoms of mania were rapidly controlled. The patient resumed a regular sleep schedule, abandoned his previous delusions, and exhibited appropriate social inhibition and goal-oriented, linear thought processes, with no acute episodes of aggression or agitation. He was medically discharged 1 week later on prednisone 30 mg/day, tapered to 10 mg/day over the next month. With no psychiatric symptoms, clonazepam was discontinued at discharge, and haloperidol was tapered off over the next couple of weeks. Psychiatric symptoms remained well controlled at 2-month follow-up. Figure 1 provides graphical representation of the clinical timeline.

Discussion

We cannot parse with certainty whether clonazepam, haloperidol, or both led to our patient's rapid remission of post-steroid manic symptoms following the paradoxical response to olanzapine. However, there is reason to believe that clonazepam played a pivotal role. Previous reports suggest that atypical antipsychotics like olanzapine sometimes trigger a promanic response due to outsized antagonism of 5-HT_2 receptors, indirectly attenuating dopamine inhibition in the prefrontal cortex at a level outweighing its direct D_2 antagonism.[6] Due to limited serotonergic activity, haloperidol is not vulnerable to the same mechanism and may have contributed to our patient's rapid psychiatric remission. Even so, olanzapine has a half-life of up to 54 hours[7] and, despite abrupt discontinuation, likely remained partially psychoactive over the following 3 days. Besides its relatively long half-life, clonazepam is unique among benzodiazepines as a serotonin agonist via upregulated synaptic 5-HT.[5] By enhancing 5-HT availability, we hypothesize that clonazepam hastened the reversal of the putative serotonergic mechanism underlying olanzapine's paradoxical effect. Our patient's presentation may have been as much serotonergic as dopaminergic

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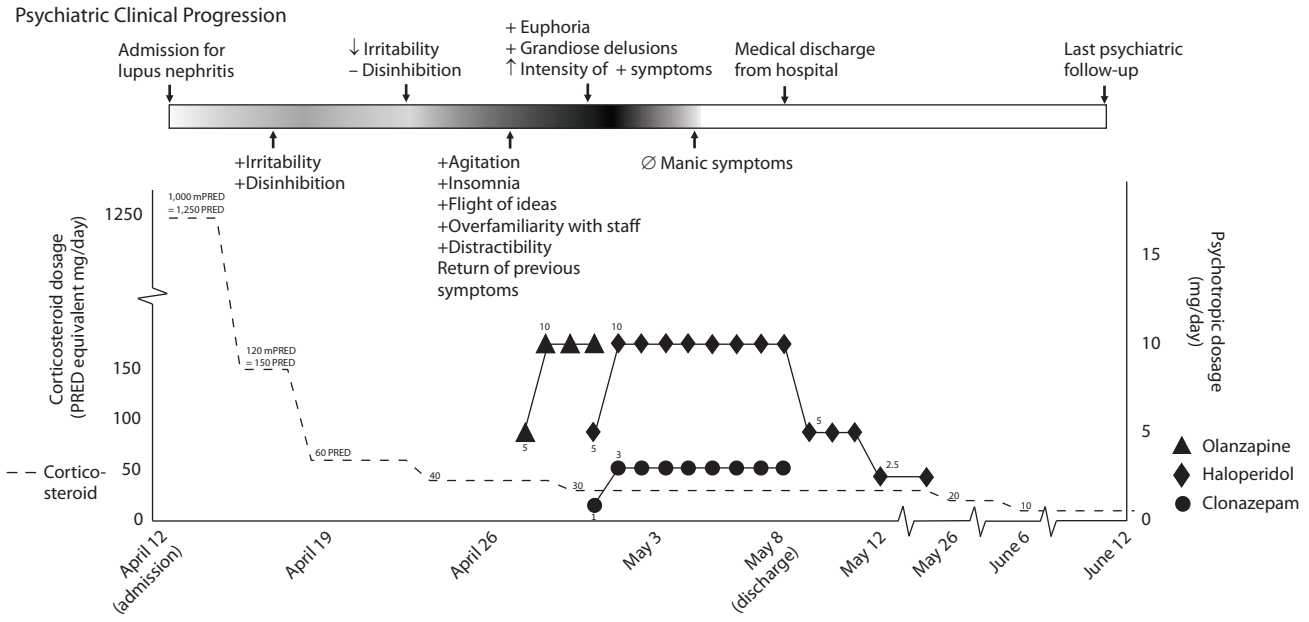
Figure 1. Timeline of Psychiatric Clinical Progression Alongside Steroid Administration and Psychotropic Intervention



Symbols: + = positive, – = negative, ↑ = increased, ↓ = decreased, ∅ = none.
Abbreviations: mPRED = methylprednisolone, PRED = prednisone.

in etiology, consistent with evidence that corticosteroids lower serotonin levels[8] and that a 5-HT deficit plays a role in the pathophysiology of mania.[9] The use of clonazepam following a paradoxical response to an atypical antipsychotic, particularly when treating post-steroid mania, deserves further exploration.

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