Tramadol Induced Rapid-Cycling Bipolar Disorder

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Rationale

- Depression is one of the most commonly reported and treated disorders in psychiatry
- Many mental health patients also suffer from concurrent chronic pain requiring pharmacological treatment and may be at increased risk of addiction
- Tramacet (acetaminophen 325 mg/tramadol 37.5 mg) is used to treat acute and chronic pain with less potential for physiological and psychological dependence
- Tramadol is an atypical, centrally-acting opioid analgesic with highest affinity for the µ-opioid receptor
  - Also weakly inhibits the reuptake of serotonin (5-HT) & norepinephrine (NE), acting like a weak serotonin-norepinephrine reuptake inhibitor (SNRI)
  - Exhibits greater SNRI effects at higher doses
  - Prodrug requiring CYP 2D6 to convert tramadol to its active (+) o-desmethyltramadol or 'M1' metabolite
  - Therefore, susceptible to genetic polymorphisms
  - Renally excreted (30% unchanged; 60% as metabolite)
- Serotonergic medications have been documented as potential inducers of activation, hypomania, and rapid-cycling Bipolar Disorder

Case Description

- A 55-year-old Caucasian male presented to an outpatient psychiatric clinic with a long history of depression and anxiety
- Both patient and spouse describe:
  - Abrupt onset of rapid mood cycling with daily periods of irritability/emotional lability
  - Episodes consistent with hypomania interspersed with longer depressive periods
- Past Medical History: Crohn’s Disease with ileostomy, Ménére’s Disease, DM-II, HTN, chronic renal failure, OSA, OA, and avascular hip necrosis
- Past medication trials/exposure: duloxetine 30 mg daily, quetiapine 12.5 mg daily, desvenlafaxine 50 mg daily, clonazepam 0.5 mg at bedtime, and past steroid use

Interpretations of Causality

- SSRIs and SNRIs have been documented to induce rapid-cycling mood states
- Temporal link between initiation of tramadol and onset of mood cycling was established using patient and collateral history, as well as pharmacy records
- No alternative causes could, on their own, have caused this mood cycling
- There was some improvement of symptoms when taking tramadol less often
- Previous SNRI trials were at low doses or short trials, but did not cause ADR
- Pharmacy records confirmed tramadol was started < 1 month before ADR

Naranjo Probability Score

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous conclusive reports of this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Did the ADR appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Did the ADR improve when the drug was discontinued?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the ADR reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Are there alternative causes that could, on their own, have caused the ADR?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Did the ADR reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the drug detected in the blood or other fluids in known toxic concentrations?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the ADR more severe with increased doses or less severe with decreased doses?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar drugs in previous exposures?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the ADR confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

TOTAL SCORE: 7

Score:
- 9 = Highly Probable; 5-8 = Probable; 1-4 = Possible; 0 = Doubtful

Evaluation of the Literature

- Serotonergic drugs have been well documented as potential inducers of mania and rapid-cycling Bipolar Disorder
- Several case reports have described mania or mood alterations attributable to the combined use of Tramadol and an SSRI
- One case report of tramadol-induced mania (200 mg/day) in a patient with a history of Bipolar Disorder
  - A temporal link was established

Relevance to Clinicians

- Pain and depression have a strong interface, and are often used as marketing strategies for some SNRIs
- Tramacet-induced rapid cycling Bipolar Disorder in the absence of other serotonergic medications is not discussed in the product monograph and has yet to be documented in medical literature
- Psychiatrists seeing patients with rapid mood cycling or manic symptoms should consider including tramadol on Axis III as a potential contributor to Axis I presentation
- Inter-professional collaboration may help identify some answers where unusual responses are noted by psychiatrists
- All prescribers of tramadol should be aware that it has the potential to induce rapid-cycling Bipolar Disorder

References