Donepezil as a precipitating factor of mania: a case report

Jonathan G Leung, PharmD, BCPS, BCPP
Psychiatric Clinical Pharmacist
Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center
Adjunct Assistant Professor of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Objectives

• Describe the presentation, hospital course, and management of a patient with donepezil-induced mania

• Understand the association between mania and acetylcholine

• Devise a treatment plan for a patient who develops donepezil-induced mania
The Patient Case

• CC: “I am here to be a better man”
• HPI:
  – A 70 year old AAM was jailed for public intoxication
    • 6 days later he was transferred to an inpatient psychiatric unit
    • Increased disorganization, auditory hallucinations
  – Long history of paranoid schizophrenia with multiple psychiatric hospital and state hospital admissions
  – History of alcohol dependence, delirium tremens
    • No significant signs/symptoms of alcohol withdrawal
The Patient Case

- **Past Psychiatric History:** Schizophrenia - paranoid type, alcohol dependence, cognitive disorder NOS
- **Past Medical History:** COPD, HTN, hypothyroidism, iron deficiency anemia
- **Family History:** Unknown
- **Social History:**
  - Substance use: “Tried everything but only drinks now”
    - Unable to quantify his consumption of alcohol
  - Reports smoking 1 pack of cigarettes per day
  - Recently retired - janitor
The Patient Case

• Medications on admission
  – Risperidone 0.25 mg daily
  – Quetiapine 150 mg at bedtime
  – Valproic acid 250 mg twice daily
  – Levothyroxine 50 mcg daily
  – Ferrous sulfate 325 mg twice daily
  – Ascorbic acid 250 mg twice daily
  – Amlodipine 5 mg daily
  – Spironolactone 25 mg daily
  – Hydrocholorothiazide 25 mg daily
The Patient Case

• The Initial Mental Status Exam

  – **Appearance**: Unkempt, malodorous (smelling of urine), excessive pacing, poor eye contact
  – **Speech**: Disorganized, loud
  – **Affect/Mood**: Irritable, mood congruent
  – **Thought content**: Denied suicidal or homicidal ideation, voiced being able to communicate directly with God
  – **Thought process**: Non-linear, illogical, and perseverative
  – **Judgment and insight**: Poor
  – Alert and oriented only to place
April 12
- Extremely disorganized and confused
- Poor attention to ADLs
- Wife noted that this was an acute change from baseline
- Discontinuation of risperidone, quetiapine, valproic acid
- Initial workup to rule out delirium, negative
The Patient Case

- Vital signs: BP 175/84; HR 65; RR 18; T 36.2 °C
- Weight: 64 kg  Height: 158 cm
- Laboratory findings:
  - CBC: WNL
  - UDS: negative
  - TSH: 1.32 uIU/mL
  - Valproic Acid: undetectable
  - NH3: 23
  - U/A: negative
  - B12/folate: WNL
  - Head CT: No acute findings, small vessel ischemic changes
April 14-April 27

• Titration of haloperidol to 5 mg twice daily (however significant drooling occurred)

• ADLs improved significantly, needing minimal prompting

• To address side effects, residual disorganized behaviors, and poor sleep (2-3 hours per night) haloperidol was slowly cross tapered to quetiapine 500 mg/day
The Patient Case

April 28-May 13

• Speech and thought process continued to improve
• Persistent cognitive limitation (Montreal Cognitive Assessment: 13/30)
• Donepezil 5 mg daily and memantine 5 mg daily were initiated
• No adverse events were noted and donepezil was titrated to 10 mg daily after two weeks (5/13)
May 14- May 25

• Mood was **euphoric** and rate of **speech** increased; difficult to interrupt
• Continuous cleaning throughout the day and night noted
• **Psychomotor agitation**; during a daily interview began suddenly exercising
• Sleep further decreased from 3-4 hours per night to 0-1 hour per night
• The patient denied subjective restlessness; akathisia ruled out
• Donepezil was discontinued (5/24)

4/12-4/13
4/14-4/27
4/28-5/13
5/14-5/25
The Patient Case

May 26 - June 10
• Symptoms peaked in severity with rapid speech, FOI, continued cleaning activities, sexual inappropriateness, sleep 0-1 hour; gradual resolution

June 11 - June 26
• Mood low and affect restricted, minimal cleaning, sleep 3-7 hours

June 27 (Discharged)
• Speech with regular rate and rhythm, mood good/congruent affect, thought process linear/logical/goal directed, no S/I or H/I
Mania and Acetylcholine

- Pathophysiology of mania is not well understood
  - 1972: Proposal of the cholinergic-adrenergic hypothesis
    - Based on this hypothesis, cholinesterase inhibitors should IMPROVE mania
    - Physostigmine was reported to have benefits for mania
  - Led to the study of donepezil for mania
    - 1999: An open-label trial showed promise
    - 2006: A follow-up randomized controlled trial did not show benefit
    - 2008: A trial assessing cognitive dysfunction in bipolar disorder warned of worsening or emergence of manic/hypomanic symptoms
Medication-Induced Mania

• Medications/medication classes reported to induce mania:
  – Antidepressants
  – Anti-infective agents (Antibiomania)
    • E.g. Fluoroquinolones, macrolides, isoniazid
  – Anabolic steroids
  – Corticosteroids
  – Levodopa
  – Efavirenz
  – Sympathomimetics
  – Thyroid replacement therapy

Review of Literature: Trials

• Trials leading to FDA approval did not identify mania/hypomania as an adverse events
  – Neuropsychiatric adverse events in ≥ 2% of patients
    • Insomnia, hallucinations, emotional lability
  – “Frequent”
    • Aggression, delusions, irritability, restlessness

• No reports of mania/hypomania found in off-label trials
  – Other dementia types
  – Schizophrenia
  – Tardive dyskinesia
  – Traumatic brain injury

Aricept package insert. Eisai Inc. 2010
Int Psychogeriatr. 2006;18:429-36
Stroke. 2003;34:2323-30
J Head Trauma Rehabil. 2008 ;23:171-80
Review of Literature: Cases

- 8 cases of cholinesterase inhibitor-induced mania since 1998
  - 3 male/5 female
  - Mean age: 71.3 ± 10.3 years old
  - History of bipolar disorder in 4 cases, family history in 1 case
  - Cholinesterase inhibitors reported
    - Donepezil 5 mg (n = 5) and 10 mg (n= 1)
    - Galantamine PO 16 mg (n = 1)
    - Rivastigmine Transdermal 4.6 mg (n = 1)
  - Time to manic/hypompanic episode: 1 day to 3 weeks
  - Resolution within 1 day to 2 weeks
  - Rechallenge in 2 patients resulted in reproducible mania

Citations included in Appendix A
Management

- Limited reports thus no clear guidance
- Case reports indicate
  - Discontinuation is warranted
  - Changing agents may not resolve the issue as multiple cholinesterase inhibitors have implicated
  - A rechallenge may cause another manic episode
- Changing to memantine may be a viable option
  - Shown to have mood stabilizing properties for patients with mania
  - However, cases of memantine-induced psychotic symptoms exist in the literature
Contributing factors?

- The patient’s poor sleep on admission?
- Underlying unknown bipolar/affective diathesis?
- Memantine?
Lessons Learned

• The pathophysiology of donepezil-induced mania is not well understood
  – Contradicts the controversial cholinergic-adrenergic hypothesis

• Donepezil-induced mania should be considered after donepezil initiation/dose increase when correlated to new symptoms of mania

• This adverse event may represent a class effect

• Although rare, clinicians should be aware of this potential adverse event especially as off-label use grows
Self Assessment

Question 1
Based on available literature the most appropriate management of suspected donepezil-induced mania would be:
A. Switch to a different cholinesterase inhibitor
B. Increase the patient’s current dose of donepezil
C. Discontinue donepezil and monitor for resolution of manic symptoms
D. Initiate lithium and target a concentration of 0.6-0.8 mEq/L until symptom resolution

Question 2
In addition to donepezil the following medication has been also associated with inducing manic symptoms:
A. Isoniazid
B. Tamoxifen
C. Verapamil
D. Haloperidol
Questions?
## Appendix A: Review of Cases

<table>
<thead>
<tr>
<th>Report, Year (Demographic)</th>
<th>Medication (Dose)</th>
<th>Time to Event</th>
<th>Time to Resolution (After Discontinuation)</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazzi, 1998 (78 y/o F)</td>
<td>Donepezil (5 mg)</td>
<td>3 days</td>
<td>“Days”</td>
<td>Rechallenge/ severe mania</td>
</tr>
<tr>
<td>Benazzi, 1998 (64 y/o F)</td>
<td>Donepezil (5 mg)</td>
<td>1 week</td>
<td>1 week</td>
<td>History of bipolar, type I</td>
</tr>
<tr>
<td>Benazzi, 1999 (68 y/o M)</td>
<td>Donepezil (5 mg)</td>
<td>1 day</td>
<td>1 day</td>
<td>Rechallenge/ severe mania</td>
</tr>
<tr>
<td>Benazzi, 1999 (74 y/o F)</td>
<td>Donepezil (10 mg)</td>
<td>&lt;1 week</td>
<td>&lt;1 week</td>
<td>History of bipolar, type I</td>
</tr>
<tr>
<td>Rao, 2008 (50 y/o M)</td>
<td>Donepezil (5 mg)</td>
<td>3 weeks</td>
<td>Not reported</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Collins, 2011 (76 y/o F)</td>
<td>Donepezil (10 mg)</td>
<td>A few weeks after dose increase</td>
<td>“Quickly”</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td>Ehrt, 2011 (81 y/o F)</td>
<td>Rivastigmine (4.6 mg)</td>
<td>1 week</td>
<td>1 week</td>
<td>History of bipolar</td>
</tr>
<tr>
<td>Ehrt, 2011 (76 y/o M)</td>
<td>Galantamine (16 mg)</td>
<td>9 days after dose increase</td>
<td>2 weeks</td>
<td>History of bipolar</td>
</tr>
</tbody>
</table>