Case 2: The woman who couldn’t handle her lips smacking any longer

The Question: Is tardive dyskinesia permanent?

The Psychopharmacological Dilemma: Finding various options for treating tardive dyskinesia

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Pretest self-assessment question (answer at the end of the case)

What are the approved treatments for tardive dyskinesia?

A. Deutetrabenazine (Austedo)
B. Propranolol (Inderal)
C. Olanzapine (Zyprexa)
D. Diphenhydramine (Benadryl)
E. Aripiprazole (Abilify)
F. Valbenazine (Ingrezza)

Patient evaluation on intake

• A 50-year-old female with the chief complaint of persistent lip smacking

Psychiatric history

• The patient has diagnoses of schizoaffective disorder depressed type and posttraumatic stress disorder
• As a child, she experienced physical abuse by her stepfather and mother and sexual abuse by her aunt
• Her first psychotic episode requiring hospitalization was in her early 30s and she has been on various antipsychotic treatment regimens since then
• She has been hospitalized five times for psychosis and once after a suicide attempt by overdosing
• She has been disabled since 2009, receiving social security income due to ongoing and persistent episodes of psychosis and depression with suicidal ideation in addition to other medical comorbidities such as narcolepsy
• Her primary symptoms include command auditory hallucinations, paranoia, racing thoughts, depression, nightmares, and suicidal ideation
• She spends most of her time alone reading her Bible to help drown out the negative hallucinations
• She developed orofacial tardive dyskinesia after a brief trial of haloperidol (Haldol) 5 months ago that continued with treatment of risperidone (Risperdal)
### Medication history
- The patient has been on numerous psychotropic medications including antipsychotics, mood stabilizers, benzodiazepines, and antidepressants
- Current medications have improved her hallucinations, delusions, and depressed symptoms

### Psychotherapy history
- The patient has had a few attempts with various psychotherapists over the years but does not consistently follow through

### Social and personal history
- The patient never knew her biological father. Starting around 6 years of age, she began to undergo physical abuse by her stepfather and biological mother
- She was sexually abused by an aunt from 9 years of age until her early teenage years
- She dropped out of high school in 10th grade, went to a vocational school and became a teacher’s aid
- She was able to work as an aid until becoming completely disabled in 2009 following another hospitalization for psychosis
- She was married for 8 years but divorced. She does not have any biological children. She helped raise three foster children but was not able to adopt them after she and her husband separated
- She was physically abused by her ex-husband
- The patient lives with her biological mother

### Medical history
- Narcolepsy
- Restless leg syndrome
- Hypothyroidism
- Arthritis/chronic pain

### Family history
- Mother with depression
- She does not know about her biological father’s family history

### Patient evaluation on initial visit
- Severe and persistent tardive dyskinesia involving only her mouth, lip smacking
- An Abnormal Involuntary Movement Scale (AIMS) examination was 7 with regard to facial oral movements, 4 for lip smacking (severe)
and 3 for jaw clenching (moderate). The total AIMS was 18 after adding 11 for global judgments. She has no issues with her teeth and does not wear dentures

- The patient is aware of the involuntary movements, which cause severe distress and embarrassment
- She developed the involuntary movements within the last couple months after a trial of haloperidol (Haldol)
- After haloperidol was discontinued, the involuntary movements persisted with risperidone (Risperdal) treatment
- She denies depression and manic/hypomanic symptoms, and has no current suicidal ideations
- She denies paranoia but has occasional auditory hallucinations that she describes as always in the background but not necessarily distressing

**Current medications**

- Risperidone (Risperdal) 2 mg twice per day
- Trazodone (Desyrel) 300 mg at bedtime
- Prazosin (Minipress) 5 mg at bedtime
- Lorazepam (Ativan) 1 mg three times per day as needed for anxiety
- Topiramate (Topamax) 125 mg twice per day (for psychotropic-induced weight gain)
- Levothyroxine (Synthroid) 200 μg daily for thyroid
- Omeprazole (Prilosec) 20 mg daily for gastroesophageal reflux disease
- Tramadol (Ultram) 50 mg four times per day as needed for pain
- Mixed amphetamine salts (Adderall) 20 mg three times per day for narcolepsy

**Attending physician’s mental notes: initial visit**

- This patient has tried a variety of antipsychotics in the past and continues to have occasional hallucinations but is currently improved compared with past medication trials
- When she decompensates, she requires prolonged hospitalization for paranoia, command auditory hallucinations, and suicidal ideation
- She developed orofacial tardive dyskinesia with a trial of haloperidol (Haldol) about 5 months ago, and it persists after switching to risperidone (Risperdal)
- The patient is reluctant to try different medications because she currently feels relatively stable
Further investigation

Is there anything else you would especially like to know about this patient? What about further details about the tardive dyskinesia and whether she has tried one of the approved treatments for it?

- The tardive dyskinesia has been persistent for 5 months and it seems to have been worsening over time despite switching from haloperidol (Haldol) to risperidone (Risperdal)
- The involuntary movements only affect her mouth, primarily just lip smacking, which is causing conflict with her mother
- The patient has never tried one of the approved treatments for tardive dyskinesia

Case outcome: first interim follow-up visit at week 2

- The patient continued to take risperidone (Risperdal) 2 mg twice per day due to good benefit of psychosis and mood
- She was started on valbenazine (Ingrezza) 40 mg daily with a partial response of involuntary orofacial movements. Subjectively, the patient had a 50% improvement
- Valbenazine was increased to 80 mg daily

Case outcome: second interim follow-up visit at week 6

- The patient no longer displays any involuntary movements in the office and reports the movements are completely gone at home
- AIMS score has reduced from 18 to 0
- She continues to report very occasional auditory hallucinations but wishes to remain at the current dose of risperidone (Risperdal)

Case outcome: third interim follow-up visit at week 12

- The patient stopped taking valbenazine (Ingrezza) 2 weeks ago because she wanted to see if the tardive dyskinesia was gone without the medication
- During the visit, she again displayed persistent involuntary lip smacking
- The patient wanted to continue treatment with risperidone (Risperdal) as it was still providing benefit with psychosis and mood
- The patient was restarted on valbenazine 40 mg daily for 1 week and then increased back to 80 mg daily
Further investigation

Would you resume treatment with valbenazine (Ingrezza) or change strategy?

- Resume treatment with valbenazine and titrate again to 80 mg daily
- Increase the dose of risperidone (Risperdal) without adding valbenazine
- Increase the dose of risperidone and add valbenazine
- Decrease the dose of risperidone and add valbenazine
- Switch to a different antipsychotic before prescribing valbenazine again or trying deutetrabenazine (Austedo)
- Try to decrease amphetamine which may be exacerbating the movements

Attending physician’s mental notes

- The patient appears to have responded to valbenazine (Ingrezza), helping to confirm that this was a case of orofacial tardive dyskinesia
- Increasing the dose of risperidone (Risperdal) may decrease the severity or resolve the involuntary movements briefly, but in time tardive dyskinesia will likely return and perhaps worsen
- Her psychotic and mood symptoms are responding to the current dose of risperidone
- She has been taking antipsychotics for nearly the last 20 years. Is the tardive dyskinesia a culmination of long-term antipsychotic use over that time or was it caused directly by haloperidol (Haldol) and risperidone, or a combination of everything?

Case outcome: fourth interim follow-up visit at week 16

- Although the patient restarted and titrated valbenazine (Ingrezza) back to 80 mg daily where she had previously found complete resolution of tardive dyskinesia, this time it is not providing her with much benefit
- She continues to complain of nearly unrelenting lip smacking, which is clearly visible in the office. Her AIMS score is 6 with regard to oral facial movements, with a total of 17 with global judgments
- The patient desired at this point to try a different antipsychotic as she had never experienced tardive dyskinesia prior to haloperidol (Haldol) and risperidone (Risperdal). The risks of tardive dyskinesia with all antipsychotics were discussed
- The patient was started on aripiprazole (Abilify) 10 mg daily and risperidone was discontinued
Attending physician’s mental notes

- Aripiprazole (Abilify) is a partial dopamine agonist with some cases showing improvement of tardive dyskinesia with its use, possibly due to masking of the movements due to the very high-potency partial agonist actions at dopamine D_2 receptors
- She may not experience the same benefits for controlling psychosis with aripiprazole that she found with risperidone (Risperdal)
- It should be noted that all antipsychotics, even aripiprazole, have the risk of developing or worsening tardive dyskinesia

Case outcome: fifth interim follow-up visit week 18

- The patient reports her lip smacking seems to have reduced by about 50%. She still has involuntary movements of her mouth during the visit but they are certainly reduced from 2 weeks ago
- The patient complains of more frequent persecutory auditory hallucinations
- Aripiprazole (Abilify) was increased to 20 mg daily

Case outcome: sixth interim follow-up visit at week 22

- The patient reports complete resolution of tardive dyskinesia. Her AIMS score is 0
- She continues to have worsening auditory hallucinations, which are distracting and causing some distress
- She denies command auditory hallucinations and denies suicidal ideations
- Aripiprazole (Abilify) was increased to 30 mg daily

Case outcome: seventh interim follow-up visit at week 26

- The patient continues not to have any involuntary movements
- Her psychotic symptoms have responded to higher doses of aripiprazole (Abilify), but although not subjectively as good as risperidone (Risperdal) in treating auditory hallucinations, the patient is pleased with the absence of lip smacking
- The patient has found other means to help alleviate any persistent auditory hallucinations, such as meditation and reading her Bible

Case debrief

- After 20 years of being treated with antipsychotics, the patient developed tardive dyskinesia after a trial of haloperidol (Haldol), which continued once haloperidol was discontinued and switched to risperidone (Risperdal)
The patient initially responded to valbenazine (Ingrezza), one of the FDA-approved treatments for tardive dyskinesia. However, she stopped taking it because she thought she was cured. She was restarted on valbenazine a second time but the involuntary movements persisted.

The patient was switched from risperidone to aripiprazole (Abilify) due to some evidence showing improvement of tardive dyskinesia because of its partial agonist on dopamine D2 receptors rather than full antagonism.

After titrating aripiprazole to the least-effective dose to treat her psychosis, she no longer displayed symptoms of tardive dyskinesia, which has remained stable for a few months.

Take-home points

- One of the more severe and debilitating potential side effects of antipsychotics is the development of tardive dyskinesia.
- Providers should be aware that the incidence of tardive dyskinesia is greater with typical antipsychotics; however, there is a risk, regardless of whether typical or atypical medications are used.
- Not all cases of tardive dyskinesia are “classic”. Tardive dyskinesia is characterized by involuntary and abnormal muscle movements, usually by long-term use of neuroleptics, but can also occur rather quickly.
- Tardive dyskinesia most often affects the mouth, lips, tongue, and facial muscles, but in some cases may affect the arms, legs, neck, and trunk.
- The only FDA-approved treatments for tardive dyskinesia are valbenazine (Ingrezza) and deutetrabenazine (Austedo), which are both vesicular monoamine transporter-2 (VMAT2) inhibitors.
- Although the patient is no longer experiencing tardive dyskinesia, it is possible that the high dose of aripiprazole (Abilify) is masking the symptoms rather than providing a long-term cure.
- If psychotic symptoms return in the future, the need to either titrate aripiprazole or switch to another antipsychotic may reintroduce involuntary movements.
- A trial of deutetrabenazine rather than another trial of valbenazine may be indicated for emergent tardive dyskinesia in the future, as there is more dose flexibility and titration possible with deutetrabenazine and the patient may require a higher degree of VMAT2 inhibition.
Performance in practice: confessions of a psychopharmacologist

What could have been done better here?

• Was the differential diagnosis for this being tardive dyskinesia too narrow? Could this have been “rabbit syndrome” of perioral Parkinson’s tremor instead?
• Rabbit syndrome is a form of extrapyramidal syndrome that resembles the chewing movements of the mouth and could be resolved by using either higher anticholinergic medications or less potent antipsychotics; however, orofacial exam revealed not the fine, rapid, rhythmic tremor of rabbit syndrome, but irregular lip movements of lower frequency
• Should the patient have been given a trial of deutetrabenazine (Austedo)?

Is there anything else that could be a potential culprit for the involuntary movements?

• The patient is on mixed amphetamine salts (Adderall) for narcolepsy, which act directly on dopamine by inhibiting its reuptake and increasing its release. Although more likely with illicit amphetamines due to the neurotoxicity, there is still a possibility with prescribed stimulants that they are exacerbating her tardive dyskinesia movements

What are the chances that this patient may have ongoing tardive dyskinesia in the future?

• It is likely that this patient may develop symptoms of tardive dyskinesia again in the future. Perhaps the mechanism of aripiprazole (Abilify) is only masking the underlying tardive dyskinesia, which may present more severely in the coming years

What is the mechanism of action of aripiprazole that was thought to play a role in improving this patient’s tardive dyskinesia?

• Aripiprazole has a unique mechanism of action as a partial D₂ receptor agonist, a partial 5-HT₁A receptor agonist and a 5-HT₂A receptor antagonist, and is thought to normalize dopamine upregulation compared with other antipsychotics that cause striatal dopamine receptor hypersensitivity
• It is also thought that activation of the 5-HT₁A receptor mediates the release of dopamine in the striatum, decreasing extrapyramidal side effects without affecting the antipsychotic properties within the mesolimbic system
Tips and pearls

What are the risk factors for tardive dyskinesia?

• Advanced age, female gender, alcohol or other substance abuse, pre-existing extrapyramidal symptoms, long-term treatment with antipsychotics particularly high-potency first-generation, severe negative symptoms of schizophrenia, low levels of brain-derived neurotrophic factor (BDNF), and polymorphisms in the enzymes involved with metabolism of the offending drug

How can you diagnose tardive dyskinesia with your eyes closed?

• History taking: has the patient been treated with a dopamine receptor blocking agent such as various antipsychotics, tricyclic antidepressants, or some antiemetics?
• How long has the patient been treated with these agents? Take into account the age of the patient and the other risk factors as described above
• What happened with the tardive dyskinesia symptoms when there was a dose reduction or discontinuation? It may worsen initially before it improves
• What happened with the tardive dyskinesia symptoms when there was a dose increase? It improves initially but later worsens
• What happened when an anticholinergic agent was added? It would worsen tardive dyskinesia

Two-minute tutorial

Tardive dyskinesia

• 5% of patients on typical antipsychotics develop tardive dyskinesia every year, and this may be as high as 25% in elderly patients within the first year of exposure to a typical antipsychotic
• It is usually caused by long-term blockade of D_2 receptors in the nigrostriatal dopamine pathway, which leads to upregulation of these receptors causing the hyperkinetic involuntary motor movements of tardive dyskinesia (Figure 2.1)
• It may be reversible if the offending agent is discontinued early, allowing the dopamine receptors to “reset” themselves
• It most often affects the face (facial grimacing/chewing), lips (smacking, puckering), and tongue (darting/protrusions), but may also affect the neck, arms, and legs with quick jerky movements
• Tardive dyskinesia occurs more often with high-potency typical antipsychotics but is possible with atypical antipsychotics, tricyclic antidepressants, and certain antiemetics
Treatments for tardive dyskinesia

- The FDA has approved two treatments: valbenazine (Ingrezza) and deutetrabenazine (Austedo), which are both VMAT-2 inhibitors.
- These treatments reduce dopamine availability to the hypersensitive and upregulated postsynaptic D₂ receptors in the motor striatum (Figure 2.2).
- Valbenazine is converted to only one active metabolite, (+)-α-dihydrotetrabenazine and is only selective for VMAT2.
- Deutetrabenazine is metabolized into four active isomers, two of which act on VMAT2 with a longer half-life, allowing less-frequent dosing.
- Other experimental treatments for tardive dyskinesia include donepezil (Aricept), melatonin, vitamins E and B₆, dextromethorphan, clonazepam (Klonopin), propranolol (Inderal), amantadine (Gocovri), and branched-chain amino acids or other antioxidant supplements.

AIMS examination

- This is a 12-item clinician-rated scale.
- It is completed while the patient is sitting on a firm chair without arm rests.
- Ask whether the patient wears dentures and whether they or their teeth are bothering them.
- Ask whether the patient notices any movements in their hands, face, mouth, or feet, and to what extent it bothers them.
Figure 2.2. The multiple factors that affect the concentration of dopamine within the synaptic cleft including the activity of vesicular monoamine transporter-2 (VMAT2) inhibitors within the presynaptic neuron. VMAT2 inhibition decreases presynaptic dopamine concentration, which results in a downstream effect of reducing synaptic and postsynaptic dopamine levels.

- Observe the patient’s movements with their hands on their knees and feet on the ground
- Ask the patient to open their mouth and observe tongue movements; then ask them to protrude their tongue twice
- Have the patient tap each finger with their thumb as fast as possible for 10–15 seconds, one hand at a time
- Flex and extend the patient’s arms, one at a time
- Have the patient stand up and observe all their limbs and face again
- Ask the patient to extend both arms out in front with their palms facing down
- Ask the patient to walk a few paces back and forth two times
- Score the procedure: 0 = none, 1 = minimal (may be extreme normal), 2 = mild, 3 = moderate, 4 = severe
  - Muscles of facial expression (eyebrow, forehead, periorbital, cheeks, which includes frowning, blinking, grimacing)
  - Lips and perioral (puckering, smacking, pouting)
  - Jaw (biting, clenching, chewing, mouth opening, lateral movements)
  - Tongue (only increase in movement both in and out of mouth)
– Upper extremities (arms, wrists, hands, fingers, which includes choreic and athetoid movements only, not tremors)
– Lower extremities (legs, knees, ankles, toes, which includes tapping, heel drop, inversion/eversion of foot, lateral movements)
– Trunk (neck, shoulders, hips, which includes rocking, twisting, squirming, pelvic gyrations, diaphragmatic movements)
– Global judgments: severity of abnormal movements (based on highest single score above scored 0–4), incapacitation due to abnormal movements (scored 0–4), and patient’s awareness of abnormal movements (scored 0–4))

Posttest self-assessment question and answer

What are the approved treatments for tardive dyskinesia?

A. Deutetrabenazine (Austedo)
B. Propranolol (Inderal)
C. Olanzapine (Zyprexa)
D. Diphenhydramine (Benadryl)
E. Aripiprazole (Abilify)
F. Valbenazine (Ingrezza)

Answer: A and F

References