BC PROVINCIAL DEPRESCRIBING WEBINAR

February 8, 2023

Dr. Jill Norris (family physician, Victoria, BC)

Dr. Alison Gregson (consultation/liaison psychiatrist, Royal Jubilee Hospital, Victoria, BC)

No disclosures or conflicts of interest to declare

New patient

Woman in her 50’s, history of PTSD, depression, AUD in remission, high ACE score, experience of racism. Prior failed serious suicide attempt. Initially managed by a psychiatrist, later unable to continue f/u.

Medication list August 2022:

1. quetiapine 1100mg/d
2. zopiclone 15mg/d
3. clonazepam 1mg/d
4. gabapentin 1800mg/d
5. escitalopram 20mg/d
6. bupropion XL 300mg/d
7. prazosin 2mg/d
8. rosuvastatin 10mg/d
9. pantoprazole 40mg/d

Clinical Presentation

- Sedated
- Parkinsonism
- Symptomatic orthostatic hypotension with falls
- LDL 6.2mM, fasting glucose 7.1mM
- Prolonged QT on ECG
- Ongoing depressive symptoms
- Functional status poor

DR. NORRIS (FP) CONCERNS:

- **EEKS!**
- drug interactions and side effects
- Rx’d by a specialist!
- Harm of deprescribing?
- Patient’s fears re deprescribing
- Inadequate access to psychiatrist support

Tentative Slow Deprescribing

Original list
AUGUST 2022

1. **quetiapine 1100mg/d**
2. zopiclone 15mg/d
3. clonazepam 1mg/d
4. **gabapentin 1800mg/d**
5. escitalopram 20mg/d
6. bupropion XL 300mg/d
7. **prazosin 2mg/d**
8. rosuvastatin 10mg/d
9. pantoprazole 40mg/d

Changes by FP
SEPTEMBER 2022

1. **quetiapine 900mg/d**
2. zopiclone 15mg/d
3. clonazepam 1 mg/d
4. **gabapentin 600 mg/d**
5. escitalopram 20 mg/d
6. bupropion XL 300 mg/d
7. **STOP prazosin**
8. rosuvastatin 10 mg/d
9. pantoprazole 40 mg/d

Opportunity for Supported Deprescribing

- Elective cardiac surgery (October 2022)
- POD#2 Consult Liaison Psychiatry
- Plea for help with ongoing deprescribing after D/C

Dr. Gregson: Post-op psychiatric assessment

Mental Status Exam (in hospital):

- **hallucinating, distractible, disoriented, mumbled speech, somnolent, NG tube in place**

Psychiatric drugs just before admission (as reduced by FP):

1. quetiapine XR 400mg HS + 100mg AM and 125mg HS (625mg/d)
2. zopiclone 15mg/d
3. clonazepam 1 mg BID (2mg/d)
4. gabapentin 300mg BID (600mg/d)
5. escitalopram 20 mg/d
6. bupropion XL 300 mg/d

Psychiatric Diagnosis

- Delirium (hypoactive): multifactorial polypharmacy, cardiac surgery, ICU environment
- Alcohol Use Disorder, full remission: No evidence of alcohol W/D
- Previous diagnosis of PTSD, depression

Plan in hospital (Dr. Gregson)

1. quetiapine: REDUCE 900mg/day to 150 mg/d (50 mg AM, 100 mg HS)
2. clonazepam: REDUCE 1mg BID to 0.5mg BID
3. gabapentin: REDUCE 300mg BID to 100mg BID
4. zopiclone: CHANGE to prn

Course in hospital

- Delirium cleared gradually by POD#6
- No evidence of benzo withdrawal
- No acute worsening of PTSD symptoms
- Mood remained stable
- Anxious about possible deterioration in mood & sleep when home
- Non-medication strategies reviewed
- Discharged home POD#8 on markedly reduced meds with plan to f/u with GP (offered psych output referral but declined)

Medications at hospital D/C autumn 2022:

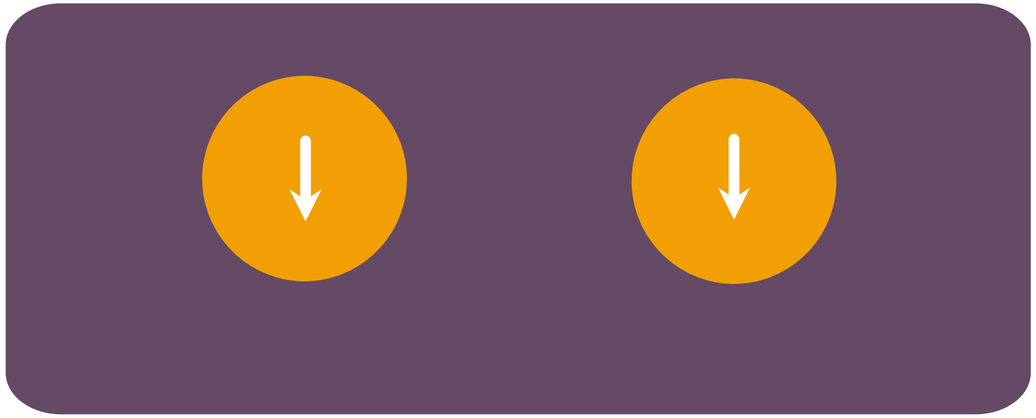
1. quetiapine 150mg/d
2. clonazepam 1 mg/d
3. gabapentin 200mg/d
4. escitalopram 20mg/d
5. bupropion XL 300 mg/d
6. rosuvastatin 10 mg/d
7. pantoprazole 40 mg/d
8. temporary post-op : metoprolol, clopidogrel, ASA, trimethoprim/sulfa

~~zopiclone **STOPPED**~~

Further changes since discharge:

1. **buproprion REDUCED from 300mg/d to 150mg/d (due to insomnia)**
2. **melatonin 10 mg/d STARTED**

~~**rosuvastatin and pantoprazole STOPPED**~~



Changes since reducing drugs (Dr. Norris):

“most future oriented & engaged with life I’ve ever seen her”

- **more emotions: pleasant and unpleasant.**
- **experienced family connection**
- **recognition of “prison/refuge” of social isolation, medicated numbness**
- **Rx: human connection and activation**
- **Her mood has since declined**

Patient’s view on deprescribing

“It has been good and bad. When I first came home I felt really happy with myself, like I could do this, not need to be on all these meds, always popping pills. It felt like when I came off alcohol and realized I didn’t need it anymore.

“My daughter noticed I was more willing to be social. I wanted to come off all of the pills…But as the weeks have progressed, I’m feeling more depressed and anxious.

“I want to find a balance - not overmedicated and sedated, but not close to the edge of wanting to kill myself.

“I want to find a dose where I can live each day to the most."

What do you want doctors to know?

- You don’t need to automatically give huge doses
- You need to know your patient.
- And thank-you.

Key Learnings as Family Doctor

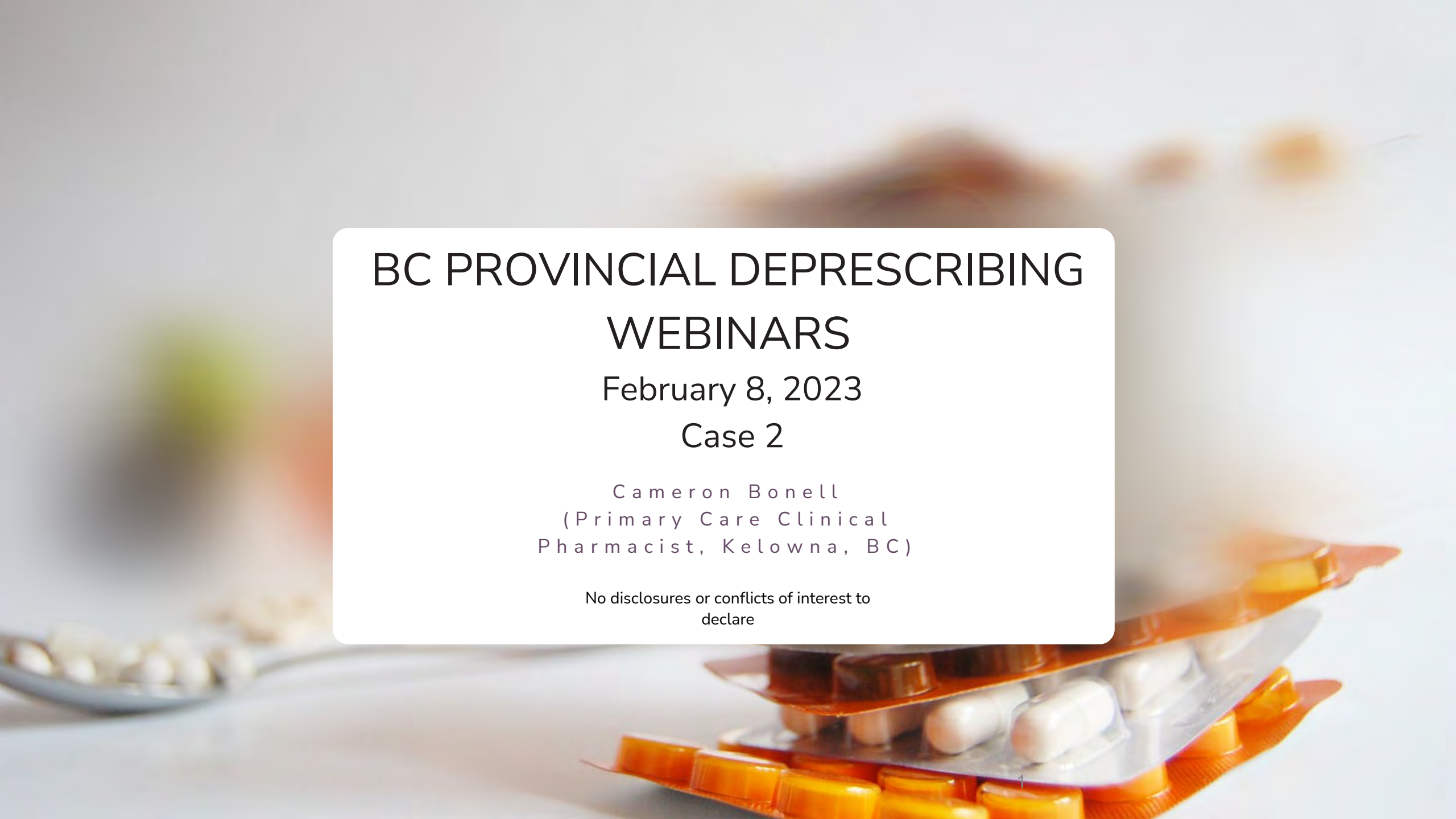
Deprescribing take-aways

- Deprescribing requires trust, a relationship and alignment with patient goals.
- Look for opportunities to deprescribe.
- Anticipate your and your patient’s impulse to increase meds.
- Complex regimens increase risk of errors.
- Reverse prescribing cascades.
- Recognize over-attribution of medication effectiveness by patients and physicians.
- Appropriateness of high dose antipsychotics is often time limited.
- Medications can’t fix loneliness.

Key Learning from Psychiatry:

Opportunities for deprescribing

- When patient asks
- Side effects/adverse events
- Polypharmacy
- Change in diagnostic impression
- Change in risk benefit analysis



BC PROVINCIAL DEPRESCRIBING WEBINARS

February 8, 2023

Case 2

Cameron Bonell
(Primary Care Clinical Pharmacist, Kelowna, BC)

No disclosures or conflicts of interest to declare

Referral from FP to primary care pharmacist September 2022

“She has an extensive mental health history and has taken multiple medications for a long time."

“Recently she struggles with constant headaches, digestive issues, and memory changes, possibly related to polypharmacy.”

Medication list (September 2022):

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

Woman age < 40

History:
Major depressive disorder, extensive list of “failed” medications, ECT (2-3 years ago). Last hospitalized early 2022 for depression with suicidal ideation. Followed in hospital by psychiatrist, and Q6-12 months as outpatient.

Ongoing patient management by family physician. She complains of:

- Daily headaches
- Nausea and stomach pain
- Daytime sedation: takes 1-2 hours to wake up in the morning
- No attention span
- Can’t think straight

FP also referred her to neurologist

"To review chronic daily headaches with reduced mental acuity and daytime sedation"

Neurologist responded:
"Prior to seeing patient, I recommend medication review for potential medication contributors to these complaints, and also to screen for drug interactions prior to initiating preventive headache medications. I am likely to consider valproate or topiramate. I also recommend imaging her brain."

Pharmacist's approach:

Medication Management

Ask the patient:

1. Do you think any of these medications are causing problems for you?
2. Do you think any of these medications are unnecessary?
3. What is your biggest concern with your medications?

Her views:

- She does not attribute adverse effects to medications
- She does not think methylphenidate is “working” – still easily distracted and loses train of thought
- Does not want to touch sleeping medications because in hospital she was not sleeping for 2-3 weeks until this combination was assembled

Initial medication list September 2022:

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

Her views:

My worst problems now are:

- attention and memory problems
- chronic daily headaches
- mild to moderate daily nausea

Her complaints had worsened over several months before assessment.

New drugs since hospital D/C:

- methylphenidate April 2022
- bupropion June 2022
- pantoprazole June 2022

Initial medication list September 2022:

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

Verbatim from initial visit

- I can’t wake up in the morning
- I can’t think straight – no attention span
- I could fall asleep anytime in day, but not at night
- I scared my mom on a recent trip home, when I was wandering incoherently at night to get snacks
- I often wake up with food wrappers and remnants in my bed

Initial medication list September 2022:

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

MY CONCERNS AS CONSULTING PHARMACIST

- EEKS - too many drugs, doses too high!
- Will she be destabilized (harmed) by deprescribing?
- She fears she will never sleep without this regimen
- Are psychiatrist, family doctor and patient on the same page?
- Neurologist wants me to document/predict drug interactions

LEXICOMP

27 Results

View interaction detail by clicking on link(s) below.

D	Levothyroxine Ferrous Sulfate (Iron Preparations)
D	QUEtiapine (CNS Depressants) HydrOXYzine
D	Temazepam (CNS Depressants) HydrOXYzine
D	Vortioxetine BuPROPion
D	Zopiclone (CNS Depressants) HydrOXYzine
C	Benztropine (Anticholinergic Agents) HydrOXYzine (Anticholinergic Agents)
C	Benztropine (Anticholinergic Agents) QUEtiapine (Anticholinergic Agents)
C	Levothyroxine (Thyroid Products) Vortioxetine (Selective Serotonin Reuptake Inhibitors)
C	Lithium (Serotonergic Agents (High Risk)) Methylphenidate (Dexmethylphenidate-Methylphenidate)
C	Methylphenidate (Agents With Seizure Threshold Lowering Potential) BuPROPion
C	Methylphenidate (Dexmethylphenidate-Methylphenidate) QUEtiapine (Antipsychotic Agents)
C	Methylphenidate (Sympathomimetics) Levothyroxine
C	QUEtiapine (Agents With Seizure Threshold Lowering Potential) BuPROPion
C	QUEtiapine (Antipsychotic Agents) Lithium
C	QUEtiapine (Antipsychotic Agents) Methylphenidate (Agents With Seizure Threshold Lowering Potential)
C	QUEtiapine (Antipsychotic Agents) Vortioxetine (Serotonergic Agents (High Risk))
C	QUEtiapine (CNS Depressants) Temazepam (CNS Depressants)
C	QUEtiapine (CNS Depressants) Zopiclone (CNS Depressants)
C	Temazepam (CNS Depressants) Zopiclone (CNS Depressants)
C	Vortioxetine (Selective Serotonin Reuptake Inhibitors) Lithium (Serotonergic Agents (High Risk, Miscellaneous))
C	Vortioxetine (Serotonergic Agents (High Risk)) [illegible]

Potential drug interactions:

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

Potential drug interactions:
Bupropion may increase plasma [vortioxetine]

Title Vortioxetine / BuPROPion

Print

Risk Rating D: Consider therapy modification

Summary BuPROPion may enhance the adverse/toxic effect of Vortioxetine. BuPROPion may increase the serum concentration of Vortioxetine. **Severity** Major **Reliability Rating** Good

Patient Management The vortioxetine dose should be reduced by 50% when used together with the strong CYP2D6 inhibitor bupropion. Following cessation of bupropion, the vortioxetine dose should be returned to the normal level. Monitor patients for increased vortioxetine toxicities including seizures and serotonin syndrome.

Discussion The vortioxetine AUC and maximum serum concentration (Cmax) were an average of 2.3- and 2.1-fold higher, respectively, when vortioxetine (10 mg/day) was given with the strong CYP2D6 inhibitor bupropion (75 mg twice/day for 3 days, then 150 mg twice/day for 11 days) in a cohort of 30 healthy subjects.[1,2] Of note, there was an increase in the report of adverse effects associated with the use of this combination (89% vs. 63% with any reported AE), with headache, nausea/vomiting, insomnia, and dizziness the most commonly reported adverse effects.[1] However, in a separate cohort designed to assess the effects of vortioxetine on bupropion pharmacokinetics, the addition of vortioxetine to bupropion therapy was not associated with an increase in adverse effects (63% vs. 61%), with headache and nausea/vomiting being the most commonly reported adverse effects.[1] Because of the expected magnitude of this interaction, the vortioxetine prescribing information recommends that the vortioxetine dose should be reduced by 50% when used together with a strong CYP2D6 inhibitor such as bupropion.[2]

The likely mechanism for this interaction is inhibition of the CYP2D6-mediated metabolism of vortioxetine leading to an increase in vortioxetine concentrations. CYP2D6 is the primary enzyme responsible for vortioxetine metabolism, though several other enzymes (CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4) also participate.[2]

In addition to this pharmacokinetic interaction, the concomitant use of bupropion and vortioxetine may increase the risk for seizures, as both agents have been associated with a lowering of the seizure threshold and their effects may be additive.[2,3] Bupropion and vortioxetine prescribing information recommend using caution in settings where the seizure threshold is lower.[2,3]

Lastly, bupropion has been implicated in reports with other SSRIs suggesting that concurrent use of these agents with bupropion may increase the risk for serious toxicities such as serotonin syndrome.[4,5,6,7,8,9] Of note, many of these cases involve multiple serotonergic medications or were the result of an overdose, making the role of bupropion unclear. Additionally, at least one commentary strongly argues that bupropion lacked involvement in suspected serotonin syndrome, as the antidepressant effects of bupropion are largely dopamine-based as opposed to serotonin-based.[10,11,12,13]

The mechanism(s) for any possible interaction is(are) unclear. Based on the information presented in these cases together with other available data concerning bupropion's actions, it seems unlikely that it would directly cause any enhanced serotonergic activity that could account for observed serotonin syndrome-like presentations. However, bupropion is a strong inhibitor of CYP2D6,[14] which is at least partially responsible for the metabolism of some SSRIs (including vortioxetine). This suggests that some bupropion-SSRI combinations may be associated with increased concentrations of the SSRI, and increased SSRI concentrations may increase the risk for serotonin syndrome.

My initial recommendations

Please consult psychiatrist and consider:

1. Reduce vortioxetine to 10mg daily

2. Increase bupropion to 300mg daily after 1-2 weeks

3. Discontinue methylphenidate (patient doesn't want it)

4. If needed, neurology can add valproate (preferable) or topiramate for headache prophylaxis (interactions minimal)

5. Consider suggestions for tapering of:
   - quetiapine and benztropine
   - hydroxyzine
   - zopiclone and temazepam

Initial changes made by FP

1. Reduce hydroxyzine from 50mg to 25mg QHS
2. Reduce quetiapine from 350mg to 300mg QHS
3. Reduce benztropine from 1mg BID to 1mg QAM
4. Reduce methylphenidate from 36mg to 18mg QAM

2 week review:

1. quetiapine reduced to 300mg/d without problem

2. still taking benztropine 1mg BID

3. unable to sleep with 25mg hydroxyzine: 50mg HS

4. did not function well with 18mg/d methylphenidate: back to 36mg/d

4 week review:

She had a frightening episode while visiting relatives

- wandering house incoherent/unresponsive to questions
- told she looked like a zombie
- relative's children were terrified

She decided to stop temazepam and zopiclone "cold turkey'

I spoke with her on day 6 after stopping them:

- no irritability, anxiety/agitation, or worsening mood
- some sleep latency, but otherwise "sleeping OK"

7 weeks after “cold turkey”:

- remains off temazepam and zopiclone
- successfully reduced benztropine to 1mg/d

Initial medication list September 2022:

1. benztropine 1mg BID
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 350mg QHS
10. temazepam 45mg QHS
11. vortioxetine 20mg QPM
12. zopiclone 7.5mg QHS
13. acetaminophen 500-1000mg up to QID PRN for headache

Current medication list January 2023:

1. benztropine 1mg QAM
2. bupropion 150mg QAM
3. ferrous SO4 300mg QPM
4. hydroxyzine 50mg QHS
5. l-thyroxine 25mcg QAM
6. lithium CO3 600mg QHS
7. methylphenidate 36mg QAM
8. pantoprazole 40mg BID
9. quetiapine IR 300mg QHS
10. ~~temazepam~~ STOPPED on her own
11. vortioxetine 20mg QPM
12. ~~zopiclone~~ STOPPED on her own
13. acetaminophen 500-1000mg up to QID PRN for headache

Current issues January 2023

- still has daily headaches, but less fixated on this
- lost her job: less stress now but this may be a stressor later
- lost 40 pounds (intentionally) since October 2022
- complains she's clumsy, bumping into and dropping things

Next Recommendations:

1. vortioxetine: dose high, interaction with bupropion; discuss further
2. quetiapine: continue to taper
3. lithium: repeat plasma [Li+] – it was low "therapeutic" in 2022, but she now weighs 20% less
4. iron: reassess, as ferritin and CBC normal & she has GI symptoms

What really surprised me in this case:

Patient with a strong motivation can stop high dose sedatives abruptly, with few apparent problems

- I had assumed (bias from numerous other patients) that this patient would experience difficulty stopping temazepam and zopiclone
- I was prepared with a 4-6 month tapering plan
- Abrupt cessation of these drugs is NOT ideal – but it worked for her!

Patient’s view on deprescribing

I’m glad we’re discussing this topic. People get “stuck on meds” and think it will never change.

I think it’s great that people want to learn from each other.

Key Learnings from Pharmacist's perspective: Deprescribing take-aways

How to approach a daunting drug list:

1. What drug(s) does patient see as problematic?
2. What drugs, doses, combinations are likely to be posing risk?
3. Are there any drugs that are unlikely to be beneficial?
4. Can therapeutic duplication be eliminated or minimized?
5. Are there dose rationalization opportunities?
6. Are there drugs that were once necessary in time of crisis but can now be cautiously deprescribed?