Canadian Geriatrics Society

RESPONSE TO "MANAGEMENT OF AGITATION IN AN ACUTE CARE HOSPITAL SETTING: DESCRIPTION OF A PRACTICAL CLINICAL APPROACH EMPLOYED AT THE OTTAWA HOSPITAL"

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Abstract

Key points:
1. Due to the pharmacodynamics and pharmacokinetics of trazodone, patients with behavioural psychologic symptoms of dementia vary in their response.
2. Trazodone's adverse cognitive effects in vulnerable older adults are due, in part, to its metabolite, m-CPP, which has anxiogenic effects.
3. Clinicians should exercise caution when prescribing trazodone to older adults on other drugs known to inhibit the CYP2D6 isoenzyme. The Flockhart Table is a useful resource to assess CYP mediated drug-drug interactions.

This article has been peer reviewed.

Conflict of Interest: None

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Key words:
delirium, dementia, medication optimization/polypharmacy

Response to the CME article "Management of Agitation in an Acute Care Hospital Setting: Description of a Practical Clinical Approach Employed at the Ottawa Hospital"

The article titled "Management of Agitation in an Acute Care Hospital Setting: Description of a Practical Clinical Approach Employed at the Ottawa Hospital"[1] provides a step-wise approach to inpatient agitation in older adults. Based on a review of available literature combined with clinical expertise, the paper illustrates using low dose trazodone as a part of a useful framework employed by The Ottawa Hospital (TOH) in managing agitation. Due to increased awareness of the risks of benzodiazepines and antipsychotics, trazodone use for the off-label treatment of agitation and insomnia is growing in Canada.[2–5] We agree with Dr. Rabheru's emphasis on the judicious and tailored use of trazodone and discussion of its pharmacology. While generally well tolerated, there are case reports describing worsened neuropsychiatric symptoms, including delirium and acute extrapyramidal events.[6,7]

These adverse cognitive effects are explained by trazodone's unique pharmacology which warrants additional discussion.

Trazodone is metabolized by cytochrome (CYP) P450 isoenzyme, CYP3A4, to an active metabolite, meta-chloro-phenylpiperazine (mCPP), which possesses dose-dependent anxiogenic and at higher doses, hallucinogenic effects. [8–11] mCPP's clearance is mediated by CYP2D6 metabolism and the P-glycoprotein drug transporter (also known as ABCB1), which can vary between individuals.[8,12] Individuals with decreased CYP2D6 metabolizing capacity due to concomitant interacting medications (e.g. fluoxetine) or pharmacogenomics may experience higher mCPP levels and its anxiogenic effects.[8,10,13,14] Furthermore, advanced age decreases phase 1 metabolism resulting in longer elimination half-lives of trazodone and mCPP.[15,16]

We hope this evidence-based geriatric drug infographic[17] of trazodone may serve as a helpful tool to clinicians when prescribing and monitoring trazodone to their older adult patient (Figure 1).

Key Points

1. Due to the pharmacodynamics and pharmacokinetics of trazodone, patients with behavioural psychologic symptoms of dementia vary in their response.
2. Trazodone's adverse cognitive effects in vulnerable older adults are due to its metabolite, m-CPP, which has anxiogenic effects.
3. Clinicians should exercise caution when prescribing trazodone to older adults on other drugs known to inhibit the CYP2D6 isoenzyme. The Flockhart Table (https://drug-interactions.medicine.iu.edu/MainTable.aspx) is a useful resource to assess CYP mediated drug-drug interactions.[18]

Figure 1.

Trazodone

Antidepressant
Serotonin Receptor Antagonist and Reuptake Inhibitor (SARI)

What to tell my patient

Benefits

Indicated for major depressive disorder (MDD). Effective in MDD; however, rarely used in older adults for this indication due to its potential for sedation and orthostatic hypotension.

Overall little evidence to support its use for insomnia (off-label use).

The American Academy of Sleep Medicine 2017 Clinical Practice Guidelines recommend against its use for insomnia versus no treatment.

No good evidence to support use in treating behavioural and psychological symptoms of dementia (BPSD, off-label use) more broadly; however one small trial found a benefit in frontotemporal dementia.

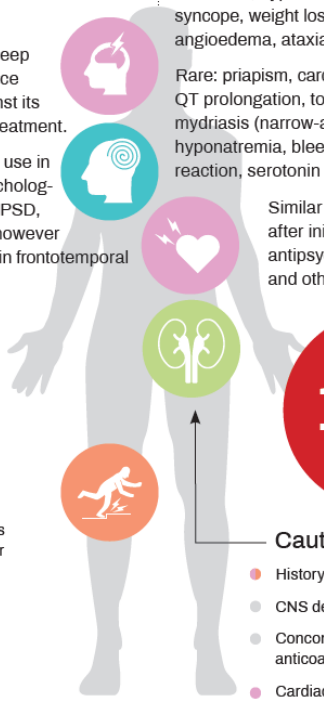
Adverse effects and risks

Common: nausea, drowsiness, xerostomia, dizziness, anxiousness/nervousness, fatigue, vision blurred, headache.

Less Common: constipation, diarrhea, confusion, hypotension (includes ortho-static), syncope, weight loss or weight gain, angioedema, ataxia, myalgia, tremor, insomnia.

Rare: priapism, cardiac dysrhythmia, seizures, QT prolongation, torsades de pointe (TdP), mydriasis (narrow-angle glaucoma), SIADH/hyponatremia, bleeding, hypersensitivity reaction, serotonin syndrome, suicidal ideation.

Similar risk of falls in first 90 days after initiation compared to atypical antipsychotics, benzodiazepines and other antidepressants.



HR 1.54
95% CI 1.28-1.87
Falls

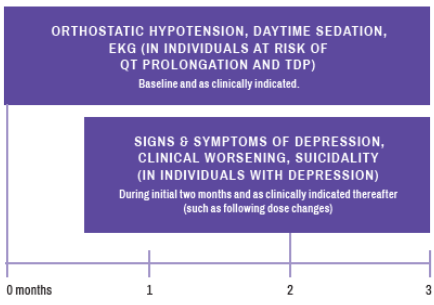
Contraindications

- Hypersensitivity.
- Use of MAO inhibitors (concurrently or within 14 days of discontinuing MAO inhibitor or trazodone).

Caution

- History of seizures or falls
- CNS depression
- Concomitant use of NSAIDs/aspirin/anticoagulants
- Cardiac disease and/or other risk factors for TdP
- Use during acute recovery phase following myocardial infarction not recommended
- Bipolar disorder (may worsen psychosis or cause shift to mania or hypomania)
- Emergence of suicidal thoughts and behaviours, clinical worsening of depression
- Discontinuation syndrome with abrupt discontinuation
- Serotonin syndrome
- Priapism
- Hepatic or renal impairment

Monitoring



Oral dosing for older adults

INSUFFICIENT EVIDENCE TO GUIDE DOSING FOR OFF-LABEL USE.

INITIAL DOSE
12.5 mg-25 mg

Renal:
- No adjustment necessary.

Hepatic:
- Caution in impairment.

Drug interactions

Pharmacokinetic

- Substrate (major) of CYP3A4: increased trazodone exposure with strong CYP3A4 inhibitors (e.g. doubling of exposure with clarithromycin).
- Substrate (minor) of CYP2D6: increased exposure to anxiogenic metabolite mCPP with CYP2D6 inhibitors (e.g. fluoxetine), and theoretical potential for increased anxiety and agitation.
- Digoxin: may increase digoxin serum concentration.
- Phenytoin: may increase phenytoin serum concentration.

CYP3A4 (M) Substrate
CYP2D6 (m) Substrate

Pharmacodynamic

- Serotonergic drugs: caution advised with concomitant use due to risk of serotonin syndrome.
- CNS depressants: caution advised due to increased risk of CNS depression and falls.
- QT prolonging agents: may potentiate effects, increased risk of TdP.
- Antihypertensives: increased risk of orthostatic hypotension.
- NSAIDs, anti-platelet agents: caution is advised for concurrent use with other anti-platelet agents as this may result in increased risk of bleeding.

Did you know...

Mechanism of action

In general, at higher doses trazodone acts as an antidepressant via inhibition of serotonin reuptake, while at lower doses its sedative effects predominate via antagonism at serotonin and histamine receptors. Also antagonizes alpha-1 receptors.

ELIMINATION

In older adults, age-related reduction in hepatic metabolism of trazodone, results in longer half-life, reduced clearance, exposure to higher plasma concentrations, and prolonged sedative effects.

RENAL
70-75%
excreted in urine with <1% unchanged

Half-life in older adults
12 hrs

FECES
21%

For references, please see www.gerimedrisk.ca.
Disclaimer: still use own clinical judgment.

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