UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Antidepressant Adverse Drug Reactions: Focus on QT Prolongation

Background:

Antidepressants have been used for many years to treat mental health conditions such as depression and anxiety (not an all-inclusive list). Their mechanisms are somewhat unique to the class of antidepressant, for instance, tricyclic antidepressants are thought to delay the inward sodium current into cardiomyocytes, slowing cardiac depolarization. In contrast, SSRIs directly block potassium channels and disrupt hERG protein expression, both reducing potassium ion flow. Palliative care clinicians use these medications commonly in clinical practice for symptom management and should be aware of their potential side effects.

Importance:

Antidepressants can cause QTc prolongation. As stated in previous weeks, clinically significant QTc prolongation is an absolute QTc $\geq$ 500 msec, QTc $\geq$ 25% from baseline, or change of QTc $\geq$ 60 msec.[1] The degree of QTc prolongation is a *modest* predictor of the risk of Torsades de Pointes (TdP) and sudden cardiac death.[2] Still, it is important for palliative care clinicians be aware of this risk of commonly prescribed medications in our practice.

Known QTc prolongation risk factors:

- Age $\geq$ 65
- Female
- Electrolyte imbalances: hypokalemia, hypomagnesemia, hypocalcemia
- Impaired hepatic and/or renal function
- Cardiovascular Disease (CHF, AFib, MI)
- Medications: Methadone, Tyrosine Kinase Inhibitors (Crizotinib, Sunitinib, Vemurafenib, Sorafenib, Imatinib), Antipsychotics, Fluoroquinolones, Amiodarone, Antiemetics
- Drug interactions: inhibition of cytochrome P450 enzymes and subsequent increase in medication plasma levels (Antifungals, Macrolide antibiotics, ritonavir, verapamil, St. Johns Wart)

The Literature:

Ther Adv Drug Saf. 2018 Jun;9(6):297-308.

Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: a review of the evidence

Literature Review

Methods: 28 studies included + 4 review article bibliographies

Results*:

Medication Class	Change in QTc interval (msec)**
SSRIs	Citalopram#: 10.4 to 35.3 Escitalopram: -8.7 to 2.7 Fluoxetine: -5.9 to 13.0 Paroxetine: -5.6 to 12.4 Sertraline: -19.4 to 11.6
TCAs	Amitriptyline: 5.5 to 11.6 Nortriptyline: 5.6 to 35.3 Doxepin: -7.8 to 12.8 Imipramine: 11.3 to 11.8
SNRIs	Duloxetine: not significant Venlafaxine: 3.5 to 10.6
Other	Trazodone: -12.1

*Dose ranges extrapolated from the individual studies; this table does not consider the number of patients included, number of studies considered to provide the range, indication for antidepressant (depression versus pain), class-related evidence or the level of evidence.

**These numbers may seem low compared to what we would see in our clinical practice, given our seriously ill, complex patients

#Citalopram does hold a black box warning for QTc prolongation; doses greater than 20mg not recommended in older adults, those with hepatic impairment, or with significant drug interactions

Conclusion:

- TCAs and citalopram have the most consistent effect on QTc prolongation

Psychiatric Times. 2018;35(3).

QT Prolongation and Antidepressants

Commentary

Medication	QTc Prolongation Risk
SSRIs	
Citalopram	**
Escitalopram	**
Fluoxetine	*
Paroxetine	*
Sertraline	*
SNRIs	
Desvenlafaxine	*
Duloxetine	*
Venlafaxine	**
TCAs	
Amitriptyline	***
Clomipramine	**
Nortriptyline	***
Other	
Mirtazapine	*
Bupropion	*
Trazodone	*

Bottom Line:

- Literature on degree of QTc prolongation for each antidepressant differs slightly and is based on the indication for the antidepressant (ie. dose)
- Consistently, TCAs and citalopram pose the greatest risk for QTc prolongation
- Guidelines do not provide uniform recommendations with respect to ECG screening and monitoring with use of antidepressants. Could be worth monitoring if planning to escalate TCA doses for depression management and higher doses of citalopram… or not…

CLINICAL PEARL:

Recommend avoidance of TCAs and citalopram for those with prolonged QTc, or those with underlying comorbidities and risk factors for QTc prolongation