

QTc Prolongation and Psychiatric Medications

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Disclosure: Scott R. Beach, MD

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or partner) and any for-profit company in the past 24 months which could be considered a conflict of interest.

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Medications



Limitations of Available Data

- Study population
- Method of QTc measurement
- Timing of measurement
- Medication dose
- Concomitant medications
- Reported QTc: mean or clinically meaningful change?
- Thorough QT Study?
- Evaluate Credible Meds data



Antipsychotics



Typical Antipsychotics

- As a group, typicals lead to modest (< 5ms) QT prolongation compared to placebo, but this effect is likely primarily driven by phenothiazines
- In general, low-potency agents thought to cause more QTc prolongation than high-potency agents
 - Study of overdoses showed toxic and therapeutic levels of phenothiazines were associated with increased risk of QTc prolongation, whereas atypicals were not
 - Effect may be driven mainly by thioridazine, which causes greatest prolongation (30 ms) of any antipsychotic



Chlorpromazine

- QTc prolonging effect thought to be dose-dependent, though no thorough QT study has been done
- IV form often said to cause greater QTc prolongation than PO, but no head-to-head studies
- 2025 study showing risk of SCD among HD patients is less for chlorpromazine compared with haloperidol
- ***We have reclassified chlorpromazine from high-risk into medium-risk as a result of a recent literature review, as there is not sufficient evidence that it separates out from most other agents***

Nash 2025



Oral and IM Haloperidol

- Most studies suggest QTc prolongation of 5-8 ms for oral and IM haloperidol (less than most atypical agents)
- Both forms do not separate out from placebo in some studies (and IM haloperidol did not separate out from IM olanzapine)
- Some studies continue to suggest greater risk for ventricular arrhythmias or SCD
 - Compared to olanzapine, haloperidol conferred a 1.72-fold increased risk of sudden death or VA
 - Haloperidol linked to increased risk of VA or sudden cardiac death (OR 1.46)
 - Each controlled for a limited number of covariates

Howland 2014, Leonard 2013, Wu 2015, Salvo 2016, Meyer-Masseti 2010



Intravenous Haloperidol

- No thorough QT study
- Ten of 11 prospective studies, involving >1500 patients and doses up to 20mg, found no evidence of QT prolongation
- No clear evidence that IV haloperidol causes greater QT prolongation than atypical agents or oral haloperidol
- Doses above 35 mg in <6 hours may be associated with greater risk for TdP
- Vast majority of patients who developed TdP had multiple other risk factors
- One study suggests that most patients who developed TdP with IV haloperidol had a QTc of >550 ms prior to the episode
- 2024 study in JAMA Open Network finding no evidence for cardiac arrhythmias with IV Haldol when QTc is less than 550 ms
- 2025 meta-analysis finding no increased risk for arrhythmias or mortality

Meyer-Masseti et al 2010; Beach 2020; Ozeki 2010; Stollings 2024; Garcia 2025



Recommendations for Intravenous Haloperidol

- Ensure repletion of electrolytes (Mg and K to 2 mEq/L and 4 mEq/L, respectively), and minimize other risk factors.
- Use a linear correction formula such as Framingham (QT_{Fr}) or Hodges (QT_H).
 - $QT_{Fr} > 480$ ms or uncorrected QT > 436 ms may be better predictors of TdP in patients treated with IVH than QT_B .
- No ECG monitoring required if total dose < 5 mg daily and less than 2 other risk factors present.
- Check a baseline ECG in a non-emergent situation and at least one follow-up ECG, preferably 30-60 minutes following administration, for doses > 5 mg daily **OR** 2 or more risk factors.
- Consider daily ECG for total cumulative dose > 25 mg.
- Consider continuous monitoring and/or alternative agents for $QT_c > 500$ ms **OR** total dose > 100 mg.
- If there is enough concern about QT prolongation to stop using IVH, use a non-antipsychotic agent



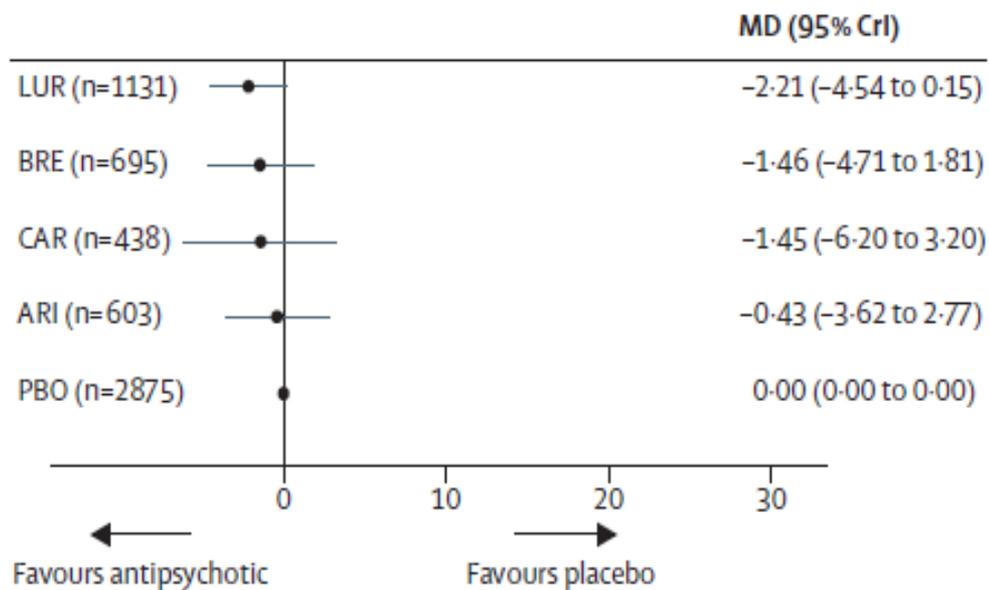
Droperidol

- 2001 – FDA issues a black box warning for QTc prolongation and TdP based on two studies and post-marketing reports
 - Recommend 2-3 hours of telemetry following administration
- Review of cases leading to FDA warning revealed that most of them involved doses >50 mg (Typical dose for agitation is 5-10 mg)
- Risk of QTc prolongation and TdP appears to be minimal with doses up to 10 mg
- Transient increases in QTc occur in 1-9% of patients, mostly within the first 15 mins
- Retrospective cohort study of 108 psychiatric inpatients receiving 5-120mg IM identified only 2 patients with QT prolongation and both had confounders
- Larger studies suggest no risk for TdP in doses up to 10 mg and AAEM now advocates using doses up to 10 mg
- In settings where there is a need for ongoing medications for agitation, dose range may be limiting

Yang 2023

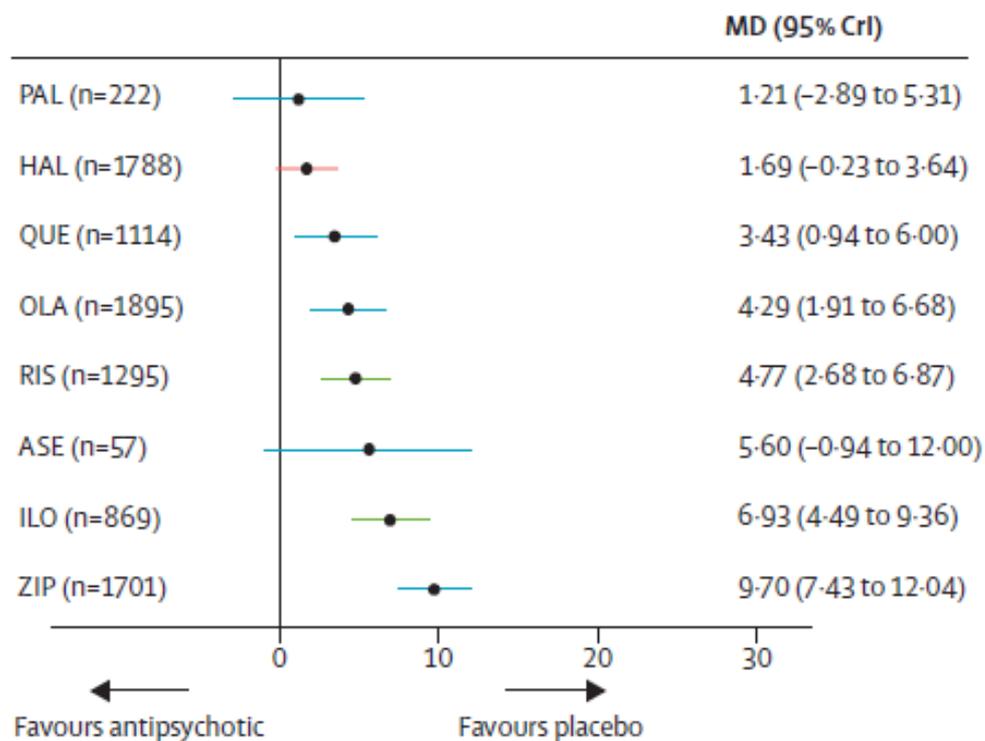


Atypical Antipsychotics



Huhn 2019

Atypical Antipsychotics



Huhn 2019

Ziprasidone

- 2002 – FDA issues black box warning for QTc prolongation
 - Avoid use in combination with other QT-prolonging agents, history of cardiac arrhythmia
- Average QTc prolongation of 10-21 ms; 20% experience >60 ms increase
- Ziprasidone performs worst in 2019 meta-analysis (similar to iloperidone)

Nielsen et al 2011, FDA 2000, Leucht et al 2013, Huhn et al 2019



Quetiapine

- In 2011, the FDA strengthened quetiapine warning
 - Avoid use with other QTc-prolonging agents, history of arrhythmias, metabolic deficits
 - Based on 12 reports, mostly in overdose or use in combination with other agents (4 cases of TdP)
- Data on quetiapine remains mixed
 - Most studies suggest mild effects, but some report 12% of people experience prolongation > 20ms
- Also associated with an increased risk of out of hospital cardiac arrest (OR=3.64; CI: 1.59-8.30)

Nielsen et al 2015, Leucht et al, 2013, Hasnain and Vieweg 2014, Weeke 2014, Fukushi 2020



Other Antipsychotics

- 2022 study shows less risk of QT prolongation with olanzapine in CCU patients compared to quetiapine
- 2021 cohort analysis of hospitalized older adults receiving quetiapine for delirium demonstrated a mean QTc increase from baseline of 6.7 ms, with 7% having a post-treatment QTc > 500 msec
- 2023 study showing clozapine blood level predicts risk for QTc prolongation (heart rate confounded?)
- 2025 real-world study suggesting ziprasidone and olanzapine have the highest risk of QTc prolongation
- First case of QTc prolongation with lurasidone in 2022
- **Risk with antipsychotics does not appear to be correlated with FDA warnings**

Hanna 2022; Pinkhasov 2021; Kim 2023; He 2025



Summary: Antipsychotic QT Prolongation Risk

- **Antipsychotics with minimal risk**
 - Aripiprazole and lurasidone
- **Antipsychotics with similar “mid-range” risk**
 - Haloperidol, chlorpromazine, olanzapine, risperidone, and quetiapine
- **Antipsychotics with the greatest risk**
 - Ziprasidone, iloperidone, thioridazine
- **Mixed data** about whether antipsychotic polypharmacy leads to greater QTc prolongation
 - If true, possibly mediated by cumulative dose

Leucht et al 2013, Huhn et al 2019



Using Antipsychotics in the Outpatient Setting

- No indication for baseline ECG with all antipsychotic initiations in the outpatient setting
- Consider baseline and follow-up ECG for patients with significant risk factors being started on low-to-moderate risk antipsychotic
- Consider baseline and follow-up ECG for patients without risk factors being started on high-risk antipsychotic
- For patients with risk factors being started on a high-risk antipsychotic, consider ECG monitoring and cardiology consult
- Avoid multiple antipsychotics for patients at risk for TdP



Using Antipsychotics in the Inpatient Setting

- Assume higher risk for TdP among inpatients
- Increased access to monitoring
- Baseline ECG prior to initiation of any antipsychotic
- Follow-up ECG's only for patients with risk factors or receiving a high-risk antipsychotic (or high-dose of moderate risk antipsychotic)
- Replete Mg and K
- Consider alternative agents if QTc >500ms, but always a risk-benefit analysis



Antidepressants



The Citalopram Controversy

- **8/24/11: FDA Drug Safety Communication**
 - Citalopram should not be prescribed at doses >40mg
 - Citalopram should not be used at doses > 20mg in those with liver dysfunction or over age 60
- Recommendations based on a single study showing increase of 8.5 msec at 20mg and 18.5 ms at 60mg
- Lots of evidence since that time supports the idea that citalopram separates out from other SSRIs and causes 5-20 ms prolongation at therapeutic doses
- Evidence is less clear for citalopram and TdP
- Perhaps citalopram increases the QT interval but the actual risk of TdP associated with this increase is not clinically significant



Prescribing Lower Doses of Citalopram Has Risks Too

- 50-65% of patients prescribed doses of greater than 40mg at the time of the warning were prescribed 40mg or less within 2 years
- Older adults were less likely to have their doses reduced to comply with guidelines recommending <20mg daily, with 30% remaining on higher doses after 1 year
- FDA citalopram warning may result in increased rates of psychiatric hospitalization and mortality
- Patients with citalopram reflexively reduced are more likely to be prescribed sedatives or anxiolytics and had higher healthcare utilization

Austin et al 2014, Friesen et al 2015, Rector et al 2016, Gerlach et al 2016, Gerlach 2018



What About Escitalopram?

- Similar pattern of dose-related QT-lengthening in thorough QT study, but no FDA warning
- Escitalopram does separate out in some studies
- Not associated with greater mortality in Tennessee Medicaid cohort
- Meta-analysis of patient level data
 - 2407 patients prescribed escitalopram compared to 1952 patients on placebo
 - Mean QTc increase of 3.5 msec
 - 1 patient had QTc >500msec and baseline change >60msec
 - Incidence and types of cardiac adverse events similar between escitalopram and placebo
- **May carry some risk of mild prolongation but unlikely to be clinically significant**

Thase et al 2013, Ray et al 2016



Antidepressants

- **SSRIs** are largely considered safe
 - Most studied in cardiac populations
 - Case reports for all agents except paroxetine linked to QT prolongation or TdP existed prior to 2011
 - Agents besides citalopram do not separate out from one another
- **Tricyclics** are sodium-channel blockers
 - Pose danger at therapeutic doses primarily in patients with pre-existing bundle branch disease or ischemic heart disease
 - Amitriptyline and maprotiline most commonly implicated in TdP

Funk & Bostwick 2013, Vieweg & Wood 2004



Other Antidepressants

- **Venlafaxine**

- Most evidence for QT prolongation of antidepressants other than citalopram or escitalopram, but most cases occurring in setting of overdose or other risk factors
- 2022 thorough QT study found a maximum mean increase of only 5.8 ms at 450 mg/day

- **Bupropion**

- Reports in setting of overdose but confounded by tachycardia
- Duloxetine, vilazodone, desvenlafaxine, vortioxetine, levomilnacipran, brexpiprazole and esketamine have no association with clinically-meaningful QT prolongation

Abbas 2022, Spindelegger et al 2014, Jasiak & Bostwick 2014, Danielsson et al 2016, Leonard et al 2011, Waring et al 2008, Straley 2022



Mirtazapine

- No thorough QT study
- 2019 study using concentration-QTc analysis (alternative to thorough QT with smaller sample sizes) found changes of 2.4 ms at 45 mg and 4.0 ms at 75 mg
- In overdose, 0 of 103 patients had QTc>500ms
- One study linked with increased sudden death but authors hesitated to make causal association
- Another study showed significantly lower risk of cardiac events than other antidepressants
- 2020 study suggesting no change with mirtazapine in hospitalized patients

Allen 2020, Gurkan



Antidepressants

Using Antidepressants in Patients w/TdP Risk

- Overall magnitude of QTc increase w/ SSRIs is small
- No indication for baseline ECG with all antidepressant initiations
- Consider baseline ECG for patients with significant risk factors being started on non-citalopram antidepressant



Antidepressants

Using Citalopram in Patients w/TdP Risk

- Citalopram appears to be the worst offender (and escitalopram to a lesser extent) but actual QT prolongation remains minimal
- Citalopram not first choice for patients with pre-existing cardiac disease (sertraline remains first-line)
- *Be mindful of multiple risk factors*
 - *2022 study suggesting PPI use increases risk of SCD in hemodialysis patients being started on citalopram and escitalopram*
- Consider baseline ECG for patients being started on citalopram with no risk factors

Simoons et al. 2018, Assimon 2022



Antidepressants

Using Citalopram in Patients w/TdP Risk

- Consider ECG monitoring and/or cardiology consult when starting citalopram in a patient with significant risk factors
- 2018 Dutch guidelines recommend ECG monitoring for patients with 2 or more risk factors (>65 years, female, cardiac disease, electrolyte disturbance, concomitant use of QT-prolonging agent, excessive dose) being started on citalopram or escitalopram
- Do not reflexively reduce citalopram dose without careful risk/benefit evaluation
- Compelling case can be made for using higher doses of citalopram in specific patients, but needs to be done judiciously and employing ECG monitoring



Other Psychiatric Medications



Trazodone

- Few case reports showing risk of transient QT prolongation with trazodone overdose
- 2019 retrospective study of trazodone use in older populations showed no increased risk
- Thorough QT study:
 - 4.5ms at 20mg
 - 12.3ms at 60mg
 - 19.8ms at 140mg

Armstrong 2019; Tellone 2020



Lamotrigine

- October 2020 FDA Warning
 - Class IB may slow ventricular conduction and increase arrhythmia risk in patients with underlying structural or functional heart disease
 - Advised against use in patients with cardiac conduction disorders, prior ventricular arrhythmias or cardiac disease or abnormalities
- Thorough QT study found that lamotrigine did not widen QRS or QTc
- QRS Widening is most common adverse outcome
 - RCT found average widening of 3.5 ms
 - Most case reports had QRS < 120 ms, though exceptions up to 214 ms

FDA 2021, Restrepo 2022

Opioids

- **Methadone**

- 2011: SAMHSA recommended that all methadone Outpatient Treatment Programs should have a cardiac risk management plan, including:
 - Baseline ECG and within 30 days for patients with significant risk factors for QTc prolongation
 - ECGs performed annually or when methadone dose exceeds 120mg daily
 - If QTc prolongation > 500ms strongly consider adoption of risk minimization strategies (reducing dose, eliminating other contributing factors, transitioning to alternative treatment such as buprenorphine, or discontinuing methadone)

Martin 2011



Opioids

- **Buprenorphine**

- Safer alternative to methadone from cardiac standpoint.
- Not shown to prolong the QT interval or have an association with TdP.
- Buprenorphine does block hERG IKr potassium channels but is a hundred times less potent of an inhibitor than methadone.

Katchman 2002, Ilback 2008, Baker 2006, Demarie 2011, Wedam 2007, Kao 2015, Fareed 2013, Hanon 2010, Ancherson 2009, Stallvik 2013, Athanasos 2008, Esses 2008



Which Medications Don't Prolong the QTc?

- Benzodiazepines
- Stimulants
- Modafanil
- Clonidine and Guanfacine
- Anti-epileptic drugs
- Orexin receptor antagonists
- Melatonin
- Buprenorphine



Non-Psychotropic Medications

Prevalence of QT Prolonging, Non-Psychotropic Medications

- **Over 100 non-psychiatric medications have been shown to prolong QT interval and/or be associated with TdP**
- **ICU:** 3-30% of patients receive QT prolonging medications and 1 in 5 are co-administered 2 or more (e.g. amiodarone, haloperidol and antibiotics)
- **ED:** Top 9 medications administered or prescribed have effects on QT
- **Outpatient:** ¼ of prescriptions and 10% of patients involve 2 or more QT-prolonging medications

Freeman et al 2008, Tisdale et al, Tay et al 2014, Danielsson et al 2016.



Non-Psychotropic Medications

Screening for QT Prolonging, Non-Psychotropic Medications

- Clinicians should inquire about over-the-counter medications, supplements and imported drugs
- Common offenders
 - Anti-arrhythmics
 - Antibiotics (e.g., macrolides and fluoroquinolones)
 - Antivirals (HIV medications)
 - Anti-emetics (e.g., ondansetron)
 - Acid blockers
 - Anti-cancer medications
 - Disease-modifying agents (e.g., hydroxychloroquine)



Psychopharmacology

Summary

- Medications are only **one** of the several possible risk factors for QTc prolongation
- Co-administration of two or more QT-prolonging medications is of **particular concern**; be aware of non-psychotropic medications that can increase this risk
- **Avoid “high-risk”** psychotropics when lower risk options are available
- Careful review of **risk-benefit** is critical and must consider both symptom control along with risk for TdP

