



The Risk of QTc Interval Prolongation with Psychotropics

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Disclosure: Christopher Celano, MD

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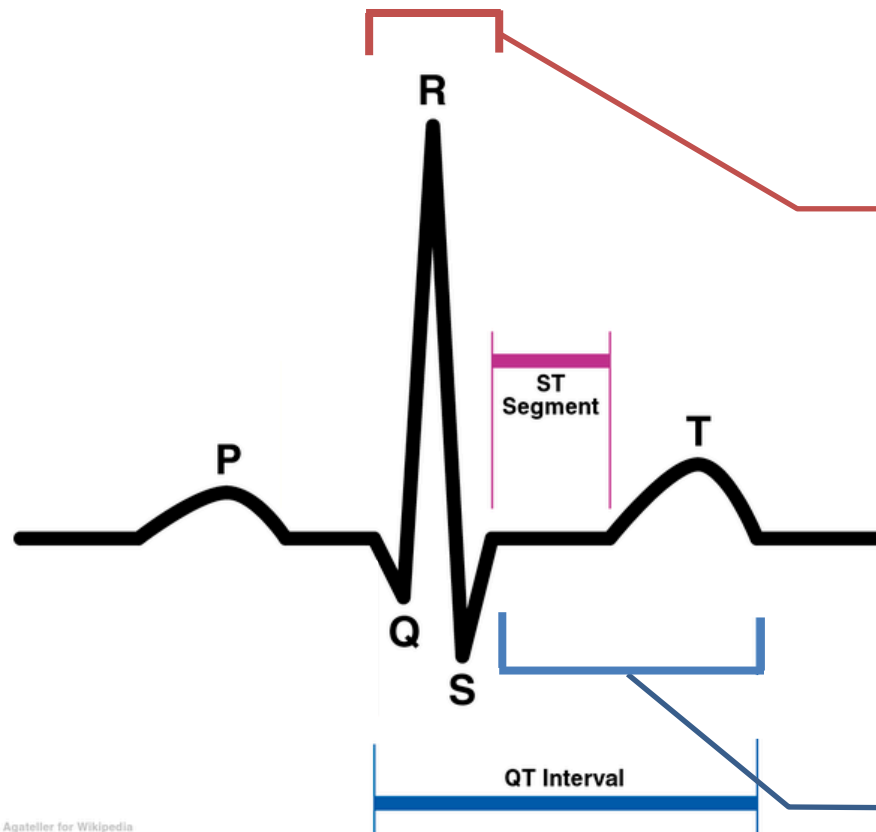
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Topics for Discussion

- QTc interval and its measurement
- Risk factors for QTc prolongation
- Relationships between psychiatric medications and QTc prolongation
- QTc monitoring in clinical practice

What is the QT interval?



QRS Complex =
ventricular depolarization

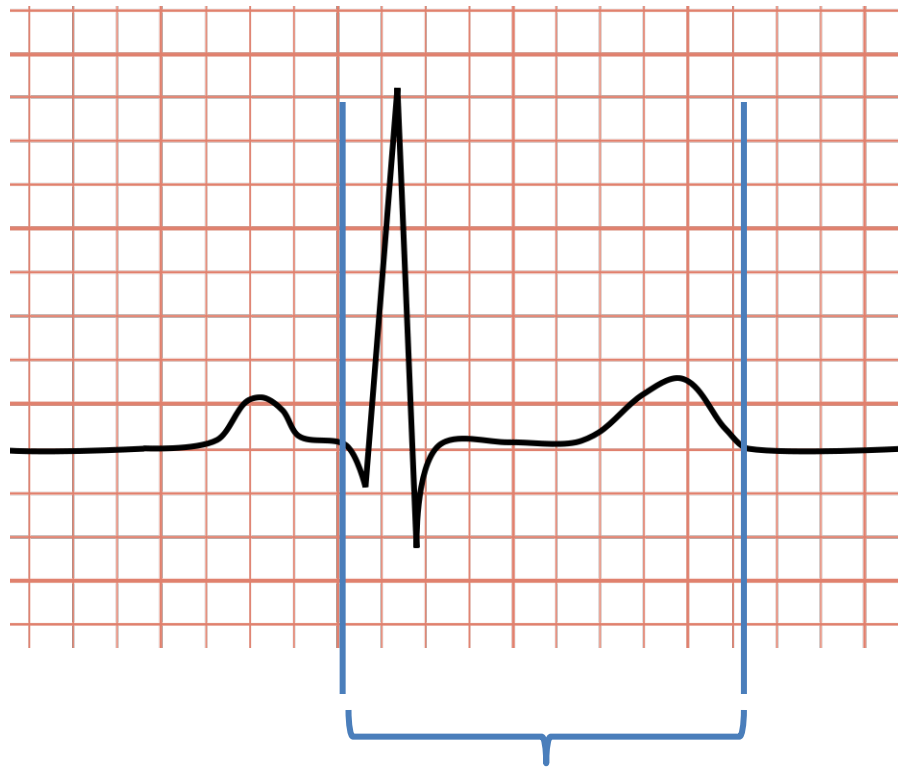
ST segment + T wave =
ventricular repolarization

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How to Measure QTc

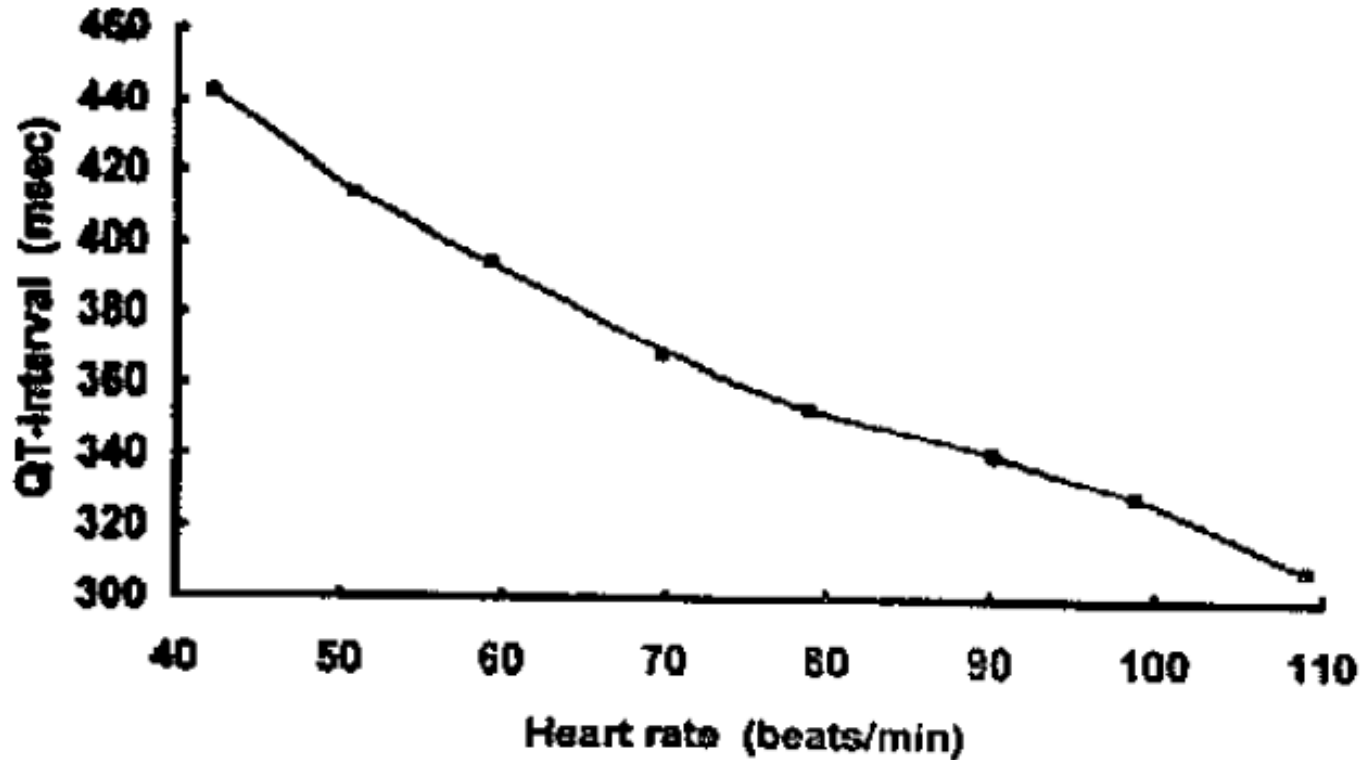
- Pick an appropriate lead on the ECG.
 - Usually II, V2, or V3.
- Measure the QT interval.
- Measure the heart rate or RR interval.
- Calculate the QTc.

Measure the QT interval



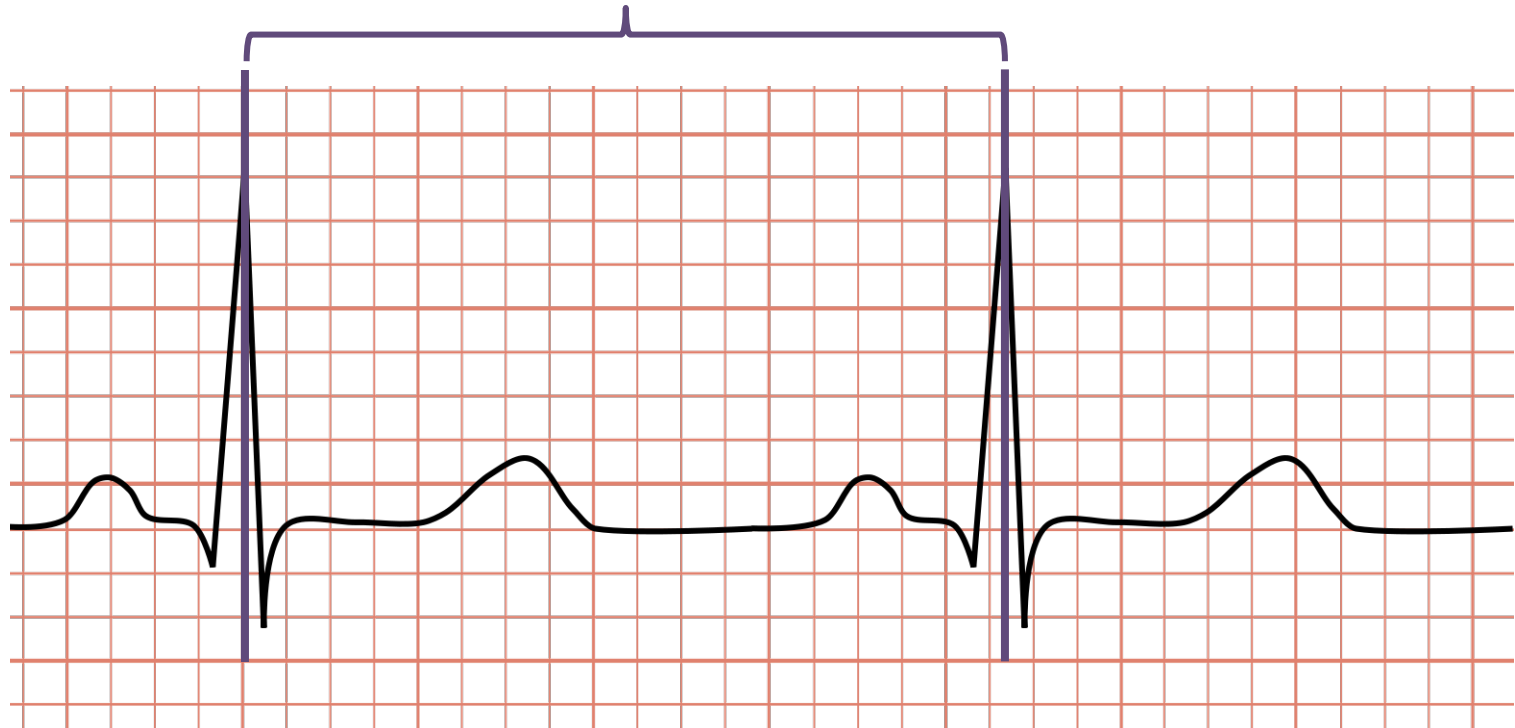
9 boxes + 10 msec
QT = 370 msec

QT intervals are HR-dependent



Measure the RR interval

17 boxes + 10 msec
RR = 690 msec

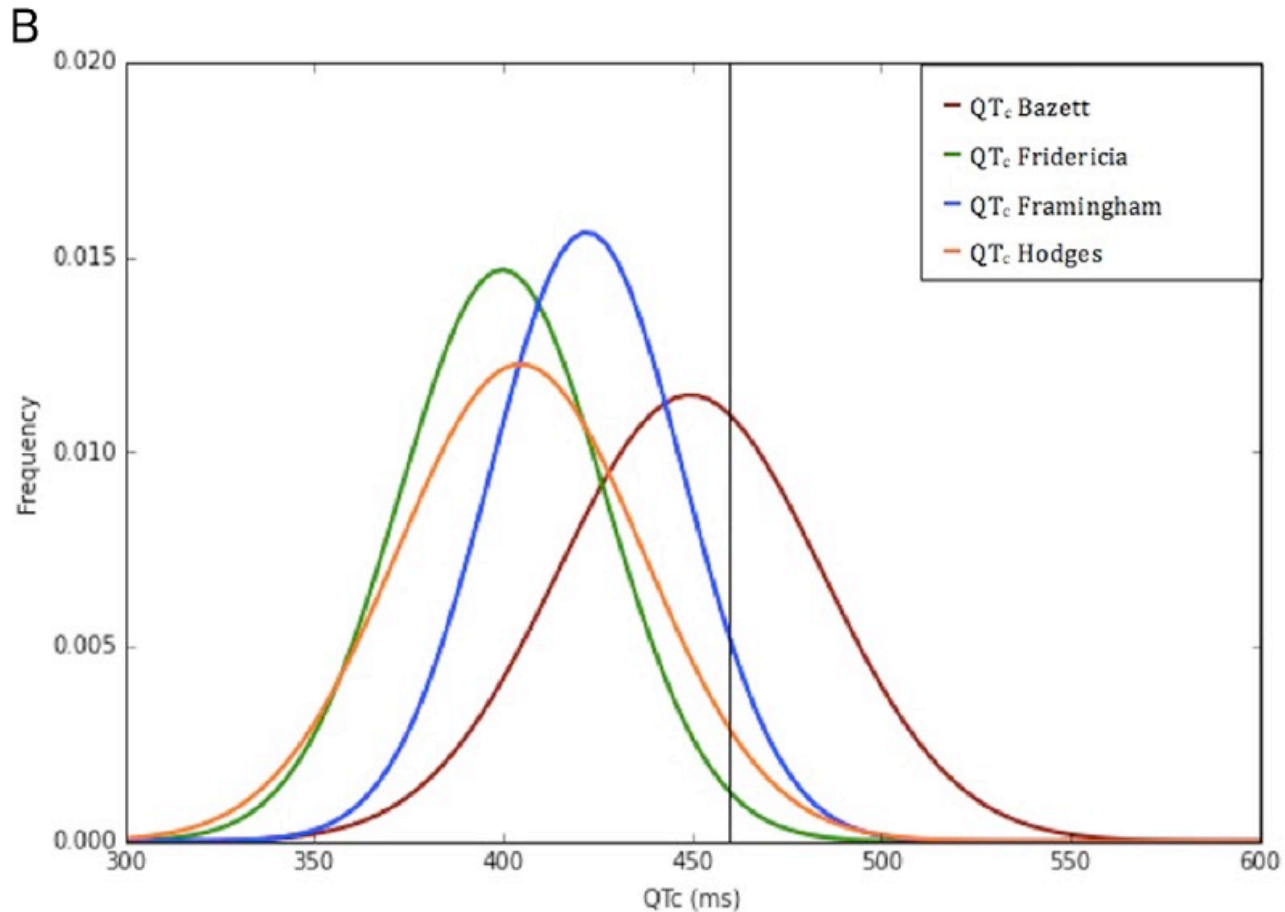


QT = 370 msec

Correction Formulae

Method	Formula
Bazett	$QTc = QT / \sqrt{RR}$
Fridericia	$QTc = QT / \sqrt[3]{RR}$
Framingham	$QTc = QT + 0.154 (1000 - RR)$
Hodges	$QTc = QT + 1.75(HR - 60)$

QTc Correction Methods



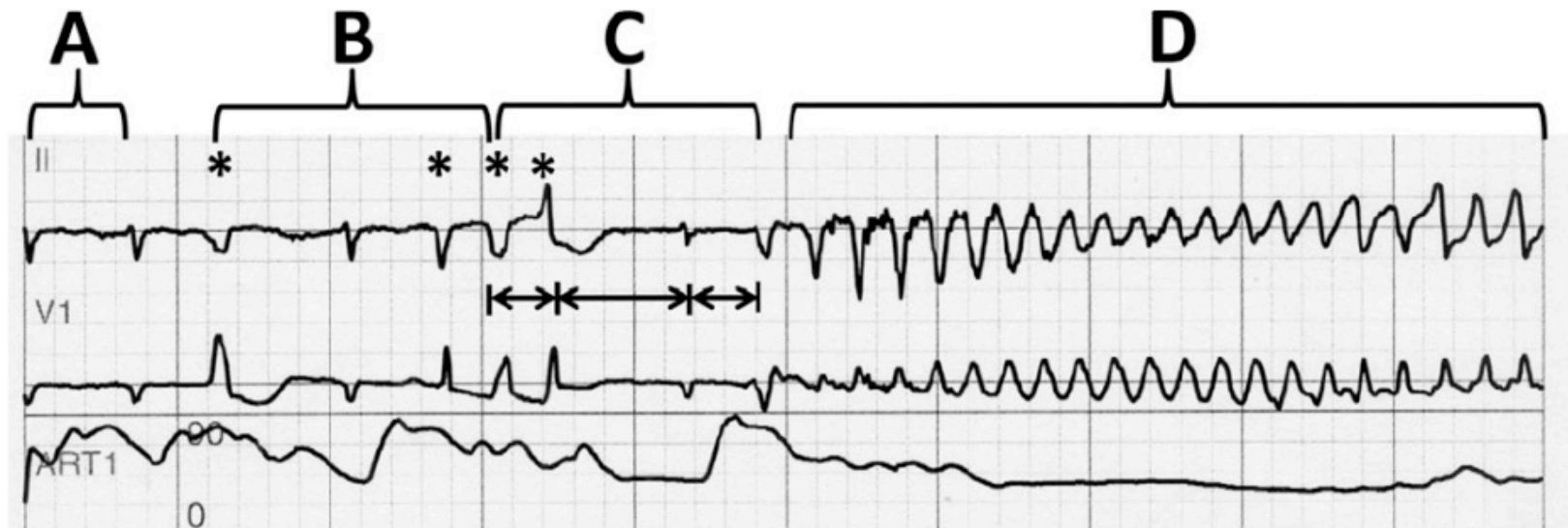
Normal Ranges

Rating	Adult Men	Adult Women
Normal	< 430 msec	< 450 msec
Borderline	431-450 msec	451-470 msec
Prolonged	> 450 msec	> 470 msec

However, we generally become more concerned if QTc > 500 msec.

Why do we worry about QTc prolongation?

- Torsades de pointes (TdP)
 - “Twisting of the points”
 - May lead to sudden syncope or dizziness



Risk Factors for QTc Prolongation

- Female gender
- Increased age
- Congenital Long QT Syndrome
- Structural Cardiovascular Disease
- Electrolyte abnormalities
- Hepatic dysfunction
- Other medications that prolong QTc
- Metabolic inhibitors

Psychiatric Medications and QTc

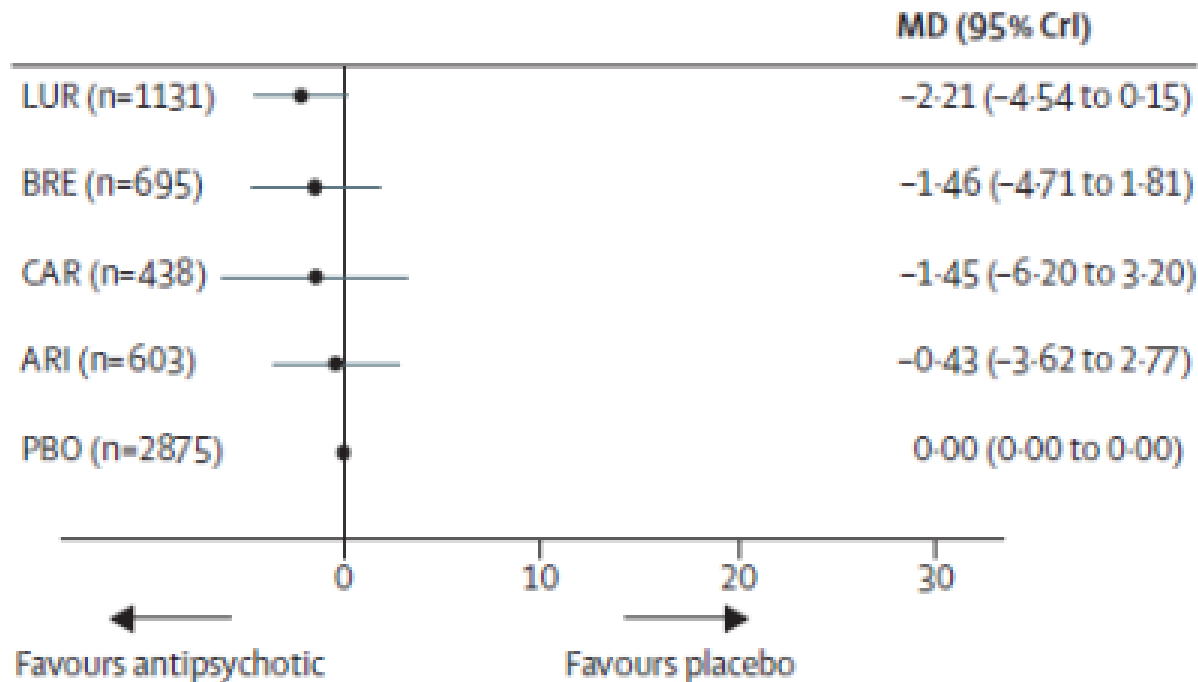
- Antipsychotic Medications
 - First Generation
 - Second Generation
- Antidepressants
 - SSRIs
 - Tricyclic Antidepressants
 - Atypical Antidepressants
- Other psychiatric medications

Antipsychotic medications

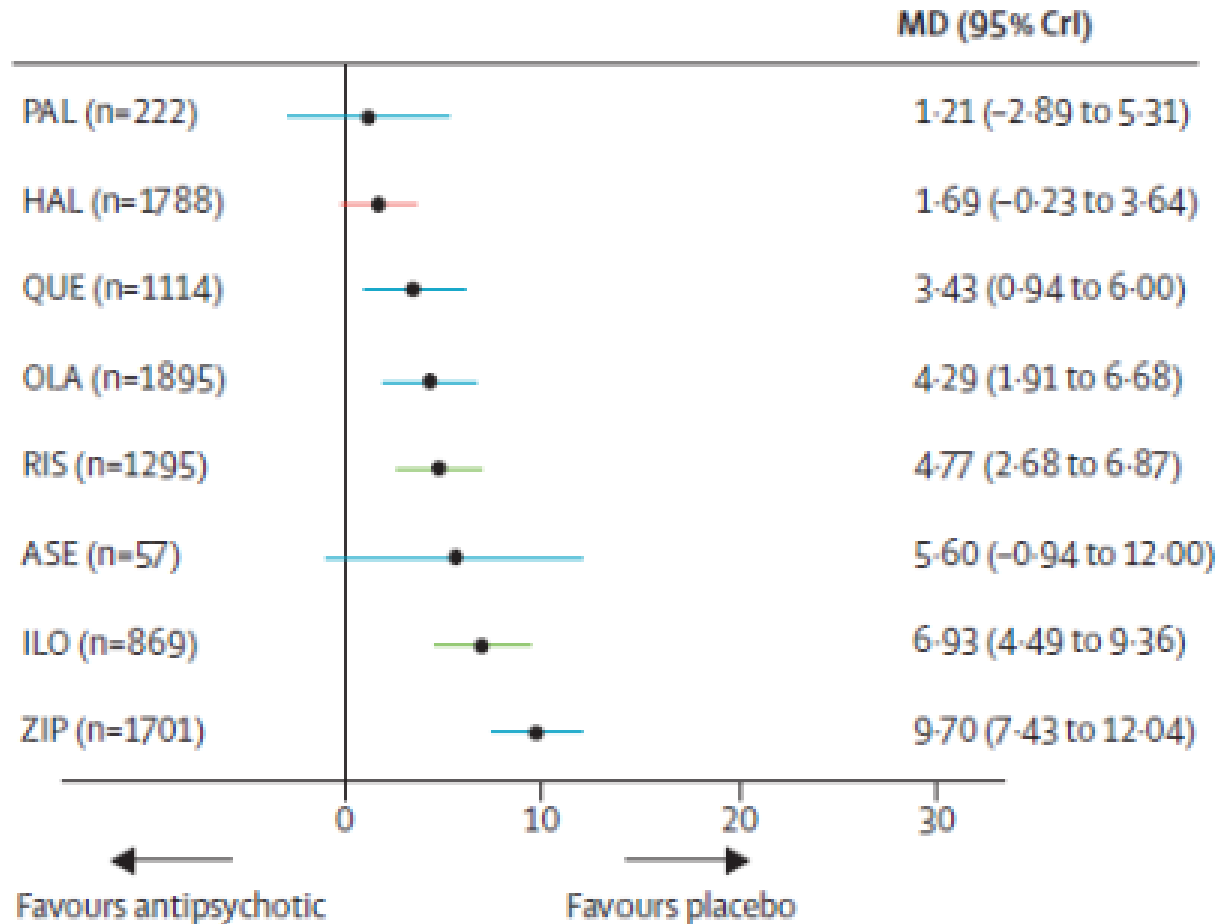
- Nearly all antipsychotics prolong QTc, but the degree of prolongation differs substantially among agents.
- Haloperidol
 - In oral form, haloperidol leads to QT prolongation that is similar to aripiprazole, quetiapine, and asenapine.
 - Intravenous form may lead to higher risk of QTc prolongation, with some caveats.
 - FDA recommends cardiac monitoring for patients receiving intravenous haloperidol.

Antipsychotic Medications

- Second generation antipsychotics



Antipsychotic Medications



Antipsychotic Medications

- Second generation antipsychotics
 - Highest risk: ziprasidone and iloperidone
 - Lowest risk: aripiprazole and lurasidone
 - FDA warnings
 - Ziprasidone (black box)
 - Quetiapine
 - Intravenous haloperidol
 - There may be a dose-response relationship for antipsychotics and QTc, but evidence is mixed.

Antipsychotic Medications and Mortality

- Both first- and second-generation antipsychotics have been linked to ventricular arrhythmias or sudden cardiac death.
 - Case-crossover study (N=17,718)
 - OR=1.53
 - Haloperidol, prochlorperazine, thioridazine, quetiapine, and risperidone were associated with increased risk.
- FDA black box warning for second-generation antipsychotics in elderly patients with dementia.

Antidepressants and QTc

- SSRIs
 - Initially thought to be quite safe
 - SADHART, ENRICHED, CREATE
 - FDA warnings:
 - Initial
 - Citalopram should not be prescribed at doses greater than 40mg
 - Citalopram should not be used at doses >20mg in those with liver dysfunction or over age 60
 - Revision
 - Citalopram is not recommended at doses greater than 40mg
 - Citalopram should be discontinued in anyone with QTc>500 ms

US FDA 2011, US FDA 2012

Citalopram and QTc

Medication and dose	QT prolongation (95% CI)
Citalopram 20mg daily	8.5 (6.2, 10.8)
Citalopram 40mg daily	12.6 (10.9, 14.3)
Citalopram 60mg daily	18.5 (16.0, 21.0)
Moxifloxacin 400mg daily	13.4 (10.9, 15.9)

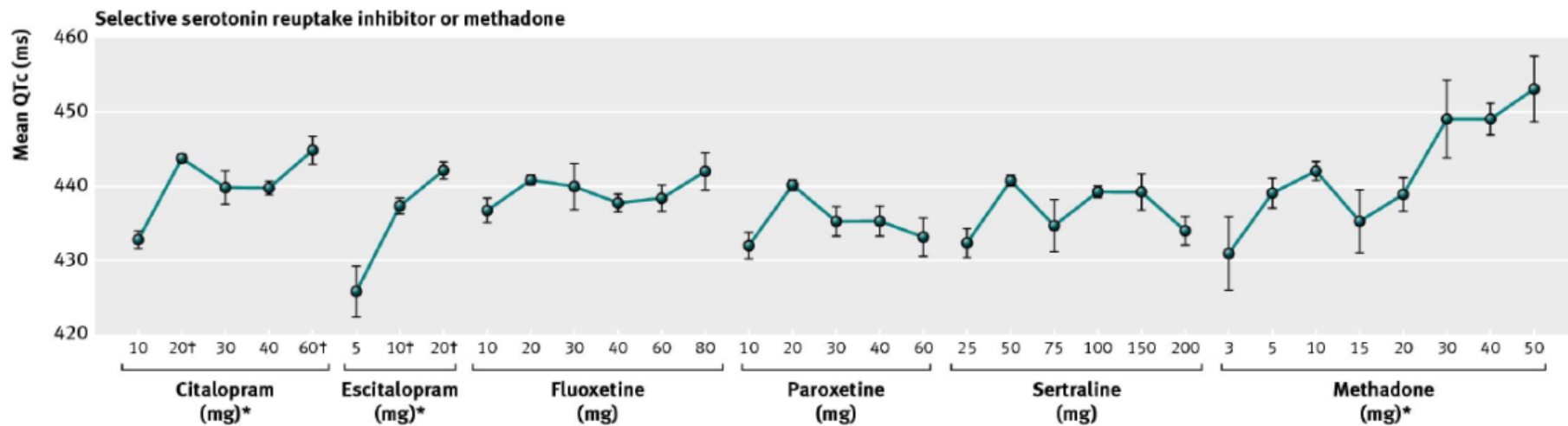
US FDA 2011

Escitalopram and QTc

Medication and dose	QT prolongation (95% CI)
Escitalopram 10mg daily	4.5 (2.5, 6.4)
Escitalopram 20mg daily	6.6 (5.3, 7.9)
Escitalopram 30mg daily	10.7 (8.7, 12.7)
Moxifloxacin 400mg daily	9.0 (7.3, 10.8)

US FDA 2012

Effects of SSRIs on QTc

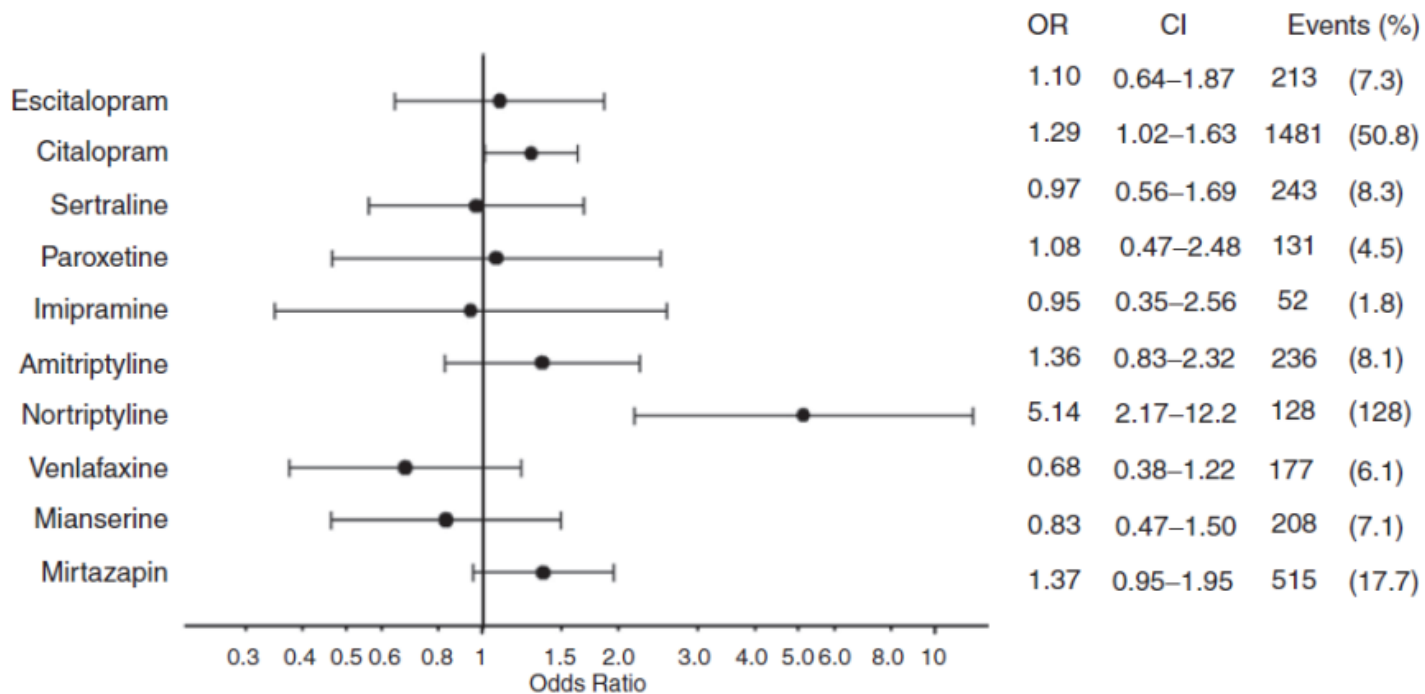


Effects of Antidepressants on QTc

Medication	N	Difference in QTc (ms)	p-value
Citalopram	696	10.58	.002
Escitalopram	360	7.27	<.0001
Fluoxetine	135	4.50	.32
Fluvoxamine	27	-5.00	<.0001
Paroxetine	1486	-1.04	.67
Sertraline	369	3.00	<.0001
SSRIs	3,079	6.10	<.001
TCAs	1,587	10.01	<.001

SSRIs and Ventricular Arrhythmias

- Evidence is less clear
 - Danish case-time-control study



SSRIs and Ventricular Arrhythmias

- Tennessee Medicaid Cohort Study
 - Retrospective cohort study of 54,220 patients receiving high dose citalopram (>40mg daily) or escitalopram (>20mg daily) or equivalent doses of other SSRIs.
 - Neither citalopram nor escitalopram had higher risks of sudden unexpected death or all-cause mortality than other SSRIs.
- Patient-level meta-analysis for escitalopram
 - Escitalopram led to mild 3.5msec increases in QTc, compared to placebo.
 - Rates of cardiovascular side effects were similar between escitalopram and placebo.

Tricyclic Antidepressants and QTc

- Tricyclic antidepressants
 - Affect sodium, calcium, and potassium channels
 - Generally are considered to be higher risk for QTc prolongation than SSRIs
 - Have other cardiovascular side effects as well

Atypical Antidepressants and QTc

- Venlafaxine
 - Minimal risk at therapeutic doses (1 case report), low risk in overdose (1%).
- Bupropion
 - Associated with QTc prolongation in overdose; possibly confounded by tachycardia
- Trazodone
 - Associated with mild QTc prolongation in overdose
- Mirtazapine
 - No clear QTc prolongation risk, though it has been associated with a higher risk of SCD or ventricular arrhythmias than paroxetine in one study
- Newest antidepressants (duloxetine, vilazodone, vortioxetine, levomilnacipran, desvenlafaxine, brexpiprazole)
 - Not associated with clinically meaningful QT prolongation

Beach 2013, Jasiak 2014, Allen 2020

Other Psychiatric Medications and QTc

- Lithium
 - Can cause QTc prolongation at levels > 1.2 mmol/L
- Anticonvulsants
 - Not associated with QTc prolongation
- Stimulants
 - Not associated with QTc prolongation
- Benzodiazepines
 - Not associated with QTc prolongation

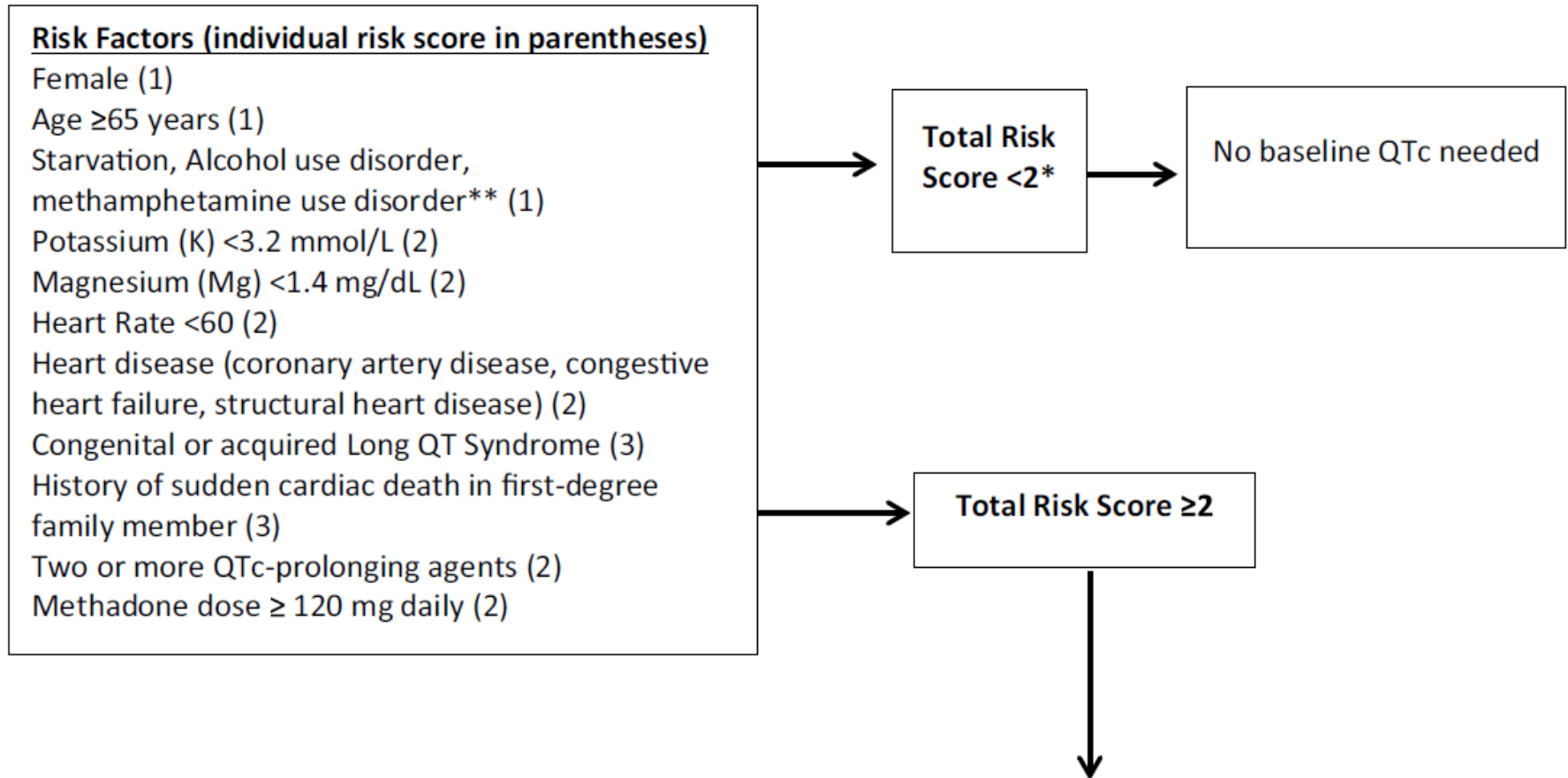
Skills for QTc Monitoring in Practice

- Know how to calculate a QTc on an ECG.
 - Do not rely on the QTc measured by the machine.
 - Use the Fridericia or Hodge's formula to correct for heart rate.
- Know the risk factors for QTc prolongation.
- Know which medications are higher-risk.
 - Antipsychotics: thioridazine, ziprasidone, possibly iloperidone
 - Antidepressants: citalopram, escitalopram, tricyclic antidepressants

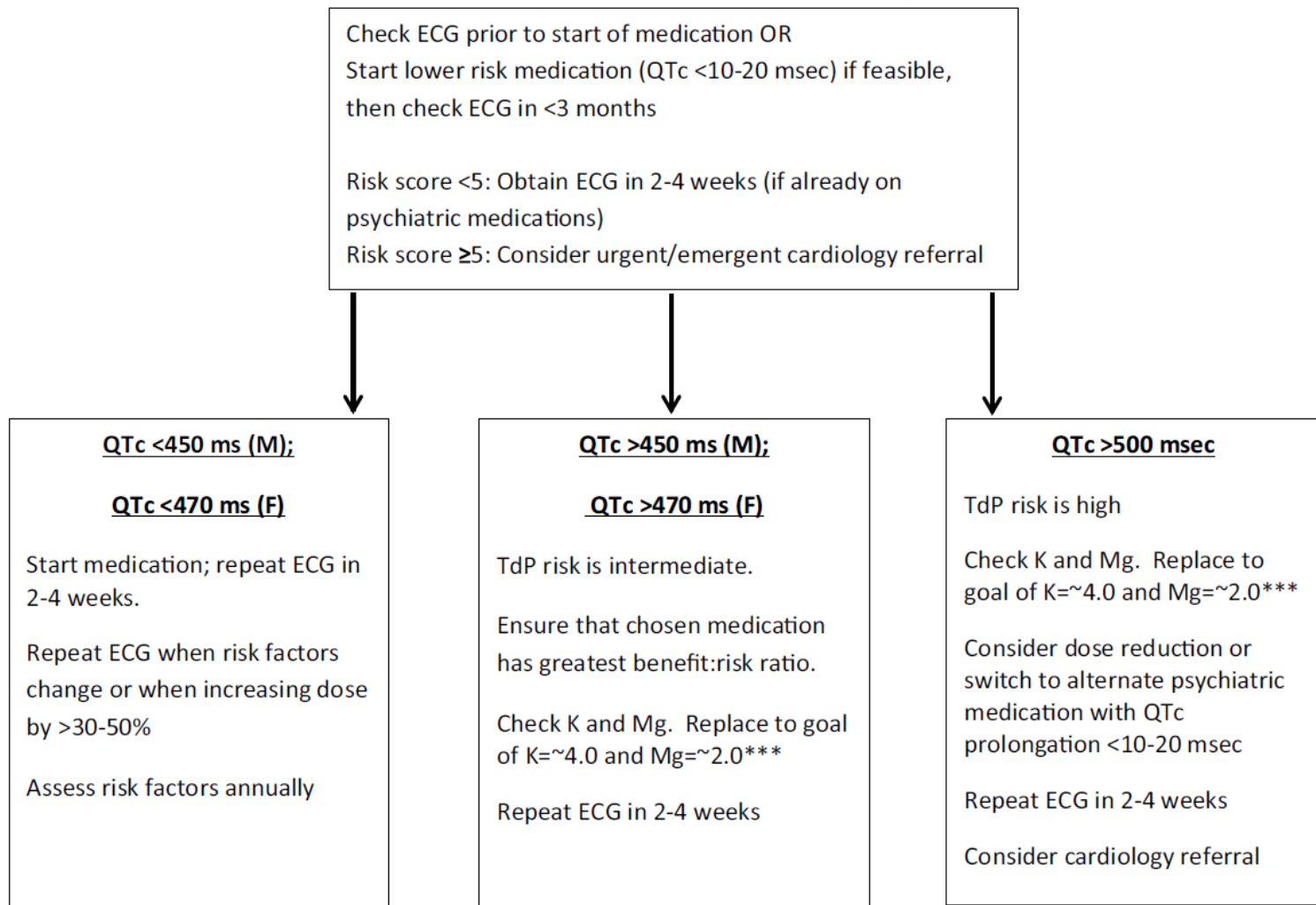
When to monitor QTc

- Know when to monitor QTc.
 - For patients without significant risk factors and on lower-risk medications, no monitoring is needed.
 - For patients with significant risk factors or on a higher-risk medication, check QTc at baseline, then again at steady-state or when risk factors change (e.g., change in dose).

Association of Medicine and Psychiatry Algorithm



Association of Medicine and Psychiatry Algorithm



Xiong 2020

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