Psychopharmacology and Cardiac Disease

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Psychological Factors and Cardiac Disease

- Link is bidirectional
  - Psychological factors common and portend worse outcomes
  - Some psychological conditions precede cardiac disease
  - Some treatments (Rx) can increase cardiac risk
- Mental disorders are associated with higher mortality
  - RR Mortality 2.22 mental disorders vs general population
  - 8million deaths worldwide attributable to mental disoders
- Cardiovascular disease is leading cause of mortality and a major public health burden

- APA, DSM-IV-TR, Washington, DC, 2000
- Walker ER, McGee RE, Druss BG. Mortality of Mental Disorders and Global Disease Burden Implications: A systematic Review and Meta-Analysis. JAMA Psychiatry. 2015, 72: 334-42
- Heidenreich PA, Trogdon JG, Khvjo OA, et al. Forecasting and Future Cardiovascular Statement from the AHA. Circulation 2011; 123:933-44.
- Piña IL, Di Palo KE, Ventura HE. Psychopharmacology and Cardiovascular Disease. JACC. 2018. Vol. 71, No. 20.

Rx<>Rx Interactions.

- Hospitalized patients:
  - 37% on psychotropic drugs
  - 27% psychiatric patients on CV drugs
- Majority of pharmacokinetic interactions involve cytochrome P450 enzymes
  - ~40 enzymes but ~6 responsible for >90% of Rx metabolism
    - CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4

- Ozturk Z, Turkylmaz A. Concominant Prescription of Psychotropic and Cardiovascular Drugs in Elderly Patients. Psychiatry Clin Psychopharmacology. 2017; 27: 374-9
- Lynch T, Price A. The Effect of Cytochrome P450 on Drug Response, Interactions, and Adverse Effects. American Family Physician. 2007; 76:391-6.
- Ogu CC, Maya JL. Drug Interactions Due to Cytochrome P450. Proceedings (Baylor University Medical Sciences). 2000: 13: 421-3.

TABLE 3 Clinically Significant Drug-Drug Interactions Among Psychotropic and Cardiovascular Drugs

Psychotropic Drugs	Cardiovascular Drugs	Interaction	Mechanism	Monitoring
Fluoxetine Fluvoxamine	Warfarin	Enhanced anticoagulant activity and increased risk for bleeding	Inhibitory effect of CYP2C9 mediated metabolism of warfarin	Signs and symptoms of bleeding
SSRIs* SNRIs* Vilazodone Vortioxetine	Antiplatelet agents* Anticoagulant agents*	Enhanced anticoagulant activity and increased risk for bleeding	Inhibition of serotonin uptake by platelets	Signs and symptoms of bleeding
Citalopram Escitalopram Fluoxetine Fluvoxamine Duloxetine Bupropion	Carvedilol Metoprolol Nebivolol Propranolol Timolol	Increased exposure of beta-blocker	Inhibitory effect of CYP2D6 mediated metabolism of beta-blocker	Heart rate; dose reduction of beta-blocker may be required
SSRIs* TCAs* Trazodone	Amiodarone Type Ia antiarrhythmic agents*	Increased risk for cardiotoxicity	Additive effects on QT interval	QT interval, Torsades de pointes
Fluvoxamine	Simvastatin	Increased plasma concentration of simvastatin	Inhibitory effect on CYP3A4-mediated metabolism of simvastatin	Signs and symptoms of myopathy and rhabdomyolysis
Alprazolam	Amiodarone	Increased bioavailability and pharmacodynamic effects of alprazolam	Inhibitory effect of CYP3A4 mediated metabolism of alprazolam	Enhanced drowsiness or fatigue, nausea, vomiting, or diarrhea
Mirtazapine	Warfarin	Increased INR	Unknown	Signs and symptoms of bleeding
Bupropion	Digoxin	Decreased plasma concentration of digoxin	Increased renal clearance of digoxin	Routine therapeutic drug level monitoring
TCAs*	Quinidine	Increased TCA exposure and risk for cardiotoxicity	Inhibitory effect of CYP2D6 mediated metabolism of TCA	Avoid combination or consider dose reduction of TCA
TCAs*	Sublingual NTG	Decreased absorption of NTG	Dry mouth inhibits oral absorption	Avoid combination
SSRIs*	Thiazide diuretics	Potential for severe hyponatremia	SSRI-induced SIADH in conjunction with thiazide sodium effects	Signs and symptoms of hyponatremia, routine sodium monitoring

*Class effect.

INR = international normalized ratio; NTG = nitroglycerin; SIADH = syndrome of inappropriate antidiuretic hormone release; other abbreviations as in Tables 1 and 2.

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TABLE 4 Overall Recommendations When Using Both Psychotropic and Cardiovascular Drugs

Carefully monitor blood pressure, especially in older patients.
Avoid orthostatic hypotension, which could worsen angina.
Data are not clear in the use of antidepressants after ACS. Consult a mental health expert before initiating antidepressant therapy.
SSRIs are preferred because of their low cardiac toxicity.
SSRIs and atypical agents have few side effects and can probably be used safely with cardiac drugs.
In chronic stable heart failure, SSRIs are safe to use. When a dose is uncertain, consult with a mental health expert.
In patients with heart failure, avoid episodes of hypotension with drugs such as TCAs.
Avoid MAO inhibitors because of multiple interactions and hypertensive episodes.
Avoid TCAs in patients with heart disease because of their proarrhythmic potential.
Avoid TCAs, along with nefazodone and trazodone, because of their QT prolongation, especially in patients at risk for ventricular arrhythmias.
Intermediate to long acting BZDs can be used as anxiolytics in patients with concomitant cardiac drugs but should be routinely evaluated for safety and efficacy.
Buspirone is a non-habit-forming anxiolytic that can be used long term with no significant cardiovascular adverse drug events.

ACS = acute coronary syndrome; MAO = monoamine oxidase; other abbreviations as in **Tables 1 and 2.**

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Antidepressants Effects on CV System: MAO I's

- Monoamine Oxidase Inhibitors
  - Increase available monoamines SE and Catecholamines
  - MAO-A and MAO-B, Reversible and Irreversible
    - Break down Monoamines and Tyramine
  - Tyramine Rich Foods
  - MAO Inhibitor and sympathomimetics or tyramine rich foods
    - -> Hypertensive Crisis

- Huffman, J. C., Celano, C. M., & Januzzi, J. L. (2010). The relationship between depression, anxiety, and cardiovascular outcomes in patients with acute coronary syndromes. *Neuropsychiatric Disease and treatment*, *6*, 123.
- Tahrier Sub Laban, Abdolreza Saadabadi. Monoamine Oxidase Inhibitors. Stat Pearls. [Internet] 2021, Aug. 6.

Antidepressants: TCA's

- Tricyclic Antidepressants
  - Varying degrees of Anti-cholinergic activity
    - [X] Muscarinic receptor = tachycardia
  - Varying degrees of alpha-1 receptor blockade
    - [X] = Hypotension

- Huffman, J. C., Celano, C. M., & Januzzi, J. L. (2010). The relationship between depression, anxiety, and cardiovascular outcomes in patients with acute coronary syndromes. *Neuropsychiatric Disease and treatment*, *6*, 123.

Antidepressants: SSRI's +SNRI's

- SSRI's
  - Well Established Safety Profile
  - NO significant HR or BP effects
  - But…
    - Paroxetine – some anti-Ach = tachycardia
    - Platelet effects: block platelet SE pump and decrease platelet aggregation and increase bleeding risk
      - Monitor if on blood thinning medications
- SNRI's (ie: venlafaxine, desvenlafaxine, duloxetine, levomilnacipran)
  - Also block NE reuptake and can lead to HTN

- Huffman, J. C., Celano, C. M., & Januzzi, J. L. (2010). The relationship between depression, anxiety, and cardiovascular outcomes in patients with acute coronary syndromes. *Neuropsychiatric Disease and treatment*, *6*, 123.

QT Prolongation and Antidepressants

- TCA's
  - Sodium channel blockade: weak Class 1a Antiarrhythmic:
    - Widen QRS and prolong QT
  - Significant at therapeutic doses especially if CV disease
  - Biggest offenders: Amitriptyline, Maprotiline.
  - Less offensive ? : Clomipramine
- SSRI's
  - Safe overall
  - Case reports for all agents (except paroxetine)
  - Citalopram:
    - STAR*D Trial: various dosing 40mg-60mg = No adverse cardiac evens
    - FDA 2011, 2014 advisories

- Beach SR, Celano CM, Noseworthy PA, Januzzi JL, and Huffman JC. (2013). QTc Prolongation, Torsdades de Pointes, and Psychotropic Medications. Psychosomatics, 54 (1), 1-13.
- Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., ... & Shores-Wilson, K. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR* D: implications for clinical practice. *American journal of Psychiatry*, *163*(1), 28-40.
- Rasmussen, S. L., Overø, K. F., & Tanghøj, P. (1999). Cardiac safety of citalopram: prospective trials and retrospective analyses. *Journal of clinical psychopharmacology*, *19*(5), 407-415.
- Lespérance, F., Frasure-Smith, N., Koszycki, D., Laliberté, M. A., van Zyl, L. T., Baker, B., ... & Guertin, M. C. (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *Jama*, *297*(4), 367-379.

QT and Citalopram

- FDA 2011:
  - 1) Citalopram should not be prescribed at doses >40mg/day
  - 2) Citalopram should not be used at doses >20mg if:
    - Significant liver disease
    - Age >60yo
- FDA 2012:
  - 1) Citalopram not recommended at doses >40mg
  - 2) Discontinue citalopram if QTc >500ms
- FDA QTc Study:
  - 20mg = 8.5ms
  - 40mg (?) = 12-13ms
  - 60mg = 18.5ms
    - Placebo controlled
    - Not published in peer review journal
    - ? How many patients >500ms
    - Other SSRI's NOT evaluated

- Food and Drug Administration (2011) FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide).
  Available: http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm.

QT and Citalopram (cont)

Castro, V. M., Clements, C. C., Murphy, S. N., Gainer, V. S., Fava, M., Weilburg, J. B., ... & Smoller, J. W. (2013). QT interval and antidepressant use: a cross sectional study of electronic health records. *Bmj*, *346*, f288.
Beach, S. R., Kostis, W. J., Celano, C. M., Januzzi, J. L., Ruskin, J. N., Noseworthy, P. A., & Huffman, J. C. (2014). Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation.
Witchel, H. J., Pabbathi, V. K., Hofmann, G., Paul, A. A., & Hancox, J. C. (2002). Inhibitory actions of the selective serotonin re-uptake inhibitor citalopram on HERG and ventricular L-type calcium currents. *FEBS letters*, *512*(1-3), 59-66.
Witchel, H. J., Pabbathi, V. K., Hofmann, G., Paul, A. A., & Hancox, J. C. (2002). Inhibitory actions of the selective serotonin re-uptake inhibitor citalopram on HERG and ventricular L-type calcium , currents. *FEBS letters*, *512*(1-3), 59-66.

- Dose dependent QT interval increase of 10-15ms
- Citalopram and Escitalopram statistically greater QT increase compared to placebo
- Citalopram separates from all other agents except escitalaorpam
- WHY?
  - Human Ether-A-Go-Go Gene effects.
- Citalopram delayed because of QT prolongation and arrhythmias…. In dogs.
- However:
  - Citalopram and risk of TDP
    - 5YR Study citalopram and sertraline: No increased TDP, arrhythmia or all cause mortality
      - Zivin, K., Pfeiffer, P. N., Bohnert, A. S., Ganoczy, D., Blow, F. C., Nallamothu, B. K., & Kales, H. C. (2013). Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *American Journal of Psychiatry*, *170*(6), 642-650.
    - Tennessee Medicaid Cohort Study
      - Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2017). High-dose citalopram and escitalopram and the risk of out-of-hospital death. *The Journal of clinical psychiatry*, *78*(2), 190.

So what to do with citalopram?

- Risk of TDP and ventricular arrhythmias appears not to be significant
- QTc may increase 10-20mg
- Lower doses may carry some risk (Tennessee Cohort Study)
  - Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2017). High-dose citalopram and escitalopram and the risk of out-of-hospital death. *The Journal of clinical psychiatry*, *78*(2), 190.

Escitalopram and QT

- FDA (QT) Study:
  - 10mg = 4.5ms
  - 20mg = (?)
  - 30mg = 11ms
  - Mean QT change of 3.5ms
    - K. G., Reines, E., & Kennedy, S. H. (2013). The cardiovascular safety profile of escitalopram. *European Neuropsychopharmacology*, *23*(11), 1391-1400.
- Tennessee Medicaid Cohort Study
  - No associated greater mortality
    - Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2017). High-dose citalopram and escitalopram and the risk of out-of-hospital death. *The Journal of clinical psychiatry*, *78*(2), 190.
- Thus….
  - Mild QT prolongation but unlikely clinically significant
    - Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2017). High-dose citalopram and escitalopram and the risk of out-of-hospital death. *The Journal of clinical psychiatry*, *78*(2), 190.

Other Antidepressants

- Venlafaxine: QT Prolongation in OD.
- Bupropion: QT prolongation in OD, confounded by tachycardia
- MIrtazapine: ? ^sudden death but decreased risk of CV events
- Duloxetine, vilazadone, desvenlafaxine, vortioxetine, levomilnacipran, brexpiprazole showed no clinically significant QT effects
- Thus…
  - No strong evidence of QT effects of other antidepressants

- Spindelegger, C. J., Papageorgiou, K., Grohmann, R., Engel, R., Greil, W., Konstantinidis, A., ... & Kasper, S. (2015). Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. *International Journal of Neuropsychopharmacology*, *18*(4).Jasiak, N. M., & Bostwick, J. R. (2014). Risk of QT/QTc prolongation among newer non-SSRI antidepressants. *Annals of Pharmacotherapy*, *48*(12), 1620-1628.

Review QT and Antidepressants

- SSRi's and magnitude of QT prolongation is small
  - Citalopram [X] if previous CV disease
  - Escitalopram = limited evidence of meaningful risk
  - High dose citalopram in specific populations
  - EKG recommendations with antidepressants:
    - Not needed in routine cases
    - Citalopram: EKG if risk factors

- Beach SR, Celano CM, Noseworthy PA, Januzzi JL, and Huffman JC. (2013). QTc Prolongation, Torsdades de Pointes, and Psychotropic Medications. Psychosomatics, 54 (1), 1-13.

Antipsychotics

- Atypical or second-generation antipsychotics
  - Bind 5HT receptors and DA receptors
  - Alpha-1 blockade: Risperidone, Quetiapine
  - Anti-Ach: Clozapine, Quetiapine, Olanzapine
  - Metabolic syndrome:
    - Most but Clozapine and Olanzapine are worst offenders

Clozapine

- Oldest "atypical"
  - Tachycardia (10%)
  - Orthostasis
  - HTN
  - Myocarditis
  - Cardiomyopathies

- Curto, M., Girardi, N., Lionetto, L., Ciavarella, G. M., Ferracuti, S., & Baldessarini, R. J. (2016). Systematic review of clozapine cardiotoxicity.*Current psychiatry reports*, *18*(7), 68.

Clozapine Myocarditis

- IgE hypersensitivity
- Most occur within 2-3mos
- Tend to be in otherwise healthy youth
- 0.1 -3% incidence
- Present with:
  - Tachycardia, dyspnea, nausea, fever, dizziness, CP, Flu-like
- Considerations:
  - W/in 2mos of start
  - No CV hx and s/sx of CV Dsfxn
  - Peripheral eos
  - ^Troponin
  - EKG changes
  - MRI… Bx
- Treatment: supportive, stop Clozapine, caution with rechallenge

- Curto, M., Girardi, N., Lionetto, L., Ciavarella, G. M., Ferracuti, S., & Baldessarini, R. J. (2016). Systematic review of clozapine cardiotoxicity. *Current psychiatry reports*, *18*(7), 68.

Clozapine Cardiomyopathy

- 1:2000
- Not associated with dose or rate of increase
- Usually occurs within 6-9 mos of initiating (but up to 6yrs)
- Most w/o previous CV history
- Symptoms: dyspnea, tachycardia, CP, fatigue, or sometimes few sx
- Dx: ECHO, ^BNP
- Mortality 12.5-25%
  - If EF>25%, best prognosis
- Rx:
  - Stop Clozapine
  - Supportive
  - NO NOT rechallenge

- Curto, M., Girardi, N., Lionetto, L., Ciavarella, G. M., Ferracuti, S., & Baldessarini, R. J. (2016). Systematic review of clozapine cardiotoxicity. *Current psychiatry reports*, *18*(7), 68.

QT Prolongation and Antipsychotics

- 1st generation > 2nd generation in general
- Thioridazine, chlorpromazine and mesoridazine (1st)
- Haloperidol
  - Somewhat controversial
  - Effect ~ 2nd generation drugs
  - Notable ^ risk fo ventricular arrhythmias and of sudden death
  - FDA:
    - 58 cases of QT prolongation
    - 54 cases TDP
    - 32 cases had CV disease
    - 39 cases on other QT prolonging drugs

Carrà, G., Crocamo, C., Bartoli, F., Lax, A., Tremolada, M., Lucii, C., ... & Castellazzi, M. (2016). First-generation antipsychotics and QTc: any role for mediating variables?. *Human Psychopharmacology: Clinical and Experimental*, *31*(4), 313-318.

QT Prolongation and Antipsychotics

- 2nd generation antipsychotics
  - Ziprasidone
    - FDA 2002:
      - [X] in patients on other QT prolonging drugs
      - [X] in patients with h/o cardiac arrhythmia
    - Prolongs QTc 10-21ms
    - Up to 20% may have QTc prolongation fo > 6oms
  - Iloperidone
  - Quetiapine
    - Avoid if on other QT prolonging drugs, Hx of arrhythmia or metabolic abnormalities
    - Upt to 20% QTc >20ms

- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., ... & Kissling, W. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*, *382*(9896), 951-962.
- Leonard, C. E., Freeman, C. P., Newcomb, C. W., Bilker, W. B., Kimmel, S. E., Strom, B. L., & Hennessy, S. (2013). Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *Journal of clinical & experimental cardiology*, (6), 1.

QT and Other 2nd Generation Antipsychotics

- Agents with limited QTc effects:
  - Aripirazole > Lurasidone >>Olanzapine > Risperidone > Clozapine
- In general…
  - Total QT prolonging drugs (polypharmacy), cumulative and relative doses matter

- Leonard, C. E., Freeman, C. P., Newcomb, C. W., Bilker, W. B., Kimmel, S. E., Strom, B. L., & Hennessy, S. (2013). Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *Journal of clinical & experimental cardiology*, (6), 1.
- Ozeki, Y., Fujii, K., Kurimoto, N., Yamada, N., Okawa, M., Aoki, T., ... & Kunugi, H. (2010). QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(2), 401-405.

Last Words on Antipsychotics and QT

- Hierarchy "Best to Worst"
  - Best: Aripirazole and Lurasidone
  - Worst: Ziprasidone, Iloperidone, Thioridazine, IV Haloperidol
- Recommendations:
  - Baseline EKG and at least one f/u and intermittently therafter
  - Attention to magnesium, potassium
  - What other QT prolonging meds are prescribed?
  - If QTc >50ms… consider alternative options

- Leonard, C. E., Freeman, C. P., Newcomb, C. W., Bilker, W. B., Kimmel, S. E., Strom, B. L., & Hennessy, S. (2013). Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *Journal of clinical & experimental cardiology*, (6), 1.
- Ozeki, Y., Fujii, K., Kurimoto, N., Yamada, N., Okawa, M., Aoki, T., ... & Kunugi, H. (2010). QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(2), 401-405.
- Rowland, R. H. (2014). Atypical antipsychotics are not all alike: side effects and risk assessment. *Journal of psychosocial nursing and mental health services*, *52*(9), 13-15.

Antipsychotics and Patients with Dementia

- FDA:
  - Antipsychotics are associated with increased mortality in patients with dementia
    - Due to cerebrovascular disease
    - Due to cardiac events
- Increased ventricular arrhythmia risk
  - It may not be correlated with QT prolongation
- Thioridazine, Quetiapine, Olanzapine, Risperidal, Haloperidol and Clozapine all have been associated with ~1.5x risk of ventricular arrhythmia and sudden death

- Salvo, F., Pariente, A., Shakir, S., Robinson, P., Arnaud, M., Thomas, S. H. L., ... & on behalf of Investigators, L. H. (2016). Sudden cardiac and sudden unexpected death related to antipsychotics: a meta-analysis of observational studies. *Clinical Pharmacology & Therapeutics*, *99*(3), 306-314.
- Wu, C. S., Tsai, Y. T., & Tsai, H. J. (2015). Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *Journal of the American Heart Association*, *4*(2), e001568.

Mood Stabilizers (Lithium and AEDs)

- Lithium
  - Associated with Sick Sinus Syndrome and AV Blockade
  - Limited QT prolongation in therapeutic range
    - >1.2 mmol/L can prolong QTc
    - F>M
    - Low potassium
- Carbamazepine
  - In overdose can slow AV conduction
  - May decrease QT at higher doses
- Oxcarbazepine shows no significant CV or QT effects
- Valproate is without significant CV effects and can decrease QT dispersion
- Lamotrigine shows no significant CV effects and decrease QT interval
- Topiramate and Gabapentin show no significant CV effects or QT effects.

- Beach, S. R., Celano, C. M., Noseworthy, P. A., Januzzi, J. L., & Huffman, J. C. (2013). QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics*, *54*(1), 1-13.
- Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet (London, England). 2000;355:1048-1052.
- Hsu, C. H., Liu, P. Y., Chen, J. H., Yeh, T. L., Tsai, H. Y., & Lin, L. J. (2005). Electrocardiographic abnormalities as predictors for over-range lithium levels. *Cardiology*, *103*(2), 101-106.
- Mamiya, K., Sadanaga, T., Sekita, A., Nabeyama, Y., Yao, H., & Yukawa, E. (2005). Lithium concentration correlates with QTc in patients with psychosis. *Journal of electrocardiology*, *38*(2), 148-151.

Other Psychiatric Medications

- Benzodiazepines:
  - Decreased catecholamine release
  - Decreased coronary vascular resistance
- Trazodone:
  - Alpha-1 Blockade and orthostasis
  - Active metabolite
  - Some QT prolongation and ^ arrhythmia risk (esp in OD)
    - Levenson, J. L. (1999). Prolonged QT interval after trazodone overdose. *American Journal of Psychiatry*, *156*(6), 969a-970.
    - Dattilo, P. B., & Nordin, C. (2007). Prolonged QT associated with an overdose of trazodone. *The Journal of clinical psychiatry*, *68*(8), 1309
- Stimulants:
  - No significant QT prolongation or TDP and no strong evidence of increased CV risk
  - Can increase HR and BP but seemingly to limited degree
  - FDA: recommend against use in patients with CV disease
    - Goodnick, P. J., Parra, F., & Jerry, J. (2002). Psychotropic drugs and the ECG: focus on the QTc interval. *Expert opinion on pharmacotherapy*, *3*(5), 479-498

Miscellaneous

- Acetylcholinesterase inhibitors (Donepezil, Donepezil transdermal, Galantamine, Rivastigmine):
  - Some risk of QT prolongation
  - Some increased risk of TDP
  - More risk in older patients and patients with multiple comorbidities

- Kitt, J., Irons, R., Al-Obaidi, M., & Missouris, C. (2015). Case Report: A case of donepezil-related torsades de pointes. *BMJ case reports*, *2015*.

- Opioids:
  - Methadone: significant risk of QT prolongation and TDP
  - Buprenorphine: seems to carry less QT risk

- Abramson, D. W., Quinn, D. K., & Stern, T. A. (2008). Methadone-associated QTc prolongation: a case report and review of the literature. *Primary care companion to the Journal of clinical psychiatry*, *10*(6), 470.
- Wedam, E. F., Bigelow, G. E., Johnson, R. E., Nuzzo, P. A., & Haigney, M. C. (2007). QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Archives of internal medicine*, *167*(22), 2469-2475..

Good Resources

- QT prolongation and medications:
  - https://www.crediblemeds.org/
  - Gören, J.L., Tuan Anh Dinh. Psychoytropics and Sudden Cardiac Death. RI Med J (2013) Mar 1; 96(3):38-41. (http://www.rimed.org/rimedicaljournal/2013/03/2013-03-38-cont-psychotropics.pdf)
- "Psychopharmacology and Cardiovascular Disease" JACC State-Of-The-Art-Review:
- https://reader.elsevier.com/reader/sd/pii/S0735109718341627?token=B397EF471C307B4AB6CA185C98161B7271BF2164EFEDB3196B1352893975AF54C651C4FC401B4FF6F4CF5D7C60080E4F&originRegion=us-east-1&originCreation=20220327224618

One more…

- European Heart Journal: https://academic.oup.com/eurheartj/article/35/20/1306/2293020