Anticholinergic, Sedative Burden, and LQTS

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Objectives

At the end of this activity, the learner should be able to:

• Explain the risks associated with anticholinergic and sedative medication use in older adults
• Compare and contrast methods for quantifying anticholinergic and sedative burden
• Apply basic electrophysiological concepts to the understanding of underlying mechanisms of QT prolongation and Torsade de Pointes
• Conduct a review of the predisposing factors to drug-induced Long QT Syndrome and apply these concepts to management of individual cases
Disclosure

• I, Lauren Steffen, declare to not have any real or apparent conflicts of interest or financial interests with any pharmaceutical manufacturers, medical device companies, or in any product or service, including grants, employment, gifts, stock holdings, and honoraria related to the content of this presentation.

• I am an employee of Tabula Rasa HealthCare

Each of the planning committee members has listed no financial interest/arrangement or affiliation that would be considered a conflict of interest.
Anticholinergic and Sedative Pathophysiology
Cholinergic Deficiency

Cholinergic pathway

Memory loss

Dementia

Neurotransmission disruption

Cholinergic neuron
Alterations in the Blood Brain Barrier
P-glycoprotein Activity Comparison: Young vs. Older Adults

P-glycoprotein activity in young & elderly subjects as a function of age

Vd of (R)-verapamil in brain in young & elderly subjects as a function of age
Anticholinergic and Sedative Pharmacology
The Anticholinergic Hypothesis

- Acetylcholinesterase inhibitor (e.g., donepezil) blocking breakdown of ACh
- ACh successfully binds to muscarinic receptor
- Anticholinergic drug (e.g., diphenhydramine) blocking ACh at receptor
- ACh successfully bound to acetylcholinesterase for breakdown

- ACh (i.e., Acetylcholine)
- Acetylcholinesterase (enzyme responsible for acetylcholine breakdown)
- Acetylcholinesterase inhibitor (e.g., donepezil)
- Acetylcholine muscarinic receptor
- Anticholinergic drug (e.g., diphenhydramine)
Anticholinergic Hypothesis

• Most anticholinergics interact with muscarinic ACh receptors
  • A few can also affect the nicotinic ACh receptors (e.g., glycopyrrolate)

• The anticholinergic activity expressed by a drug is directly related to its potential to bind to muscarinic ACh receptors

• Presuming the cholinergic hypothesis is correct then one would expect the elderly & those with AD to be especially sensitive to the cognitive impairing effects of anticholinergic drugs
  • Indeed, substantial data to support this premise have been published
Anticholinergic Drug Interactions

- Clinically-important drug-drug interactions
  - Cholinergic / muscarinic agonists – Pharmacodynamic
    - Direct: Bethanechol
    - Indirect: Acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine)

- CYP450-mediated drug interactions (competitive inhibition) – Pharmacokinetic
  - Drug specific

- Clinically-important drug-disease interactions
  - Benign prostatic hyperplasia
  - Constipation
  - Dementia
  - Glaucoma (narrow-angle)
Multiple CNS Mechanisms

• Agonism of the benzodiazepine receptor (GABA-A complex)
  • Benzodiazepines & barbiturates

• Antagonism of histamine H1 receptors
  • Antihistamines, antipsychotics, & TCAs

• Binding to the μ-opioid receptor
  • Opioids

• Antagonism of α1-adrenergic receptors
  • Antipsychotics

• Blockage of muscarinic receptors
  • Smooth muscle relaxants (urinary antispasmodics)
Sedative Drug Interactions

• Clinically-important drug-drug interactions
  • CNS effects – Pharmacodynamic
    • Concomitant administration with other drugs that cause CNS depression
    • e.g., Opioid + Benzodiazepine + Antidepressant
  • Respiratory effects – Pharmacodynamic
    • Concomitant administration with other drugs that cause respiratory depression
    • e.g., Opioid + Benzodiazepine
  • CYP450-mediated drug interactions (competitive inhibition) – Pharmacokinetic
    • Drug specific (e.g., opioids are weak substrates for the CYP2D6 isoenzyme)

• Clinically-important drug-disease interactions
  • Use of opioids in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve
    • COPD, cor pulmonale, morbid obesity
  • Use of sedative drugs in patients at high-risk for falls
    • History of falls, orthostatic hypotension, syncope
Reduced functional activity of this efflux transporter in older adults exposes the brain to higher levels of drug substrates such as antidepressants (e.g., amitriptyline, venlafaxine), potentially resulting in prolonged and/or more pronounced sedation.

Glucose Transporter 1 (GLUT-1)

Large-neutral Amino Acid Transporter 1 (LAT-1)

Organic Anion Transporter Protein B1 (OATP1B1)

P-glycoprotein (P-gp)
Adverse Effects of Anticholinergic and Sedative Medications
Older Adults’ Susceptibility to Adverse Effects

• Older adults are particularly vulnerable to anticholinergic and sedative-related adverse effects for several reasons:
  • They have a high probability of being exposed
  • High medical comorbidity & polypharmacy

• They are more sensitive to experience serious effects
  • Especially cognitive adverse effects (e.g., gait instability & falls)

• Age-related physiological changes
  • Increase in blood-brain barrier permeability
  • Decline in hepatic drug metabolism and renal drug clearance
  • Reduction in central cholinergic activities (i.e., decreased neurons & receptors, decreased acetylcholine-mediated transmission)
  • Increase in % of adipose tissue (increased distribution of lipophilic drugs, e.g., diazepam)

Anticholinergic Toxidrome

“Blind as a Bat”
- Dilated pupils
- Mydriasis

“Hot as a Desert”
- Hyperthermia

“Mad as a Hatter”
- Confused

“Dry as a Bone”
- Dry mouth
- Urinary retention

“Red as a Beet”
- Flushed skin

Tachycardia

Absent bowel sounds

Anticholinergic Risks

• Agitation / delirium
  • Onset or worsening BPSD
  • Loss of independence
  • Institutionalization

• Cardiac dysrhythmias
  • Arrhythmias

• Constipation
  • Fecal impaction
  • Paralytic ileus
  • Pain

• Urinary retention
  • Increased UTI
  • Loss of independence
  • Acute kidney injury (AKI)

• Dry mouth
  • Dysphagia
  • Dental caries
  • Impaired communication

• Blurred vision (ACB) + Dizziness (SB)
  • Gait disturbances / falls

Sedative Risks

- Daytime sleepiness
  - Sedentary
  - Social isolation

- Memory impairment
  - Anterograde amnesia

- Depression

- Blurred vision (ACB) + Dizziness (SB)
  - Gait disturbances / falls

- Dependence
  - Physical
  - Psychological

- Tolerance
  - Abuse
  - Withdrawal

Anticholinergic Morbidity

• Cause or worsen cognitive impairment & delirium
  • Myriad studies have found a significant association between anticholinergic burden and either cognitive impairment or delirium

• Increase the risk of dementia & Alzheimer’s Disease
  • Recent publication (2019): Exposure to drugs with strong anticholinergic properties, such as antidepressants, bladder antimuscarinic drugs, anti-Parkinson drugs, and antiepileptic drugs are associated with an increased risk of dementia (approx. 50%).
  • Higher cumulative anticholinergic drug use is associated with incident dementia (2015)
    • The risk was statistically significant among patients with the highest exposure (dementia: adjusted HR, 1.54 [95% CI, 1.21-1.96]; Alzheimer’s disease: adjusted HR, 1.63 [95% CI, 1.24-2.14]) compared with those with no use

Anticholinergic Morbidity

• Drugs with moderate to strong anticholinergic activity
  • Associated with brain atrophy
    • Whole brain & temporal lobe atrophy
    • In cognitively normal older adults
  • Associated with poorer cognition (e.g., immediate memory recall & executive function) and reduced glucose metabolism
  • The effect appeared additive
    • An increased anticholinergic burden was associated with worsening executive function & increased brain atrophy

Anticholinergic Morbidity

• Higher anticholinergic burden is significantly associated with falls
  • In a longitudinal study of community-dwelling older adults >65 years without dementia, in men, the use of drugs with definite anticholinergic activity was associated with greater risk of subsequent injurious falls (aRR, 2.55 [95% CI, 1.33-4.88])

• Recent study (2015) reveals 16% greater risk of injury in older adults currently using anticholinergic drugs compared with non-users
  • Included falls (with injury) but not exclusively injuries as a result of falls
Anticholinergic Morbidity

- Possibly cause pneumonia
  - New study reveals link between anticholinergic drug use and CAP
    - Acute & chronic use
    - Low- & high-potency drugs
  - Possible mechanism involves:
    - Sedation & altered mental status
    - May contribute to poor pulmonary hygiene, atelectasis & aspiration

- Increase risk of hospitalization
  - When using $\geq 2$ anticholinergic drugs

Anticholinergic Mortality

• Association with increased risk of death has been reported
  - In a longitudinal study of community-dwelling and institutionalized participants, two-year mortality was greater for those taking definite & possible anticholinergics
    - Definite anticholinergics: OR, 1.68 (95% CI, 1.30-2.16), P<.001
    - Possible anticholinergics: OR, 1.56 (95% CI, 1.36-1.79), P<.001
    - For every additional point (above 5) scored on the ACB tool, the odds of dying increased by 26%

Sedative Morbidity

- Increase risk of cognitive decline / impairment
  - Complex relationship with other risk factors
  - In the Health, Aging and Body Composition Study, researchers found that combined use of CNS medications was associated with cognitive decline (adjusted HR, 1.37 [95% CI, 1.11-1.70]) over 5 years
  - Further, longer duration (adjusted HR, 1.39 [95% CI, 1.08-1.79]) & higher doses (adjusted HR, 1.87 [95% CI, 1.25-2.79]) of CNS medications conferred greater risk

- Increase risk of delirium
  - Paradoxical aggressive or hyperactive behavior


Medication Risk Identification and Mitigation
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Sedative Morbidity

- Cause or worsen physical inactivity
- Decline in muscle strength
- Reduced balance & mobility
- Impaired performance in ADLs/IADLs
- Increased risk of falling & fractures

- A threat to independent living among older adults
  - Large-scale studies indicate that sedative-hypnotics increase the risk of postural instability, falls and fractures in the elderly
  - Non-benzodiazepine sedative-hypnotics do not appear to be safer

Sedative Morbidity

• Cause or contribute to motor vehicle accidents
  • In a study of 72,685 drivers involved in injury-related road traffic accidents, the risk of being responsible for a traffic accident was higher in users of benzodiazepine hypnotics (OR, 1.39 [1.08-1.79]; P<0.01)  
  • Plausibly related to impaired physical function (e.g., poorer performance in coordination, grip strength and/or mobility)

• Risk of respiratory failure, particularly in susceptible patients
  • Chronic obstructive pulmonary disease (COPD)
    • In a matched case-control study, the use of benzodiazepine receptor agonists was associated with an increased risk of respiratory failure (adjusted OR, 1.56 [95% CI, 1.14-2.13])

Sedative Morbidity

• Increase risk of ED visits and hospitalizations
  • ADEs from the therapeutic use of psychiatric medications are responsible for nearly 90,000 ED visits annually in the United States, and almost 1 in 5 of those ED visits (19.3%, 95% CI, 16.3%-22.2%) results in hospitalization
  • Among psychiatric medications, antidepressants, antipsychotics, and anxiolytics and sedatives are the most implicated
  • The majority of ADE-related ED visits caused by psychiatric medications are from ADRs and unintentional overdoses or supratherapeutic dosages

Sedative Mortality

• No association overall
  • Between sedative drug use and mortality

• Certain drug classes
  • Antipsychotics have been linked to an increased risk of death (in dementia)
    • Plethora of good-quality evidence
    • A meta-analysis of 15 placebo-controlled trials, 10 to 12 weeks in duration and enrolling 5,110 patients, revealed a risk of death in antipsychotic users of approximately 1.6 times the risk of death in patients using placebo
    • Risk is greatest in the first 30 days
    • Nevertheless, risk appears to be unrelated to sedative effects (i.e., sudden death)
  • Results of studies with other sedative drugs in comparison are inconsistent

Sedative Mortality

• Overdose deaths

• In 2010, the latest year for which these data are available, there were 38,329 drug ODs in the United States; most (57.7%; 22,134) involved pharmaceuticals

• Of the pharmaceutical-related overdose deaths, the majority (74.3%; 16,451) were unintentional

• Opioids (75.2%; 16,651), benzodiazepines (29.4%; 6,497), and antidepressants (17.6%; 3,889) were the pharmaceuticals most commonly involved in these overdose deaths

• Further, among overdose deaths involving opioids, the pharmaceuticals most often also involved in these deaths were benzodiazepines (30.1%; 5,017), antidepressants (13.4%; 2,239), and antipsychotics and neuroleptics (4.7%; 783)

Quantifying Drug Burden
Basis of Drug Burden

- Different drugs, even within similar drug classes, have varying degrees of anticholinergic and sedative activity
  - Affinity for muscarinic (anticholinergic) & other receptors (sedative)

- Some drugs have well-recognized activity
  - First-generation antihistamines (e.g., diphenhydramine)
  - Urinary antispasmodics (e.g., oxybutynin)
  - Anticholinergics (e.g., hyoscyamine)
  - Opioids (e.g., morphine)
  - Anesthetics
  - Benzodiazepines & sedative hypnotics

Basis of Drug Burden

• However, clinicians may not be aware that some commonly used drugs also have anticholinergic activity
  • Anticoagulants (e.g., warfarin)
  • Antidepressants (e.g., paroxetine)
  • Diuretics (e.g., furosemide)

• They also may not realize that using multiple drugs with weaker activity can be additive and/or synergistic
  • Also there may be a cumulative effect (i.e., exposure [dose & duration])
Methods for Quantifying

**Anticholinergic Burden**
- Serum anticholinergic activity (SAA) assay
- In vitro measurements
  - Anticholinergic activity
  - Muscarinic receptor affinity
- Expert-based tools
  - Anticholinergic Cognitive Burden (ACB)
  - Anticholinergic Risk Scale (ARS)
  - Anticholinergic Drug Scale (ADS)

**Sedative Burden**
- Expert-based tools
  - Sedative Load Model
  - Sloane Model
  - Drug Burden Index
  - CNS Drug Model
Expert-Based Tools

• Based on experts’ experiences & opinions combined with available drug information (e.g., adverse effects, pharmacology)

• Simple list of drugs with known & different degrees of anticholinergic & sedative activity
  • Help clinicians decide the degree of risk a drug & combination of drugs may pose for individual patients

• May be the only method clinically useful for assessing the central or cognitive effects of drugs

Expert-Based Tools: ACB

- Prioritizes ranking criteria
  - Drugs with cognitive adverse effects and those that permeate the BBB
  - Drugs with peripheral anticholinergic activity also are included
  - Excludes topical, ophthalmic, otologic & inhaled drug preparations

- Uses categorical scoring
  - Possible anticholinergics = score of 1 (mild)
    - Score of 1 – in vitro data (i.e., SAA or affinity for muscarinic receptors but little to no clinically relevant effects)
  - Definite anticholinergics = score of 2 or 3
    - Score of 2 – clinical anticholinergic effect (moderate)
    - Score of 3 – drug may cause delirium (severe)

Expert-Based Tools: ACB

- Cumulates on numerical scoring
  - Sum (∑) drug scores for a cumulative ACB
- Clinically meaningful scores
  - ACB score ≥3
### Expert-Based Tools: Sedative Burden

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Sedative Load Model</th>
<th>Sloane Model</th>
<th>Drug Burden Index (if applicable)</th>
<th>CNS Drug Index (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional antipsychotics</td>
<td>rating: 2</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>Tricyclic antidepressants and non-selective MAO inhibitors</td>
<td>rating: 2</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>SSRIs</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>Second generation antidepressants</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>rating: 2</td>
<td>rating: 6</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Other anxiolytics and hypnotics (clomethiazole, valerian, barbiturates, first generation antihistamines, buspiron, chloral hydrate)</td>
<td>rating: 2</td>
<td>rating: 3</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Opioids</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>included</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Antiemetics (metoclopramide, scopolamine)</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Antispasmodics with psychotropics</td>
<td>rating: 1</td>
<td>no</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Centrally acting muscle relaxants</td>
<td>rating: 1</td>
<td>no</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Anticholinergic anti-parkinson drugs</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>included</td>
<td>not included</td>
</tr>
<tr>
<td>Indomethacin (with ethylmorphine)</td>
<td>rating: 1</td>
<td>rating: 3</td>
<td>not included</td>
<td>not included</td>
</tr>
<tr>
<td>Other drugs scored in a model</td>
<td>Xanthines, antitussives with sedating components and antiemetics and drugs for dizziness incl. psychotropics, anticholinergic drops for eyes: rating 1</td>
<td>donepezil, atenolol, clonidine, levodopa, doxazosin, terazosin, prazosin: rating 1</td>
<td>wide range of other anticholinergic drugs*</td>
<td>not included</td>
</tr>
</tbody>
</table>

Expert-Based Tools: Sedative Burden

• Assigns sedative ratings categorically
• Bases ratings on drug characteristics
  • Primary sedatives = rating of 2
  • Prominent side effect = rating of 1
• Cumulates on numerical scoring
  • Sum (Σ) drug scores for a sedative load
• Clinically meaningful scores
  • SLM score ≥3
  • ≥2 CNS-active drugs (e.g., Beers criteria)

Limitations of Methodologies

• Hundreds of drugs are thought to have anticholinergic and/or sedative activity and, thus, these methods may not be all inclusive
  • Non-prescription drugs, namely herbals & supplements, may are not captured in these methods
• There are individual differences in pharmacodynamics, pharmacokinetics, especially drug interactions, and blood-brain barrier permeability that are not accounted for in these methods
  • Similarly, drug dosages can affect receptor potency yet may not be accounted for in these methods
• Endogenous factors affect physiologic activity
Limitations of Methodologies

- Most clinically relevant but least standardized method (subjective)
  - Depends on the expert’s perspective, knowledge & experience
- Not routinely updated
- The combination of drug lists & clinical tools, such as the MMSE, is not sensitive enough to detect mild drug-induced cognitive changes
- Intra-class variation in regard to drug activity is not accounted for (e.g., some antidepressants / antipsychotics are more sedating than others within the drug class)
  - Should we be rating individual drugs on their anticholinergic/sedative potential?
Limitations of Methodologies

• Do not include doses of drugs
  • The presence of dose-response relationship is commonly regarded as evidence for causality of an ADR (i.e., Naranjo)

• May or may not take into account PRN usage
  • Commonly, sedative drugs are used PRN by older adults

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse event reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE: [ ]

Utility of Methodologies

- Expert-based tools are simple lists of medications with individual anticholinergic & sedative activity scores
  - Can be incorporated into clinical decision support (CDS) systems to determine cumulative drug burden

- These tools could be used as a component of MTM services to identify older adults who are at higher risk for potential anticholinergic and sedative effects
  - Pharmacists are ideally positioned to address or prevent unintended sequelae of drug burden & preserve the QoL and overall health status of older patients
While several scales are available to quantify anticholinergic burden, the ACB scale prioritizes ranking drugs with ___________ adverse effects?
Take-Away Points

• Drugs with anticholinergic and sedative properties can negatively affect cognitive & physical function in older adults considerably
  • Associated with poor outcomes
  • Threat to independent living

• Knowing a patient’s medication risk aids in personalizing a medication care plan
  • A tailored, systemic approach can reduce anticholinergic and sedative burden
Aggregated Long QT Syndrome
ECG and Electrical Activity of the Myocardium

1. Atrial depolarization begins
2. Atrial depolarization complete
3. Ventricular depolarization begins, Atria repolarize
4. Ventricular depolarization complete
5. Ventricular repolarization begins
6. Ventricular repolarization complete

- Orange = Depolarization
- Green = Repolarization
ECG of Prolonged QT Interval

- PR Interval
- QRS Complex
- ST Segment
- J-Point
- Prolonged QT Interval

- P Wave
- Q Wave
- R Wave
- S Wave
- T Wave
Which of the following is a risk factor for developing Torsade de Pointes?

- Bradycardia
- Hyperkalemia
- Aspirin use
- Male gender
Predisposing Factors to Torsade de Pointes

- Bradycardia, pause
- Gender and Age
- Hypokalemia
- Hypomagnesemia
- Diuretics
- Antiarrhythmics
- QT prolonging drugs
  - Drug-drug Interactions
- Comorbidities
- QTc interval
Risk Factor: Bradycardia

Caution with β-blockers in elderly patients

---

Risk Factor: Bradycardia

Risk Factor: Pause

Increase in the heterogeneity of repolarization times, increases the likelihood of reentrant excitation.
Risk Factor: Gender and Age

• Research is being done into relationship of hormone status to Long QT Syndrome
  • Theory that sex differences in QTc interval is due to the effects of testosterone causing QTc shortening in males
  • Similar QTc intervals are seen in both men and women once they reach 50 years old
  • Regardless, men and women have been found to respond similarly when given QTc-prolonging medications
Predisposing Factors to Torsade de Pointes

- Bradycardia, pause
- Gender and Age
- Hypokalemia
- Hypomagnesemia
- Diuretics
  - Hypokalemia – Loop diuretics and Thiazides
  - Block IKs – Indapamide, Triamterene
- Antiarrythmics
- QT prolonging drugs
  - Drug-drug Interactions
- Comorbidities
- QTc interval
What is an important factor to consider when looking at a medication's potential to cause Torsade de Pointes?

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 for block of Na+/K+ exchanger</td>
</tr>
<tr>
<td>Effect on LDL-C</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>Effect on Mg2+ current</td>
</tr>
</tbody>
</table>
## Risk Factor: Antiarrhythmics

<table>
<thead>
<tr>
<th>Class III</th>
<th>Class IA</th>
<th>Class IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>Quinidine</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Procainamide</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Disopyramide</td>
<td></td>
</tr>
<tr>
<td>Bretylium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Predisposing Factors to Torsade de Pointes

- Bradycardia, pause
- Gender and Age
- Hypokalemia
- Hypomagnesemia
- Diuretics
  - Hypokalemia – Loop diuretics and Thiazides
  - Block IKs – Indapamide, Triamterene
- Antiarrythmics
- QT prolonging drugs
  - Drug-drug Interactions
- Comorbidities
- QTc interval
Risk Factor: QT-Prolonging Drugs

- Non-antiarrhythmics have also been shown to cause QT-prolongation
  - Mostly due to IKr blockade
  - Examples: ciprofloxacin, citalopram, haloperidol, vandetanib
- Important to consider both pharmacokinetic + pharmacodynamics Drug-Drug Interactions
  - Pharmacokinetics – Long QT-JT Index is input into the Long QT-JT Score
Risk Factor: QT-Prolonging Drugs

• Long QT-JT Index analyzes 160+ drugs associated with risk of drug-induced Torsade de Pointes with known $IC_{50}$ values for HERG ($I_{Kr}$) block to give a numerical value associated with risk

• Considers:
  • $IC_{50}$ for block of $I_{Kr}$ or $I_{Ks}$
  • Nav1.5 and Cav1.2 currents
  • $C_{max}$ at a test dose
  • Maximum daily dose
  • Protein binding
  • Drug-drug Interaction Coefficient (DDIC)
Risk Factor: QT-Prolonging Drugs

Drug-drug interaction coefficient (DDIC)
• High extraction drugs (1/F)
• Low extraction drugs (100/(100-MP))
  • where MP is the relative contribution of major metabolic pathways to drug clearance (CL) as:

\[
CL = CL_{\text{ren}} + CL_{1A2} + CL_{2B6} + CL_{2C9} + CL_{2C19} + CL_{2D6} + \\
CL_{3A4} + CL_{3A5} + CL_{\text{transporters}} + CL... 
\]
Drug-Specific Risk of diLQTS

CredibleMeds, AZCERT, by Woosley RL and Romero KA categorized >150 drugs associated with risk of drug-induced Torsade de Pointes

• 3 Categories of drugs
  • Known risk
  • Conditional risk
  • Possible risk

• CredibleMeds® has developed Adverse Drug Event Causality Analysis (ADECA™), a systematic approach based on the Bradford Hill criteria for determining causality
Risk Factor: QT-Prolonging Drugs

**QT Interval Length with Utilization of Multiple IKr Blockers**

- QT-prolonging Drug A
- QT-prolonging Drug B
- Combination of QT-prolonging Drug A & Drug B
Risk Factor: QTc interval

- Each 10 msec increase in QTc corresponds to a 5-7% exponential increase in risk for TdP
- Another study showed that 89.5% of drug-induced TdP occurred when QTc was greater than 500 msec
- TdP is rare when QTc is <500ms, accounting for less than 10% of all cases
- QTc interval length was a significant predictor of mortality with a hazard ratio of 1.13 (1.12-1.14, p<0.001)

Zareba 1998
Bednar 2002
Haugaa 2013
Case Example- Focus on Long QT Syndrome

JW is an 82 year-old female taking the following medications:

- Acetaminophen 325mg po 3 times daily as needed for pain
- Amiodarone 200mg po daily
- Atorvastatin 20mg po daily
- Baclofen 20mg po twice daily
- Citalopram 20mg po daily
- Docusate 100mg po daily
- Lorazepam 0.5mg po daily at bedtime
- Omeprazole 40mg po daily
- Quetiapine 100mg po daily at bedtime

Pertinent Objective Findings

HR 62 bpm
Mg 1.4 mEq/L
K 4.2 mEq/L
Take-Away Points

What is Long QT Syndrome?
• Prolongation of the QT interval on the surface ECG
  • QTc >450 msec in men
  • QTc >470 msec in women

How does LQTS occur?
• Mostly from delayed ventricular repolarization
  • Disrupted balance between inward currents (Ca and Na channels) and outward currents (K channels – IKr and IKs)
  • Drug interactions are critical to monitor; acute changes in medication profiles can lead to significant risk

Why does LQTS matter and what should we do to prevent it?
• May lead to ventricular arrhythmias, such as Torsade de Pointes, which may be associated with sudden death
• ECG and electrolyte levels may be checked every 3-6 months for patients at high risk