Common Non-cardiac Drugs Causing Cardiac Problems

VORATIMA SILAVANICH
M.Pharm. (Clin. Pharm.)
Residency in pharmacotherapy
Specialized residency in Cardiology pharmacotherapy
There are the variety of pharmaceutical agents available for the medical professions to treat their patients.

One undesirable consequence of this is an increase in drug-related illness including cardiovascular disorders.
Drug-Induced Cardiovascular Disease

- Left Ventricular Systolic Dysfunction (LVSD) and Heart Failure (HF)
- Hypertension
- Acute Cardiovascular Events
- Arrhythmias
- Pericardial Disease
LVSD and HF are not synonymous but clearly there is a large degree of overlap.

Drugs may precipitate deteriorating symptoms of HF in individuals with established HF; alternatively, drugs can cause de novo LVSD in a previously well individual.
**Drugs causing LVSD**

- Cytotoxic agents
  - anthracyclines
  - trastuzumab
- Antipsychotics
  - clozapine
  - atypical antipsychotics
- Carbamazepine
- Tricyclic antidepressants
- Chloroquine
- Hydroxychloroquine
- Interferon-α
- Interleukin-2
- TNFα antagonists

**Drugs exacerbating HF**

- NSAIDs
- Corticosteroids
- Thiazolidinediones

Chemotherapy Related Cardiac Dysfunction*

1) Cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum

2) Symptoms associated with heart failure (HF)

3) Signs associated with HF, such as S3 gallop, tachycardia, or both

4) Decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms

* From Cardiac Review and Evaluation Committee; CRCE

# Cardiotoxicity classification

<table>
<thead>
<tr>
<th>Type of therapy-related cardiac damage</th>
<th>Anticancer agents involved</th>
<th>Cardiac damage Induced</th>
<th>Nature of cardiac damage</th>
<th>Biopsy presentation</th>
<th>Relationship of dose and injury</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Doxorubicin Daunorubicin Epirubicin Liposomal doxorubicin Mitoxantrone</td>
<td>Direct myocyte death</td>
<td>Permanent myocyte injury, beginning from first dose</td>
<td>Vacuole formation Myofibril disarray Necrosis</td>
<td>Cumulative dose-related effect</td>
<td>Any condition that has damaged or strained the myocardium Genetic sensitivity to these agents</td>
</tr>
<tr>
<td>Type II</td>
<td>Trastuzumab Sunitinib Imatinib Lapatinib</td>
<td>Myocyte dysfunction</td>
<td>Reversible myocyte dysfunction, with favourable prognosis</td>
<td>Minimal changes have been reported; none of the characteristic changes of the type I agents are seen</td>
<td>No cumulative dose-related effect noted</td>
<td>Prior recent exposure to anthracyclines (trastuzumab) Hypertension (sunitinib) Tendency to retain fluid (imatinib) Genetic sensitivity</td>
</tr>
</tbody>
</table>
Correlation between cumulative doxorubicin dose and the incidence of CHF

Nat Rev Cardiol. 2015;12(9), 547–58.

400-550 mg/m²
Candidate genes implicated in doxorubicin-induced cardiotoxicity

Simplified pathway depicting the presumed interaction between anthracycline and trastuzumab

## Treatment modalities and strategies to mitigate adverse cardiac effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time to presentation</th>
<th>Mitigating strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline</td>
<td>Weeks to decades</td>
<td>Prolonged infusion, Dose limitation, Dexrazoxane, Liposomal formulations, β-blockers, ACE inhibitors</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Weeks</td>
<td>Temporary interruption of administration</td>
</tr>
</tbody>
</table>

Nat Rev Cardiol. 2015;12(9), 547–58.
**Drug-Induced ADHF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

**NSAIDS** → Na/Fluid retention → ADHF

TZD and Heart failure

- In Europe, these agents have been contraindicated for patients with HF and any history of HF.
- Health Canada have recommendation to warn against use in patients with any degree of HF.
- In the U.S., thiazolidinediones have been contraindicated only for persons with NYHA class III and IV HF, highlighted by a prominent black box warning.

Drug induced Hypertension

Corticosteroids
NSAIDs

- Erythropoietin
- Combined oral contraceptives
- Ciclosporin
- Tacrolimus
- Venlafaxine

Na & water retention

- HAART
- Targeted Cancer Therapy (tyrosine kinase inhibitor, VEGF inhibitor)
Mechanism of drug induced HT

Erythropoietin

Endothelin-1

Vasoconstriction

Increased blood viscosity\(^1\)

-Systemic vasoconstriction

-Vasoconstriction in the kidney results in a ↓ renal blood flow\(^2\)

Ciclosporin

↓ NO ↓ PG

↑ ET

Treatment: DHP-CCB, BB\(^{1,2}\)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hypertension (%)</th>
<th>Before ciclosporin</th>
<th>After ciclosporin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>5-10</td>
<td>33-60</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>10</td>
<td>71-100</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>n.a.</td>
<td>65-85</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>45-55</td>
<td>67-86</td>
<td></td>
</tr>
<tr>
<td>Non-transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>n.a.</td>
<td>42-45</td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>n.a.</td>
<td>23-29</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>n.a.</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>n.a.</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of drug induced HT

Venlafaxine  \rightarrow \uparrow \text{Sympathetic activity} \rightarrow \text{HT}

Venlafaxine (dose dependent \sim 10-20\%: 150mg)

Management: monitor BP (in high dose)

Combined oral contraceptives (estrogen)

\rightarrow \uparrow \text{Renin production and angiotensinogen levels}

Management: reduced estrogen content

Targeting of Kinases and VEGF Signaling Pathways for Cancer Therapy

VEGF Signaling Pathway Inhibitors
- Bevacizumab (anti-VEGF)
- Aflibercept (VEGF trap)
- Ramucirumab (Anti-VEGFR2)

Tyrosine Kinase Inhibitors with Anti-VEGF Activity
- FDA Approved
  - Sunitinib, sorafenib, pazopanib, axitinib, regorafenib, vandetanib, ponatinib, cabozantinib, lenvatinib
- Under Investigation
  - Cediranib, tivozanib, toceranib, lucitanib

Cell survival
Angiogenesis
Prostaglandin production
Nitric oxide production

VEGF: Vascular Endothelial Growth Factor
PDGF: Platelet-Derived Growth Factor
HIF: Hypoxia Inducible Factor
PDGFR: Platelet-Derived Growth Factor Receptor
VEGFR: Vascular Endothelial Growth Factor Receptor
KIT: Karyotypic Isoform of the Tyrosine Kinase Receptor

Mechanism of hypertension after VEGF signaling Pathway inhibition


Assess risk of CV disease

- SBP < 140 mmHg and DBP < 90 mmHg
- SBP > 140 mmHg and DBP > 90 mmHg

Diagnosis of HT

Starting Targeted Cancer Therapy

- Monitor BP (q week in 1st cycle)

Treatment for HT

Stop Targeted Cancer Therapy

Flow for Starting Targeted Cancer Therapy

Drug associated with Cardiovascular Events

Drugs associated with increased risk of cardiovascular events

- COX-2 inhibitors
- NSAIDs (HT, dyslipidaemia, DM)
- Atypical antipsychotics
- Combined oral contraceptives
- HAART (dyslipidaemia)
- Erythropoietin (HT)
- Hormone replacement therapy
NSAIDs and MI

Cyclo-oxygenase (COX-2) Inhibitors and MI

NORMAL

\[ \text{PGI}_2 \quad \text{TxA}_2 \]

Pro-thrombotic

Anti-thrombotic

NSAID

\[ \text{PGI}_2 \quad \text{TxA}_2 \]

Pro-thrombotic

Anti-thrombotic

LOW-DOSE ASPIRIN

\[ \text{PGI}_2 \quad \text{TxA}_2 \]

Pro-thrombotic

Anti-thrombotic

SELECTIVE COX-2 INHIBITION

\[ \text{PGI}_2 \quad \text{TxA}_2 \]

Pro-thrombotic

Anti-thrombotic

Stepped-Care Approach to Pharmacological Therapy for Musculoskeletal Symptoms in Patients With Known CV Disease or Risk Factors for Ischemic Heart Disease

- Acetaminophen, ASA, tramadol, nonacetylated analgesics
- Nonacetylated salicylated
- Non-COX-2 selective NSAIDs
- NSAIDs with some COX-2-selectivity
- COX-2 selective NSAIDs

J Am Coll Cardiol 2014;64(24):e139-e228.
HAART and MI

• HIV virus itself may damage coronary arteries via cytokine activation and disturbance of cell signaling but this increased risk may be drug-related
• PIs are known to cause a metabolic disorder including lipodystrophy, hyperlipidaemia and insulin-resistance
• 74% of patients with HAART-associated metabolic syndromes also exhibit hypertension
TCA and MI

Alpha
adenoreceptor

TCA \(\rightarrow\) Hypotension \(\rightarrow\) Reflex tachycardia \(\rightarrow\) MI

- **SSRIs** are the agents of choice in coronary heart disease
  - However, *citalopram* is cautioned in patients at higher risk of developing Torsade de Pointes
  - *Sertraline* and is safe post MI and considered the drug of choice in these patients

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Drugs induced Arrhythmias (QT prolong Torsades de Pointes)

- Antihistamines
- Antipsychotic and antidepressant agents
  - Neuroleptic (Haloperidol, Thioridazine, Chlorpromazine)
  - Atypical antipsychotics (Sertindole, Ziprasidone, Risperidone, Zimeldine, Citalopram)
  - Antidepressants (Amitriptyline, Desipramine, Imipramine, Fluoxetine)
- Antibiotics
  - Quinolone (Sparfloxacin, Levofloxacin, moxifloxacin, grepafloxacin)
  - Macrolide (Erythromycin, Clarithromycin)
- Antimalarials (Quinine)
- Antifungal (Azole group)
- Antimotility Agents (Cisapride)
Normal values of the QT interval

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Limiting</th>
<th>Prolonged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult males</td>
<td>&lt;430</td>
<td>430-450</td>
<td>&gt;450</td>
</tr>
<tr>
<td>Adult females</td>
<td>&lt;450</td>
<td>450-470</td>
<td>&gt;470</td>
</tr>
</tbody>
</table>

corrected according to the Bazett formula

Mechanisms Of Drug - Induced QT Prolongation and Tdp

Block of block $I_{Kr}$ currents

The activity of the hERG channel accounts for the rapid potassium component ($K_r$, rapid) of the outward repolarizing current $I$ during the QT-interval.
Classic EKG of Tdps

Arrhythmogenesis of Tdps

## Antihistamine and QT prolongation

<table>
<thead>
<tr>
<th>Antihistamine</th>
<th>Special warnings and special precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole/Terfenadine</td>
<td>• Over 20 cases of fainting, ventricular tachycardia, torsades de pointes and cardiac arrests that followed administration of astemizole or terfenadine</td>
</tr>
<tr>
<td></td>
<td>• Astemizole and terfenadine were <strong>withdrawn</strong></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>• Proarrhythmic effect, due to the influence on K channels, was reported while administering medically <strong>overdosed diphenhydramine</strong></td>
</tr>
<tr>
<td>Fexofenadine (Terfenadine metabolite)</td>
<td>• Case of <strong>prolonged QT interval</strong> and VT while administering fexofenadine had been reported</td>
</tr>
<tr>
<td></td>
<td>• But the studies that followed did <strong>not confirm its negative effects</strong> on QT interval and heart rhythm, neither in high doses nor combined with ketoconazole or erythromycin</td>
</tr>
</tbody>
</table>

## Antihistamine and QT prolongation

<table>
<thead>
<tr>
<th>Antihistamine</th>
<th>Special warnings and special precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>• Excreted in the urine in 70% and undergoes minute, clinically insignificant metabolism in the liver</td>
</tr>
<tr>
<td></td>
<td>• Did not observe prolonged QT intervals, having administered a therapeutic dose of 10 mg to the patients or 50 mg doses to the healthy volunteers</td>
</tr>
<tr>
<td>Levocetirizine (enantiomer of cetirizine)</td>
<td>• Did not reveal its effect on repolarization in either therapeutic or higher doses</td>
</tr>
<tr>
<td>Loratadine</td>
<td>• Metabolized by CYP3A4 and CYP2D6 isoenzymes, thus interactions with their inhibitors are possible</td>
</tr>
<tr>
<td></td>
<td>• Concomitant dosing of loratadine with drugs that inhibit CYP3A4 increases the concentrations of the former, though generally without QT modification</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>• No QT interval prolongation</td>
</tr>
</tbody>
</table>
# QTc-Prolongation Risk Stratification for Commonly Used Antipsychotic Medications

<table>
<thead>
<tr>
<th></th>
<th>Association with QTc Prolongation</th>
<th>Association with Torsades de Pointes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Haloperidol (IV)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Haloperidol (PO/IM)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Minimal risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*The relative risks for QTc prolongation may vary depending on dose, concomitant medications, and other medical illnesses.*

*Psychosomatics 2013:54:1–13*
Intrinsic delayed rectifier potassium current (IKr) inhibitory potency & metabolic liability

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>CYP substrate</th>
<th>CYP inhibition</th>
<th>hERG inhibition IC50, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent hERG-blocking non-antimicrobials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dofetilide</td>
<td>3A4</td>
<td>no</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Sotalol</td>
<td>no</td>
<td>no</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>no</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>32.9, 45.7</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>38.9, 72.2</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>3A4</td>
<td>3A4</td>
<td>42.5</td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>no</td>
<td>1A2</td>
<td>966</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>no</td>
<td>no</td>
<td>130, 329</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>no</td>
<td>No</td>
<td>260</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>no</td>
<td>no</td>
<td>430, 827, 915</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>no</td>
<td>no</td>
<td>65, 129, 354</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>no</td>
<td>no</td>
<td>18–37</td>
</tr>
<tr>
<td><strong>Imidazoles/triazoles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>NA</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>NA</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>3A4</td>
<td>49</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>2C9, 2C19, 3A4</td>
<td>2C9, 2C19, 3A4</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>No</td>
<td>No</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Torsades de pointes (TdP) risk stratification schedules for antimicrobial agents

**Schedule I**: Highest TdP risk, potent IKr blockers, TdP risk >1%

**Schedule II**: Significant risk for TdP, particularly when coadministered with CYP inhibitors, relatively potent IKr blockade

**Schedule III**: Risk for TdP is described, IKr blockade, particularly when coadministered with CYP inhibitors

**Schedule IV**: Minimal risk for TdP, case reports of TdP, mild IKr blockade, may have CYP interactions

**Schedule V**: Questionable/ minimal risk for QT interval prolongation/TdP

* New antimicrobials to the market or still investigational, minimal to no post-marketing data; based on additional data, the drug may be re-categorised in a higher or lower schedule.
Multiple risk model for drugs-associated torsades de pointes

Adapt from: Drugs 2004; 64 (10): 1091-124.

Prescription of QT prolong drug
Drug associated with pericardial disease

Commonly used drugs associated with drug-induced lupus

**Strong association**
- Procainamide
- Hydralazine
- Quinidine

**Moderate association**
- Methyldopa
- Captopril
- Chlorpromazine
- Isoniazid
- Carbamazepine
- Penicillamine
- Sulfasalazine

Summary

• Non-cardiac drugs with cardiac problems include antidepressant drugs, antidiabetic drugs, NSAIDs, immunomodulating drugs, anti-cancer drugs

• Health professionals should aware of the potential for non-cardiac drugs that have adverse effects on the heart when prescribe medications to patients with or without cardiac disease or with cardiac risk factors