Oral Digoxin Shortage

Table 1: Canadian Suppliers of Oral Digoxin

<table>
<thead>
<tr>
<th>Product</th>
<th>Strength</th>
<th>DIN</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toloxin Tablets</td>
<td>0.0625 mg</td>
<td>02335700</td>
<td>PendoPharm Inc.</td>
</tr>
<tr>
<td></td>
<td>0.125 mg</td>
<td>02335719</td>
<td></td>
</tr>
<tr>
<td>Toloxin Elixir</td>
<td>0.05 mg/mL</td>
<td>02316870</td>
<td></td>
</tr>
</tbody>
</table>

Health Canada Approved Indications of Oral Digoxin:
- treatment of chronic atrial fibrillation (AF)
- treatment of mild to moderate heart failure (HF)

Background Information
- PendoPharm Inc. is the only Canadian supplier of oral digoxin in Canada and it is experiencing a disruption in the manufacturing of Toloxin; anticipated end date of this shortage is 21 Feb 2020.
- While end dates are never guaranteed, supply disruption does appear to be short-term.
- Digoxin bulk powder may be available to some compounding pharmacies but at considerable price; confirm with compounding pharmacies before referring patients.

General Considerations
- Determine the indication of digoxin: atrial fibrillation (AF), heart failure (HF) or atrial fibrillation with heart failure (AF+HF).
- This is a good opportunity to evaluate digoxin as it lends itself to deprescribing.
- When possible, taper digoxin dose using existing supply
  - under ideal conditions, the dose is reduced by 50% every 1-2 weeks; once at 25% of the original dose for 1-2 weeks, stop if no symptoms.
  - 0.125 mg tablets can be split in half
  - 0.0625 mg tablets are not amenable to splitting; the half-life is 36-48 hours so consider increasing the dosing intervals to every 2 days.
- in many cases supply may not allow for such tapers so taper as best as possible
- All patients need to be monitored but especially those with HF for signs/symptoms of exacerbation, which could lead to hospitalization (see information below).
- Depending on the situation, the patient’s condition may not change (and thus validates deprescribing).
- See figures below regarding next steps should signs and symptoms worsen.

Atrial Fibrillation
- Symptoms of AF include palpitations (‘heart flutters’), fatigue, dizziness, exercise intolerance, chest pain, and weakness.
- Pharmacological strategies to treat AF include rate control and rhythm control; there is no difference in terms of reduction of mortality and stroke risk between the two strategies.
- Rate control is used to slow heart rate (HR); a fast HR is one of the main features of AF and pharmacotherapy is used to ensure the HR stays below 100 beats per minute (BPM).
- For a patient with AF, failing to control a fast HR can have two main consequences:
  1) a fast HR can cause symptoms if the heart does not have enough time to fill with blood in between beats.
  2) a fast HR that is left uncontrolled for long periods of time can cause changes to the heart and cause it to become weaker.
• The mainstay of rate control is a beta blocker (βB) or a non-dihydropyridine calcium channel blocker (non-DHP-CCB) (verapamil and diltiazem). 6,8
• Digoxin is typically only used as add-on therapy to βBs and non-DHP-CCBs. 8
• See Table 1 for dosing and Figure 1 for management strategies.

Table 1: Rate Control Agents for Atrial Fibrillation 8,9

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blockers</td>
<td></td>
<td>Non-Dihydropyridine Calcium Channel Blockers</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50 to 150 mg PO daily</td>
<td>Diltiazem</td>
<td>120 to 480 mg MR PO daily</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.5 to 10 mg PO daily</td>
<td>Verapamil</td>
<td>120 to 240 mg SR PO BID</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>25 to 200 mg PO BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 to 200 mg SR PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>20 to 160 mg PO once to twice daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID = twice daily; MR = modified release and includes CD and XC; PO= by mouth; SR = sustained/slow release

No, not an option

*Avoid calcium channel blockers in patients with heart failure with reduced ejection fraction. 10
βB = beta blocker; BPM = beats per minute; HR = heart rate; non-DHP-CCB = non-dihydropyridine calcium channel blocker
**Heart Failure** (including Heart Failure with Atrial Fibrillation)

- Heart failure (HF) is associated with abnormal heart function that results in clinical signs and symptoms.
- The most common symptoms include fatigue, exercise intolerance, fluid retention and dyspnea.\(^{10}\)
- The New York Heart Association (NYHA) Functional Classification is often used to classify symptoms\(^{10,11}\):
  - Class I: no symptoms
  - Class II: symptoms with ordinary activity; comfortable at rest
  - Class III: symptoms with less than ordinary physical activity; comfortable at rest
  - Class IV: symptoms at rest or with any minimal physical activity
- Ejection fraction (EF) is also used to classify HF;\(^{10}\) It is estimated with echocardiography\(^{10}\) and patients may not know their ‘number’.
  - HF with reduced EF (HFrEF): EF ≤ 40% (systolic HF)
  - HF with mid-range EF (HFmEF): EF 41-49%
  - HF with preserved EF (HFpEF): EF ≥ 50% (diastolic HF)

**Digoxin is only used in systolic HF (HFrEF)**

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**Non-pharmacological options**\(^{12}\)

- See [RxFiles Heart Failure: Treatment Overview](#) for details
  - regular physical activity for those with stable HF
  - salt and fluid restriction

**Pharmacological Options**

- All patients should be on target doses (or, if not tolerated, highest tolerated dose) of Triple Therapy which includes\(^{10,12,13}\):
  - angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), and beta blocker, and mineralocorticoid receptor antagonist (MRA)
- See Table 2 for target doses of Triple Therapy and Table 3 for information about newer HF therapies
- See Figure 2 for management strategies

### Table 2: Target Doses in Heart Failure of Triple Therapy\(^{10,12}\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target Dose</th>
<th>Agent</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin Converting Enzyme Inhibitors</strong></td>
<td></td>
<td><strong>Angiotensin Receptor-Neprilysin Inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>10 mg PO BID</td>
<td>Sacubitril/Valsartan(^{†})</td>
<td>97/103 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>20 mg PO BID in NYHA Class IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20-40 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>4 to 8 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>5 mg PO BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin II Receptor Blockers</strong></td>
<td></td>
<td><strong>Beta Blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>32 mg PO daily</td>
<td>Carvedilol</td>
<td>25 mg PO BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg PO BID if &gt;85 kg</td>
</tr>
<tr>
<td>Valsartan</td>
<td>160 mg PO BID</td>
<td>Bisoprolol</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>150 mg PO daily</td>
<td>Metoprolol SR*</td>
<td>200 mg PO daily</td>
</tr>
</tbody>
</table>

*This is the tartrate salt; however, evidence is based on the succinate salt, which is not available in Canada.

\(^{†}\)Exceptional Drug Status for the Saskatchewan Drug Plan and Limited Use Benefit for Non-Insured Health Benefits

BID = twice daily; NYHA = New York Heart Association; PO = by mouth
**Figure 2: Heart Failure Treatment Algorithm**
(including patients who have both Heart Failure and Atrial Fibrillation)

Ensure patient is taking **HF Triple Therapy:**
- ACEI/ARB/ARNI* + βB + MRA
- at target doses or highest tolerated doses (especially βB if patient also has AF)

**Taper digoxin** as best as possible with remaining supply

**Monitor Heart Rate**

**Monitor Symptoms** (fatigue, exercise intolerance, fluid retention, dyspnea + AF symptoms if applicable)

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**Table 3: Additional Information Regarding Newer Heart Failure Therapies**

<table>
<thead>
<tr>
<th>Class Drug</th>
<th>Angiotensin Receptor-Neprilysin Inhibitors</th>
<th>Ir Current Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in Heart Failure</td>
<td>Sacubitril/Valsartan</td>
<td>Ivabradine</td>
</tr>
<tr>
<td>Initial: 49/51 mg PO BID</td>
<td>Target: 97/103 mg PO BID</td>
<td>2.5 to 7.5 mg PO BID</td>
</tr>
</tbody>
</table>

**Comments**
- Consider starting with 24/26 mg if:
  - risk of hypotension
  - not currently taking target ACEI/ARB dose
- Replaces existing ACEI/ARB (36 hour washout after stopping ACEI – risk of angioedema)
- Monitor for hypotension; be mindful of diuretic and other antihypertensive use
- Monitor potassium (hyperkalemia) and renal function
- Considered for NYHA Class II or higher patients who have HR ≥77 BPM, no AF or pacemaker and are in sinus rhythm
- Prolongs QTc
- Avoid in patients at risk of bradycardia
- Contraindicated drugs: concomitant strong CYP3A4 inhibitors, diltiazem, verapamil
- If taking moderate CYP3A4 inhibitors, consider starting ivabradine at a lower dose

* For beneficiaries of the Saskatchewan Drug Plan, exceptional drug status criteria for both ivabradine and ARNI (sacubitril/valsartan) include “under the care of a specialist experienced in the treatment of heart failure.”

14 For beneficiaries of the Non-Insured Health Benefits, criteria for limited use benefit status of sacubitril/valsartan (but not ivabradine) includes that it must be: “initiated by a physician experienced in the treatment of heart failure.”

ACEI= angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; βB= beta blocker; BPM = beats per minute; HR = heart rate; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BID = twice daily; BPM = beats per minute; PO = by mouth
References:


