Pharmacology in Stroke

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Acute Stroke Best Practices Workshop

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Learner Objectives

Upon completion of this presentation, participants will be:

1) Familiar with the Canadian Stroke Best Practice Recommendations (2017) for secondary stroke prevention with medications
2) Aware of the known Cardiovascular Effects of Cannabis
3) Conscious of Cannabis interactions with medications

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Antithrombotic Therapy for TIA or Ischemic Stroke

"All patients with ischemic Stroke or TIA should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation"

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Antithrombotic Therapy for TIA or Ischemic Stroke

- **ANTIPLATELETS (no Atrial fibrillation detected):**

  -ASA -Clopidogrel -dipyridamole/ASA

vs

- **ANTICOAGULANTS (Atrial fibrillation detected):**
  - **-Warfarin**
  - **-Apixaban -Rivaroxaban -Dabigatran -Edoxaban**

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Antithrombotic Therapy for TIA or Ischemic Stroke

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Antiplatelets

choose one*:

-ASA "Aspirin" 80-325 mg po daily

-Clopidogrel "Plavix" 75 mg po daily

-Dipyridamole/ASA "Aggrenox" 200/25 mg po twice daily

***short term (up to 21 days) combination of ASA + clopidogrel may be protective after minor stroke or TIA, with no increased risk of bleeding. Only continue double therapy beyond 21 days if other indications like coronary stents.**

Limited evidence of what to do if a patient has a stroke while on one agent but it is suggested to:

A) ensure compliance

B) switch to another antiplatelet agent

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Anticoagulation in A fib

Warfarin : a vitamin K antagonist

- **Dosed based on INR results**
- **Reversal agent : Vitamin K**
- **The only option for patients with:**
  - - MECHANICAL HEART VALVES
  - - ENDSTAGE RENAL DISEASE
  - - WEIGHT GREATER THAN 120 KG (no reliable info)

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Anticoagulation in A fib

Otherwise….use DOAC's (Direct oral anticoagulants): DABIGATRAN, APIXABAN, EDOXABAN , RIVAROXABAN (preferred over warfarin)

- Dose based on age, weight and renal function

- **Reversal agent for Dabigatran: Idarucizumab "Praxbind" rarely used due to cost; usually supportive care only**
- **Reversal agent for the other DOACs is not yet available in Canada: andexanet alfa**

- No studies comparing DOAC's to each other but there is a trend toward less GI bleeding with apixaban

- Apixaban has dosing information in renal impairment (down to a creatinine clearance of 25 mL/min)

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Lipid Management

- **"Patients who have had an ischemic stroke or TIA should have their serum lipid levels assessed and aggressively managed"**

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Lipid Management

- Dietary modification and aerobic exercise

- A statin should be prescribed to achieve the following targets:

LDL less than 2.0 mmol/L OR
more than a 50% reduction of LDL from baseline

If patient also has acute coronary syndrome (ACS) or coronary diesease:

LDL less than 1.8 mmol/L OR
more than a 50% reduction of LDL from baseline

***statins are not indicated for intracerebral hemorrhage**

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Lipid Management – what does "aggressive management"mean?

Treating to New Targets (TNT) trial (2005): Results suggest that aggressive reduction of LDL, achieved through higher doses of a statin, are associated with greater benefit than more modest reductions

Authors conclusions: "In patients with stable CAD and hyperlipidemia, atorvastatin 80 mg PO daily is associated with a greater reduction in CAD mortality, non-fatal MI not related to procedures, resuscitation after cardiac arrest, or fatal or nonfatal stroke when compared to atorvastatin 10 mg PO daily."

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Lipid Management

Approximate Dose Equivalency of Statin LDL-C Efficacy

Dose of Agent (mg/d)

Rosuva*	Atorva*	Simva	Pitava	Lova	Prava	Fluva	Approx ↓LDL-C
		10	1	20	40†	40	28-34%
5	10†	20†	2†	40†	80	80†	35-42%
10†	20	40	4	80			39-47%
20	40	(80)					46-52%
40	80						51-55%

*Atorvastatin and rosuvastatin may be *more* effective (½ and 1 doubling, respectively).
†Most commonly used dose in United States.

Adapted from: Roberts WC. *Am J Cardiol*. 1997;80:106-107.
Stein E et al. *J Cardiovasc Pharmacol Therapeut*. 1997;2:7-16. Rosuvastatin PI, Pitavastatin PI.

LIPID & METABOLIC
theheart.org
Medscape

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Blood Pressure Management

- **" Hypertension is the single most important modifiable risk factor for stroke" (ischemic and hemorrhagic)"**

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Blood Pressure Management

- **Target blood pressure after stroke or TIA:**

  less than 140/90

  OR

  less than 130/80 if diabetes present

  ***optimal time to initiate BP lowering therapy after stroke is not defined but recommendation is to initiate prior to discharge

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Blood Pressure Management

- **The Canadian Stroke Best Practice Recommendations (2018) do not define which agents to use but Hypertension Canada (CHEP) Guidelines suggest:**
- **-first line thiazide diuretic (chlorthalidone is now preferred over hydrochlorothiazide)**
- **ACE-inhibitors or ARBs**
- **Other options: CCBs like amlodipine or beta-blockers if HR management also required**
- **Specifically in the setting of stroke….let's look at the PROGRESS trial…..**

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Blood Pressure Management

Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) trial (2003)

- The primary outcome was total stroke (fatal or non-fatal). Combination therapy with **perindopril plus indapamide** lowered blood pressure by 12/5 mmHg and stroke risk by 43%. Single-drug therapy lowered blood pressure by 5/3 mmHg and produced no significant fall in the risk of stroke
- The authors' conclusion: "**Treatment with these two agents should be considered routinely for all patients with a history of previous stroke or TIA, whether hypertensive or normotensive."**

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Diabetes Management

- Diabetes increases the risk of ischemic stroke
- Stroke outcomes are worse in a diabetic patient:

- Longer hospital stays

- More morbidity (neurologic and functional disability)

" Patients with diabetes who have had an ischemic stroke or TIA should have their diabetes assessed and optimally managed"

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Diabetes Management

- The Stroke Guidelines have no specific drug recommendations.
- Current trends in Diabetes Management:

- Metformin remains 1st line (dose reduced in renal impairment to avoid lactic acidosis)

- Sulfonylureas (glyburide, gliclazide) are falling out of favour due to hypoglycemia concerns and safer agents

- Humulin R, Humulin N, Mixes like 30/70….phased out in favour of better control with long and ultra-long acting insulins once daily as well as very short acting insulins with meals

- SGTL2 inhibitors like empagliflozin have shown some cardiovascular benefit, likely as a result of mild diuretic properties (although no specific stroke benefit)

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Other Medicinal agents

Estrogen-containing oral contraceptives or hormone replacement therapy should be discouraged or discontinued in patients with TIA or ischemic stroke.

Recreational Drug Use: -avoid stimulants like cocaine, amphetamines

Alcohol: avoid heavy alcohol use

Current Health Canada recommendations-

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Smoking Cessation

- **"Patient smoking status should be identified, assessed and documented" and "offer assistance with the initiation of a smoking cessation attempt"**
- **Referral: Ottawa Heart Model being rolled out across the hospital**
- **Direct assistance: Offer nicotine replacement to all smokers – a good place to start the conversation**
- **Other 1st line agents: bupropion (Zyban) or varenicline (Champix)**

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Ottawa Heart Model of Smoking Cessation - "OMSC" intervention

Tobacco Use History	
Type of Assessment	○ Initial ○ Reassessment
Preferred Language	○ English ○ French
Have You Used Any Form of Tobacco in the Past 6 Months	○ Yes ○ No
Have You Used Any Form of Tobacco in the Past 7 Days	○ Yes ○ No
Pregnant	○ Yes ○ No
Breastfeeding	○ Yes ○ No
Use of Cessation Aids at Time of Admission	☐ Patch ☐ Inhaler ☐ Gum ☐ Lozenge ☐ Bupropion ☐ Varenicline
What Forms of Tobacco Do You Currently Use	☐ Cigarettes ☐ Pipe ☐ Cigars ☐ Smokeless Tobacco
How Much Do You Smoke per Day	(# per day) (# of cigarettes/cigars/pipes, etc)
If Not a Daily Smoker, How Much per Month	(# per month)
How Many Years Have You Smoked	(years)
How Many Quit Attempts Have You Made in the Past Year	Lasting greater than 24 hours
How Many Minutes After Waking Up Do You First Smoke	(minutes)
Do Others Smoke In Your Home	○ Yes ○ No
How Important is it to Quit Smoking (Scale of 1-5)	○ 1 - Not Important ○ 2 - Slightly Important ○ 3 - Moderately Important ○ 4 - Very Important ○ 5 - Extremely Important
How Confident Are You That You Can Quit Smoking (Scale 1-5)	○ 1 - Not Confident ○ 2 - Slightly Confident ○ 3 - Moderately Confident ○ 4 - Very Confident ○ 5 - Extremely Confident
Assessment	
Advised to Quit Smoking	○ Yes ○ No

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Take Home Message

- **All patients with ischemic Stroke or TIA should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation.**
- **Patients who have had an ischemic stroke or TIA should have their serum lipid levels assessed and aggressively managed.**
- **Hypertension is the single most important modifiable risk factor for stroke.**
- **Patients with diabetes who have had an ischemic stroke or TIA should have their diabetes assessed and optimally managed.**
- **Patient smoking status should be identified, assessed and documented and offer assistance with the initiation of a smoking cessation attempt.**

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Cardiovascular Effects of Cannabis

Health Canada Website warning: it "hurts your lungs and makes it harder to breathe" if smoked

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- No systematic scientific studies exist
- Our limited knowledge comes from a series of case reports:

- HR and BP increase immediately after smoking cannabis and can last up to 3 hours. HR increases 20-100 X resting.
- Also associated with orthostatic hypotension which explains the most common side effect: dizziness
- Immediate result of smoking cannabis is increased carbon monoxide & decreased oxygen in the blood, mixed with tachycardia and possibly coronary spasm. Has caused MIs & ischemic strokes (case reports in young, otherwise healthy, males. Some reports occurred during sports/exercise. Usually within first hour after use.)

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CV Effects of Cannabis

- Due to increased HR there have also been reports of cardiac arrhythmias (and therefore and increased risk of ischemic stroke)
- There are more side effects than benefits from a cardiovascular point of view.
- Advice: - if you don't already smoke cannabis, don't start
  - avoid smoking cannabis if you have CV disease
  - avoid sports immediately after smoking cannabis
  - common sense; approach with caution if you must

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CV Effects of Cannabis

- Ongoing research:

- heart failure and cannabis (no results yet)
- post-MI anxiety and cannabis (no results yet)

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Cannabis interactions with medications

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Cannabis interactions with medications

- Over 400 chemicals found in the Cannabis species, of which there are approximately 70 cannabinoids.
- Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC) are the main chemicals known, researched and marketed.
- Cannabis preparations have varying amounts of THC:CBD and have unique pharmacologic effects
- Various concentrations of THC:CBD products are on the Government of Ontario website for purchase. The quality and consistency of cannabis strains (containing various ratios of THC:CBD) in street preparations and unregulated dispensaries across Canada are not known

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THC interactions

- Mostly concerned with enzyme INDUCTION (like 1A2). This means the liver breaks down certain drugs FASTER than usual and the patient may need a HIGHER dose.
- Examples: naproxen, cyclobenzaprine, clozapine, duloxetine, olanzepine, haloperidol, chlorpromazine…even propofol!!!

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CBD interactions

- Mostly concerned with enzyme INHIBITION (like 2D6, 3A4). This means the liver breaks down certain medications SLOWER than usual and the patient may need LOWER doses.
- 3A4 is responsible for the metabolism of about 25% of all therapeutic agents
- Examples: warfarin, atorvastatin and other statins, HIV medications, azole antifungals, amiodarone, diltiazem, certain antibiotics, citalopram/escitalopram, and can possibly block the activation of clopidogrel, ETC…….

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Take Home Message

- Include Cannabis usage as part of your patient's medical history.
- Discourage the smoking of cannabis, especially in existing Cardiovascular/Cerebrovascular disease.
- For other forms of ingestion, CV effects are not yet known. Patients are to proceed with common sense and caution.
- There are many drug interactions with cannabis and each case must be approached thoughtfully. Interactions will vary depending on the amount of THC:CBD in the product. Patients who use cannabis should consistently use the same product, in the same amount and at the same frequency.
- Best approach is to avoid cannabis if on many meds.

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Questions

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