“Off Label” Medications

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I have no conflicts of interest to declare regarding this presentation.
Learning Objectives

• To understand the **spectrum** of what can be defined as off label prescribing
• To understand the **risks** associated with off label prescribing
• To understand the circumstances where off label prescribing may be an **acceptable** option
What is “off label” prescribing?

Using a medication for an **indication** that has **not been approved** by the drug regulatory authority.

Using a medication in a **subpopulation** of patients that has **not been approved** by the drug regulatory authority.
Controlling Off Label Use

• **Pharma – Health Canada (or FDA)**
  – Marketing

• **Physicians – Provincial Colleges (e.g. CPSO) and Litigation**
  – Standards of practice
Manufacturers cannot promote a drug for a use that is not stated on the Product Monograph.

Section 9 (1) of the Food and Drugs Act deals with false, misleading advertising and Section C.08.002 of the regulations states: "No person shall sell or advertise a new drug unless the manufacturer has filed a New Drug Submission and received a Notice of Compliance because the terms of such authorization have not yet been established and the proposed indications for use have not been verified."
Health Canada’s Role

• **Health Canada does not monitor off label use of drugs**
  
  • Several coroners' juries have recommended the department should monitor off label use
  
  • Health Canada maintains that the rules pertaining to product monographs are sufficiently clear
  
  • Occasionally Health Canada will post warnings or advisories about certain drugs that may be prescribed for uses other than what they were approved for
USA – FDA: the Zyprexa example

• Eli Lilly settled a lawsuit charging that it illegally marketed the anti-psychotic drug Zyprexa (olanzapine) in the treatment of dementia and Alzheimer’s disease. Civil litigants received $800 million.

• Lilly also paid a $615 million fine to resolve the criminal probe, and pleaded guilty to a misdemeanor violation of the Food, Drug and Cosmetic Act for promoting Zyprexa as a dementia treatment.

• Eli Lilly reportedly had sales of $4.8 billion of Zyprexa in 2007, and $37 billion since the drug was first introduced.
It is legal for physicians to use and to prescribe drugs as off label medications.
But when something bad happens.......
Physician Negligence in the Off Label Use of Drugs

1. Insufficient evidence to justify the use
2. Failure to communicate risks and benefits
3. Failure to monitor the patient
Risks associated with OFF LABEL use
There is a spectrum of risks and benefits amongst *off label* drug use

- IV sedation as a sleep aid *(NO!)*
- Drug use in children *(?)*
- Chemotherapies or biologics in the management of uncommon cancers *(?)*
- Phase IV RCT evidence but the drug label has not been revised *(YES)*
Which indications are off label for metoprolol?

- Treatment of mild or moderate hypertension
- Acute treatment of hypertensive crises
- Chronic treatment of congestive heart failure
- Acute treatment of myocardial infarction
- Chronic treatment of angina pectoris
- Prophylaxis for migraine headaches
Which indications are off label for amitriptyline?

- Prophylaxis for migraine headaches
- Treatment of fibromyalgia
- Treatment of trigeminal neuralgia
- Treatment of depression
- Treatment of anxiety in depression
- Treatment of mild depressive states and depressive reactions in bipolar disorder
Which indications are off label for ACE inhibitors?

- Essential Hypertension
- Treatment of unilateral renal artery stenosis
- Treatment following acute of myocardial infarction
- Chronic treatment of congestive heart failure
- Management of patients at Increased risk of cardiovascular events
- Chronic treatment of albuminuria
- Chronic treatment in children with heart disease
Effects of Lisinopril on Albuminuria

EUCLID study group. Lancet 1997;349:1787–1792
The Effect of Treatment with Angiotensin-Converting Enzyme Inhibitors on Survival of Pediatric Patients with Dilated Cardiomyopathy

*Lewis AB and Chabot M*

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Pediatric Cardiology Vol. 14, No. 1, 1993
More examples of off-label prescribing

- Avastin (bevacizumab) → age-related macular degeneration (AMD)
- Gabapentin (neurontin) → neuropathic pain
- Topamax (topiramate) → obesity / weight loss
- Diane-35 (cyproterone acetate / ethinyl estradiol) → oral contraceptive
How often does off label drug use occur in office-based practice?


## Determining Acceptable Use:

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Comments or Questions?