Hurts First, Kills Later: Update on Nicotine Use Disorder and Pain

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- PS holds the Vice Chair Research and Giblon Professor in Family Medicine Research, a University Named Professorship at the University of Toronto

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Learning Objectives

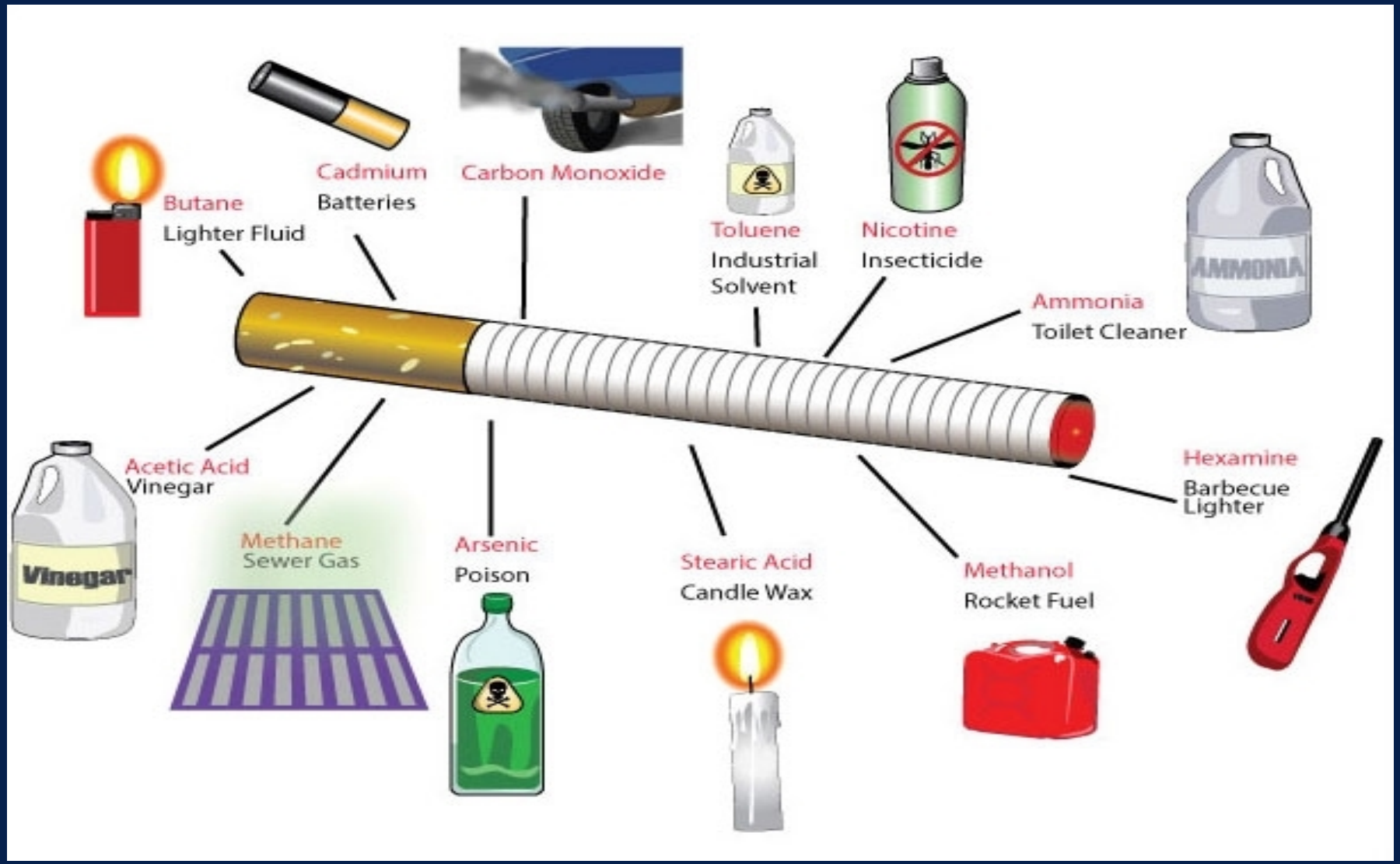
- Interpret existing evidence regarding the relationship between smoking and pain
- Identify chronic pain as a barrier to smoking cessation and abstinence

Nicotine…

- is a naturally occurring substance
- is the main reason people become addicted to tobacco products
- releases dopamine in the mesolimbic pathways (similar to other substances)
- has not been proven to cause cancers
- exposure during periods of developmental vulnerability has adverse consequences:
  - impaired brain and lung development (fetal)
  - altered cerebral cortex and hippocampus development (adolescent)

England et al 2015

Constituents of Cigarette Smoke



Drug Interactions with Tobacco Smoke

The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2)

Pharmacokinetic Interactions	
Alprazolam (Xanax)	Conflicting data on significance, but possible ↓ plasma concentrations (up to 50%); ↓ half life (35%)
Caffeine	↑ Metabolism (induction of CYP1A2); ↑clearance (56%). Caffeine levels like ↑ after cessation
Clopidogrel (Plavix)	↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite. Clopidogrel's effects enhanced in smokers (≥10 cigarettes/day only): significant ↑ platelet inhibition, ↓platelet aggregation, improved clinical outcomes in ST-segment elevation myocardial infarction
Clozapine (Clozaril)	↑ Metabolism (induction of CYP1A2); ↓plasma concentrations (18%) ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Insulin, subcutaneous	Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance. PK & PD interactions likely not clinically significant; smokers may need ↑ doses
Olanzapine (Zyprexa)	↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%) Dosage modifications not routinely recommended but smokers may need ↑ dosages.

Zevin et al. 1999

Drug Interactions with Tobacco Smoke

Most PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2)

Pharmacodynamic Interactions	
Opioids (propoxyphene, pentazocine)	Those who smoke may need ↑ opioid dosages for pain relief

Zevin et al. 1999

Evolution of the e-cigarette

- Mimic cigarettes
- Disposable
- One power setting

- Resembles pen
- Battery lasts longer
- Refillable and larger cartridge

- Mods and Customizables
- Customize power & airflow
- Refillable and larger cartridge

- Further Mods and Customizables
- Temperature control system

E-cigarette Vapour

- Vapour generated contains potentially toxic compounds

Highly reactive free radicals (associated with cancer, CVD, and COPD)	1,2-propanediol, glycerine, and nicotine	Metals including nickel, zinc, silver

Drummond & Upson, 2014; Goel et al., 2015; Fernandez et al.,2015

Comparison of Toxicants: Conventional Cigarettes vs E-cigarettes

Toxic Compound	Conventional Cigarette (µg in mainstream smoke)	E-cigarette (µg per 15 puffs)	Average Ratio (Conventional Cigarettes vs E-cigarette)
Formaldehyde	1.6 - 52	0.20 – 5.61	9
Acetaldehyde	52 - 140	0.11 – 1.36	450
Acrolein	2.4 - 62	0.07 – 4.19	15
Toluene	8.3 - 70	0.02 – 0.63	120
NNN	0.005 – 0.19	0.00008–0.00043	380
NNK	0.012 – 0.11	0.0001 –0.00283	40

NNN: N'-nitrosonornicotine
NNK: 4-(methylonitrosoamino)-1-(3-pirydyl)-l-butanone

Goniewicz et al. 2014

Chronic Pain

Chronic pain is pain that persists longer than the expected healing time

- Pain and nicotine dependence as highly co-morbid
  - Chronic pain sufferers are 2x more likely to smoke
  - Physical impairment related to pain increases likelihood of nicotine dependence

Zvolensky et al 2010; Orhurhu et al 2015; McDermott et al 2018

Bi-directional relationship?

- Current Hypotheses

1. Negative reinforcement
   i. Nicotine is used to alleviate affective pain symptoms (analgesia; withdrawal symptoms)
2. Self-medication
   i. Pharmacological properties of nicotine alleviate somatic symptoms
3. Distraction
   i. Act of smoking provides pain relief via distraction

Barriers to quitting

- Chronic pain as a significant barrier to quitting smoking and remaining abstinent
  - Smokers with chronic pain ~3.5x more likely to report pain as barrier to cessation
  - More likely expectation of severe withdrawal during quit attempts

LaRowe et al 2017

Evidence

- Evidence of the role of chronic pain as a predictor of smoking cessation is lacking
- Evidence base predominantly investigates relationship to acute or recent pain:
- Powers et al 2021:
  - Those reporting ‘significant pain in the past 2 weeks were significantly less likely to achieve 7 days of abstinence over 8 weeks
  - Indicates significant role of pain on smoking behaviour

Knowledge Gap

Does being involved in a smoking cessation intervention effect the relationship between chronic pain and smoking cessation?

Evidence

Does a chronic pain diagnosis influence smoking abstinence at 6 months among primary care patients enrolled in a smoking cessation treatment program?

Evidence

Population	Intervention	Study design	Outcomes
Smoking Treatment for Ontario Patients (STOP) participants who self-reported having ever been diagnosed by a physician as having chronic pain N=50,019	STOP Program provides NRT and behavioural counselling at no cost to patients; Type, dose, and length of treatment is personalized	Secondary analysis	Chronic pain diagnosis negatively impacts smoking abstinence; Chronic pain as a significant (10%) predictor of poorer quit outcomes

Zawertailo et al, in preparation

Final Takeaways/Summary

- Acute analgesic effects of nicotine make smoking widely used for pain management
- Smokers with chronic pain as less likely to initiate quit attempts/achieve abstinence and more likely to relapse
- Difficult for patients with chronic pain to quit smoking
- Strong association between chronic pain and nicotine dependence
- Poorer smoking cessation outcomes
- For smokers with acute or chronic pain, tailored treatment approaches are recommended

Questions & Discussion

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Thank You

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