Street Fentanyl and its Analogues
What Pharmacists Need to Know

Welcome
We will begin shortly.
The Canadian Pharmacists Association is pleased to be partnering with Prof. Michael Beazely and The School of Pharmacy, University of Waterloo

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

Special thanks to current and former School of Pharmacy Students for their contributions to aspects of this presentation: Heidi Fernandez, Morensa Lam, Alicia Oesch, and Danyah Musbah
Today’s Speaker

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Disclosure(s)

I have no current or past relationships with commercial entities

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Learning Objectives

• To understand what we know, and what we don’t know, about illicit fentanyl and its analogues

• To understand how fentanyl analogues are imported and processed

• To understand how naloxone works to reverse fentanyl overdoses
Poll Questions
Outline

Opioid refresher

Opioid overdose

Illicit fentanyl past and present

Non-fentanyl illicit opioids

Potency, purity, sources, administration

Naloxone and fentanyl
What is an Opioid?

Any chemical that activates opioid receptors can be described as an opioid:

- chemicals produced in the human brain
- chemicals found in nature
- modified versions of natural opioids
- fully synthetic chemicals
What is an Opioid Receptor?

Opioid receptors are G protein-coupled receptors

Found in many cell types, including neurons

The three main types of opioid receptors are:

μ “Mu”
δ “Delta”
κ “Kappa”
What do Opioids Do?

- relief of pain and altered pain perception
- sedation and anesthesia
- cough suppression
- constipation/treatment of diarrhea
- miosis (small pupils)
- euphoria
- tolerance, dependence, addiction
- nausea and vomiting
- sweating
- respiratory depression
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- sweating, itching
- respiratory depression
The Respiratory Centre

The respiratory centre controls breathing without conscious control

When oxygen levels fall (and carbon dioxide levels start to rise) the respiratory centre causes you to breath more and rapidly

When oxygen and CO2 levels normalize breathing slows
Opioid Overdose

Opioid receptors are present in the respiratory centre and serve a physiological role

At high doses, opioids interfere with respiratory centre function

Over-activation of opioid receptors make the respiratory centre less and less sensitive to rising carbon dioxide levels in the blood

Breathing becomes less frequent, more shallow, and ultimately stops during an opioid overdose
Opioid Overdose

In addition to respiratory depression, an overdose victim will present with unconsciousness/unresponsive, miosis, cold/clammy skin, blueish lips (https://www.youtube.com/watch?v=oT8EsHuikwY)

In addition to respiratory depression, pulmonary edema and cerebral edema may contribute to overdose deaths
Illicit Fentanyl

Fentanyl is a potent, prescription opioid, used in anesthesia, for pain, severe and/or chronic pain, pain in end of life care

Typically administered as a patch placed on the skin

Illicit (“bootleg”) fentanyl include fentanyl itself and 35+ chemically-related fentanyl analogues that are synthesized and sold outside regulatory systems
Illicit Fentanyl

(a) Fentanyl

(b) Acetyl fentanyl

(c) (Iso)butyryl fentanyl

(d) Ocfentanyl
New Crisis or 40 Year-Old Story?

“In the last week of December in 1979 two very unusual overdose deaths occurred in Orange County, California.”

Appeared to be a classic heroin overdose, except no heroin, or any drugs, were detected

As additional reports came in, links between the victims and the use of “synthetic heroin” emerged

The synthetic heroin was acetylfentanyl and came to be known as “China White”
New Crisis or 40 Year-Old Story?

Illicit fentanyl continued to persist at low levels throughout the 1980s, 1990s, and 2000s

The current “Opioid Crisis” began in the early 2010s, as cheap and readily available imported fentanyl filled a void left by reductions in the availability of diverted prescription opioids, particularly OxyContin as well as fentanyl patches

We’ve replaced pharmaceutical grade opioids, and heroin, with more potent, illicitly-produced opioids


ABSTRACT: Historically, drugs of abuse have come from two sources: plant products and diverted pharmaceuticals. Today, new, totally synthetic drugs produced by clandestine laboratories have become an increasingly important source of abused substances. Of particular concern are the fentanyls, a family of very potent narcotic analgesics, which first appeared on the streets in California in 1979 under the name “China White.” At least 10 different analogs have been identified to date and are thought to be responsible for over 100 overdose deaths. The fentanyls are not used by any particular ethnic or age group, but rather by the general heroin using population. Their use, however, does seem to be restricted to suburban, rather than urban areas, and almost exclusively to the state of California. The most potent analogs, the 3-methy- and beta-hydroxy-fentanyls, may be up to 1000 times as potent as heroin, but are not chemically related to the opiates and therefore not detected by conventional narcotic screening tests. However, using a sensitive radioimmunoassay highly specific for the fentanyls they can be measured at the very low concentrations observed in body fluids, generally less than 10 ng/mL. It is likely that, as efforts to restrict the importation of natural products and prevent diversion of pharmaceuticals become more effective, the fentanyls and other synthetics will become increasingly important drugs of abuse.

KEYWORDS: workshop, toxicology, designer drugs, fentanyl, China White

"Designer drugs" is a term that has been used recently to describe synthetic drugs of abuse [1,2]. It is not a precise scientific term and has been indiscriminately applied to a variety of contemporary drugs of abuse. More correctly, this term should be applied to only those drugs that are (1) synthesized from common chemicals, (2) exempt from control by the Drug Enforcement Administration because of their unique chemical structure, and (3) skillfully marketed under attractive, often exotic names.

Past History

The use of drugs for medical and nonmedical purposes can be traced back to man’s early history for as Aldous Huxley said, “Pharmacology is older than agriculture.” Until the nineteenth century, drugs came from two sources—unrefined plants and animal products—and were usually taken by only one route of administration—oral ingestion. Eating crude plant material offered a certain safety margin since biologically active components are usually present in small amounts and overdosing was physically difficult.

It might be argued that a major trend throughout the history of drug use and abuse is the increased hazards associated with the use of more potent drugs, either purified plant materials or new synthetic compounds. Drugs became more potent as chemists were able to extract...
## Fentanyl Potency

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Effective Dose* (pure product)</th>
<th>Lethal Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>0.001 mg</td>
<td>0.02 mg</td>
</tr>
</tbody>
</table>

*in an opioid-naive patient, i.e. no tolerance
Fentanyl Pharmacology and Administration

We assume, but do not have definitive data, that all fentanyls have a similar receptor-binding profile, exerting primarily mu-opioid receptor-mediated actions for euphoria and overdose effects.

Fentanyl and its analogues can be administered via several routes, including, oral, transdermal, sublingual, buccal, insufflation, inhalation, parenteral, rectal.

It is unclear whether there are differences between fentanyl analogues with respect to bioavailability.
Illicit Fentanyls in North America

Fentanyl, beta-hydroxythiofentanyl, 3-methylfentanyl, acetylfentanyl, acrylfentanyl, butyrfentanyl, furanfentanyl, carfentanil

What we know:
- variability in potency, all have opioid activity

What we don’t know:
- definitive human potency, duration of action, metabolism, metabolite activities, unique actions and toxicities
Example: Acrylfentanyl

Emerged in the North American market in 2017

Primary illicit fentanyl associated with overdose in Sweden in 2015 and 2016

Media reports that acrylfentanyl overdose is “resistant” to naloxone reversal

MDMA laced with acrylfentanyl seized in Denmark

http://exclusive.multibriefs.com/content/new-fentanyl-variant-makes-overdoses-tougher-to-treat/medical-allied-healthcare)
Example: Acrylfentanyl

Similar potency to fentanyl

Users report easy online availability and very low price point, e.g. 1 gram for $45

Administered via nasal spray, vaped

User reports suggest that acrylfentanyl produces fewer ADRs compared to other opioids, specifically fewer GI side effects and itch

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Reddit Web Forums. Thread: Acrylfentanyl?.

Reddit Web Forums. Thread: General acryl-fentanyl effects and preparation methods.
Non-fentanyl Illicit Opioids in North America

U-47700, AH-7921, MT-45

What we know:
- these were drugs in the pharma pipeline, we know a considerable amount about their preclinical info
- slightly more potent than most prescription opioids, less potent than fentanyl

What we don’t know:
- definitive human potency, duration of action, metabolism, metabolite activities, unique actions and toxicities
Example: U-47700

Has caused overdose deaths in Canada and the US

One set of overdoses occurred in victims that had snorted what they thought was “synthetic cocaine”

Relatively short duration of action, reports of multiple dosing and significant “urges to re-dose”

Illicit Fentanyl Trafficking

Imported (mostly via China) as bulk pure fentanyl
Diluted, typically to 1-3% or less of a bulk powder

It is sold as:
Fentanyl
Heroin
Counterfeit pharmaceutical opioids
(demerol, percocet, oxycontin)

Has appeared in:
Cocaine, Methamphetamine, MDMA
Illicit Fentanyl Trafficking

Also purchased "direct to consumer"

Buying Fentanyl from Online Black Markets

1. BUYER places order with MARKET
2. BUYER sends Bitcoin to MARKET escrow
3. VENDOR gets order and escrow confirmation
4. VENDOR ships product
5. BUYER confirms receipt
6. MARKET releases escrow to VENDOR
7. BUYER leaves feedback on MARKET
Illicit Fentanyl Trafficking
At-risk populations

Few studies to date, most small and regional

E.g. Rhode Island Young Adult Prescription Drug Study (RAPiDS) found that exposure to fentanyl-contaminated heroin was significantly correlated with:

- regular heroin or cocaine use, use of diverted prescription fentanyl, use of prescription opioids to avoid withdrawal, regular injection drug use, history of an opioid overdose
Naloxone

All fentanyl (we think) and other illicit opioids are opioid receptor competitive agonists

Naloxone is opioid receptor competitive antagonist

Receptor affinities for opioids and naloxone are all fairly similar

carfentanil > fentanyl = naloxone > morphine > oxycodone

So naloxone should, given a sufficient dose, be able to reverse any opioid overdose
Naloxone
Naloxone
Naloxone

Anecdotal stories from EMS, ER suggest that in some cases, large doses of naloxone are required to reverse overdoses, 2-10 mg+

IM naloxone is 0.4 mg/mL, intranasal is 4 mg/0.1 mL
Pharmacy Naloxone Distribution: One Size Fits All?

Is intranasal naloxone more effective than IM injections in the field?

How likely are intranasal naloxone or high-dose IM injections to cause severe withdrawal, including agitation and possible aggression, compared to standard IM doses?

How can we distribute the right naloxone product and dose to the right patient?

Would switching from IM to nasal naloxone distribution for all be cost effective?
Thank you!

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