Historical Use & Misuse of Plants as Medicines

Case Studies:

Papaver somniferum
Erythroxylum coca

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Objectives

• After this lecture, medical students should be able to:
  – Describe the history of drugs derived from the opium poppy (Papaver somniferum)
    • Identify medical and societal complications of opioid drugs
  – Describe the history of drugs derived from Erythroxylum coca
    • Identify medical and societal complications of cocaine

Pharmacognosy

• Study of medicinal substances of biological origin
  – primarily from PLANTS

• Plant-derived drugs predominated until organic chemistry revolution of the mid- and late-19th century
  – William Perkin & Mauve
Opioids

- Opium poppy = *Papaver somniferum* – “bringer of sleep”
- Morphine named after Morpheus – God of sleep

Definitions

- **Opium**
  - Extract of the exudate from cutting seed-pods
- **Opiate**
  - Naturally-occurring analgesic alkaloids found in opium
    - Morphine
    - Codeine = methyl morphine
    - many others

Definitions

- **Opioid**
  - Agents producing opiate-like effects and/or binding to opioid receptors
    - Natural: e.g. Endorphin
    - Semi-synthetic
      - Chemical modification of opiate
        - Oxycodone, Heroin
    - Synthetic
      - Structurally different from morphine, but have similar effects
        - Fentanyl, Methadone, Meperidine
History of Opium

• Referenced in Sumerian texts ~4000 yrs ago
  – “hul gil” = plant of joy

• “Thebacium” = ancient Egyptian medications
  – Poppies cultivated near Thebes
    • Thebaine = natural opiate in poppies

Opium Efficacy

• Many traditional remedies had little demonstrable or predictable effect, yet...

  “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

  Thomas Sydenham

Laudanum

• Tincture of Opium
  – Tincture = medicine made by dissolving medicine in alcohol
Opium’s Medical Indications

- Analgesic
  - Pain relief
- Antitussive
  - Cough relief
- Antidiarrheal
  - Poop relief
- Sedative
- Euphoriant

Over-the-counter morphine? Absolutely!

Invention of Heroin

- 1874: English pharmacist C.R. Alder Wright, seeking non-addictive alternative, boils morphine + acetic anhydride producing 3,6-diacetylmorphine

- 1898 - Diacetylmorphine marketed by under the tradename “Heroin”
  - named for German heroisch = heroic
  - Bayer’s 1st “blockbuster drug” (aspirin was 2nd)

Early Heroin Advertising
Felix Hoffman
First synthesized medically-useful forms of Aspirin and Heroin both in August 1898

Heroin

- Diacetylmorphine
  - Acetylation of hydroxyl groups allows heroin to cross blood-brain barrier easier than morphine (less polar)
    - Stronger euphoriant effects
  - De-acetylation occurs spontaneously

How to use Heroin

- The faster it gets into your brain, the better the euphoriant effect
- Pharmacokinetics issue
  - PO: delay in absorption
    - Opium Eating
  - Inhalation
    - Large respiratory surface area
  - Parenteral Injection
    - IV = 100% bioavailability
Heroin Inhalation

• Heroin placed on foil heated with lighter or matches
  – Liquefies into a glob (the “dragon”) and moves around foil emitting white vapor which you “chase” and inhale through a straw

• “Chasing the Dragon”
  – Associated with leukoencephalopathy

What’s wrong with “Heroin Hero”?
The ultimate first-person shooter

The Modern Plague

Biblical Plagues
- Locusts
- Frogs
- Vermin

Modern Plagues
- HIV
- Heroin
If this is not a primary public health concern I don’t know what should be.
How did we get here?

- Traditional paternalistic medicine (of only a few decades ago) relegated opiates only to treatment of the most severe pain

- Oligoanalgesia
  - oligo = “few, little”
  - analgesia = “without a sense of pain”

<table>
<thead>
<tr>
<th>Table 2: Factors Contributing To Oligoanalgesia</th>
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<tr>
<td>• A preoccupation with the diagnosis and treatment of the underlying medical problem</td>
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<td>• Concerns about masking symptoms</td>
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<td>• Fears about contributing to or causing addiction</td>
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<tr>
<td>• Overestimation of pain experienced by patient</td>
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<td>• Cultural differences in pain expression</td>
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<td>• Poor communication</td>
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<td>• Insistence of patients to complain of pain or demand pain treatment</td>
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<tr>
<td>• A pain-free interval after acute traumatic injuries</td>
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<td>• Inadequate training in the recognition and management of pain.</td>
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Attitudinal Change

- 1980s: Move to improve Pain Management
  - “opioid medications can be safely and effectively prescribed to selected patients with relatively little risk of producing the maladaptive behaviors which define opioid abuse.” Pain 1986;25(2):171
  - Pain = “5th Vital Sign”
    - Destigmatize opiates

  - Unfortunately, the risk of addiction was vastly underestimated and/or patients not selected appropriately

America Consumes 80% of the World’s Prescription Painkillers

By John Lavitz 09/20/14

Though ranking 24th in literacy and dead last among developed nations in healthcare, the U.S. is number one when it comes to taking prescription drugs.

- US = 4.6% of world’s population
- 110 tons of opiates / yr
- 136 million prescriptions of Vicodin in 2013
  - 99% of world’s hydrocodone consumption
Cocaine

- Derived from *Erythroxylum coca*
  - Shrub native to South America

- Coca leaves used by native population for >5000 yrs
  - Traditional use = leaves chewed with powdered lime (CaCO$_3$)
  - Makes freebase cocaine in your mouth!
Peru: History of Coca, “the Divine Plant” of the Incas

The distance an Indian will carry his coca—or load, of about a hundred pounds, under stimulus of one chew of coca is spoken of as a cusco, just as we might say a certain number of miles. It is really a matter of time rather than distance, the first influence being felt within ten minutes, and the effect lasting for about three-quarters of an hour, during which time three kilometres on level ground, or two kilometres going up hill, will usually be covered. Although the roads are marked out with league stones, the exact number of miles these represent is a varying quantity, and travellers soon fall into the local habit of computing distance by the cusco as more exact.

These coca—or burden bearers, which is the Quichua term or cocafores—as they are termed on the coast, commonly travel six to eight cuocos a day without any other food excepting the coca leaf used in the manner as indicated.
Coca Leaf → Cocaine

- **1859-60:**
  - Albert Neimann isolates cocaine for PhD thesis

- **1884:** Cocaine’s best year ever!
  - Karl Kollar
    - Austrian ophthalmologist
    - Cocaine = local anesthetic for eye surgery
    - Nickname = “Coca Koller”

Coca Leaf → Cocaine

- **1884:** Cocaine’s best year ever!
  - William Halsted
    - American surgeon
    - Founding professor at Johns Hopkins
    - Invented the radical mastectomy
    - First injected cocaine for regional anesthesia via nerve block
    - Later traded his cocaine addiction for a morphine addiction
Coca Leaf → Cocaine

• 1884: Cocaine’s best year ever!
  – Sigmund Freud
    • Austrian neurologist
    • Father of psychoanalysis
  – Writes “Über Coca”
    • Recommends cocaine:
      Stimulant, Anesthetic, Asthma,
      Digestive disorders, Aphrodisiac
    • Treatment of addiction to morphine and ethanol
I am Pope Leo XIII, and I approve of this message.

More Cocaine History

- Snorting becomes popular ~1905
  - 1st report of nasal damage in 1910
- 1922:
  - Outlawed as narcotic in United States
- Free-basing developed ~1976, probably in CA

- Cocaine had been sold as HCl salt
  - Easier to process
  - But you can’t smoke it!
- Free-basing converts to uncharged molecule
  - Doesn’t burn up
  - Crosses membranes easier, giving a more intense euphoric effect
How to Free-Base Cocaine

• Dissolve cocaine-HCl salt in H₂O
• Raise pH by adding lye (NaOH)
• Heat mixture over flame

How to Free-Base Cocaine

• Add organic solvent and mix
  – Free-base will enter organic phase, like separatory funnel in chem lab
• Vaporize off organic solvent with heat until only freebase is left
  – DANGER: Don’t burn yourself
• Smoke and Enjoy!

Crack Cocaine

• User-friendly product
  – Manufacturer free-bases the cocaine for you
  – No risk of self-immolation
• Small “rocks” sold in tiny glass vials
  – 0.1 gram costs $20-$40
• Called “crack” because air pockets in imperfect crystals cause rocks to break with a cracking noise when heated