Methadone — “It was the best of drugs it was the worst of drugs…”

"I started using when I was 12, by the age of 36 I was shooting up methadone between my toes...

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Quotes about Drugs

- "Doctors give drugs of which they know little, into bodies, of which they know less, for diseases of which they know nothing at all."
  Voltaire

- "All drugs are poisons the benefit depends on the dosage."
  Philippus
  Theophrastus Bombast That of Aureolus Paracelsus (1493-1541)

- “Medicines are nothing in themselves, if not properly used, but the very hands of the Gods if employed with reason and prudence.”
  Herophilus 300BC
Synthesized in Germany (WWII) – as a morphine replacement
Adverse effects precluded further development
The US obtained control and Eli Lilly & Co. started production – 1947
1960’s Vincent Dole, MD via a research grant credited with the daily dose protocol for heroin dependency
2013 – 92,000 lbs. (45.5 tons) of methadone manufactured world-wide
FDA-approved for: pain, detoxification and maintenance treatment for opioid use disorder
Methadone Pharmacology

- Mu receptor agonist (R isomer)
- NMDA receptor antagonist
- Weak serotonin-reuptake inhibition

Methadone Pharmacokinetics

- Major metabolic pathway – CYP2B6 (polymorphism); not affected by p-glycoprotein transporter

- Pharmacology – “complex”, inter- and intra-patient variability in disposition (pharmacokinetics), subject to DIs (HAART and rifampin – induction)

- Prolonged elimination half-life - 1-2 days; auto induction occurs due to CYP2B6 up regulation

The Problem

- Prolonged QT syndrome and methadone

- Consequences – torsade de pointes
  (syncope, VT, sudden death)
Methadone Screening Guidelines

1. Inform patients about risk
2. Ask about structural HD, arrhythmia, syncope
3. ECG at time 0, 30 d and yearly
4. QTc > 450 < 500 ms – monitor closely
   > 500 ms – d/c, change dose, change drug, evaluate contributors
5. Awareness of drug-drug interactions


- 6.1 per 100,000 versus 16.3 per 100,000
- Greatest increase in 55-64 age group
- **West Virginia** (41.5), New Hampshire (34.3), Kentucky (29.9), and Ohio (29.9)
- Heroin OD deaths – 8% versus 25%
- **Methadone deaths** – 12% versus 6%

https://www.cdc.gov/nchs/data/databriefs/db273df_Accessed_3-28-17
West Virginia – Methadone-Associated Deaths

- **2005-2010**
  - Total deaths – 3098
  - Mean age – 40.5 yrs
  - Methadone – 609 (19.7%)
  - Mean age – 36.9 yrs
  - Total number of drugs – 2.7± 1.3

- **2010-2014**
  - Total deaths – 2819
  - Mean Age – 42.7 yrs
  - Methadone 224 (7.9%)
  - Mean age – 40.4 yrs
  - Total number of drugs – 3.5±1.6

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