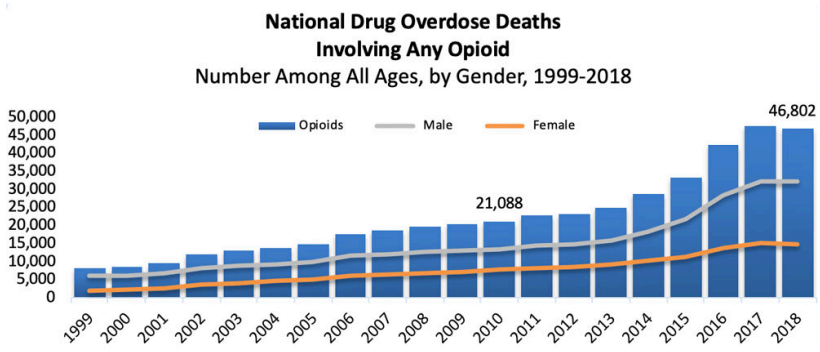
The effects of Covid-19 on the opioid crisis in America:

Scope of the problem prior to Covid-19:

- From 1999–2018, ~450,000 deaths from an opioid overdose
- Yearly death toll has increased every year other than 2017 since the 1990s
- Approximately 128 deaths per day as of 2018
- In 2019, >70,000 deaths from drug overdose, almost 50,000 of which were opioid-related, and 35,000 of which were from fentanyl and other synthetics
- CDC estimates that the "economic burden" of prescription opioid use alone is $78.5 billion per year.
- The market prices of life-saving drugs such as naloxone continue to rise despite no changes in the cost of production

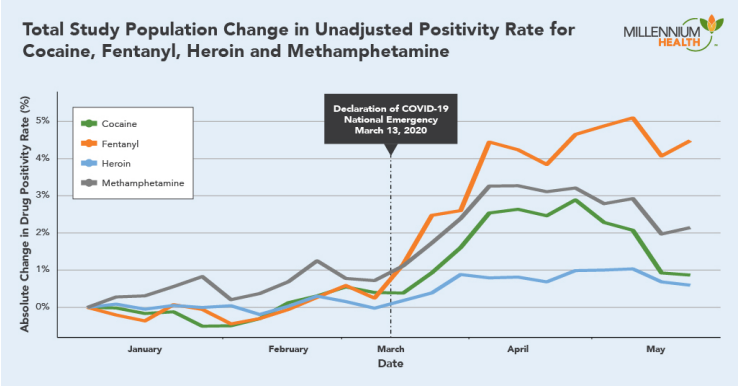


https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates

The Covid-19 pandemic has greatly exacerbated the opioid crisis:

Shelter-in-place orders and the fear of infection have led to the collapse of support systems:

- Restricted access to treatment programs
- Decreased emergency room calls, and a lack of hospital beds for overdose victims
- AA and NA meetings suspended, and inability to meet with mentors
- Methadone clinics have closed, and those that remain open harbor rampant infections
- Loss of jobs and structure addicts need to rebuild
- NIH/NIDA have suspended IRBs, clinical trials, and patient studies
- Stress is the number one factor that leads to relapse



https://www.millenniumhealth.com/news/signalsreportcovid/

Early evidence suggests:

- Since the the start of the pandemic, drug overdoses may have increased more than **20%**
- A study of >500,000 urine tests revealed a **32%** increase in non-prescribed fentanyl
- The rate of suicide among addicts has increased

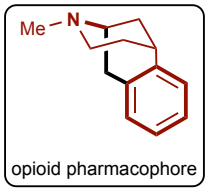
Addicts are at a much higher risk of death from Covid-19:

- Addicts are immunocompromised, and opioid use leads to respiratory depression
- Many addicts are within the prison system and low-income neighborhoods with greater risk of infection
- Self-isolation has led many to overdose alone, with nobody to call for help or administer naloxone

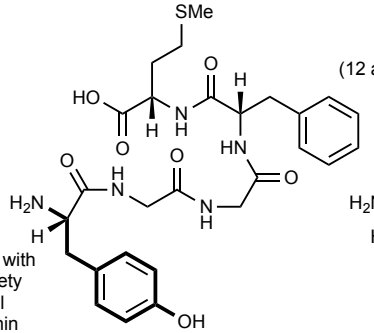
References:

- https://www.drugabuse.gov/videos/effects-covid-19-opioid-crisis-francis-collins-nora-volkow
- https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis
- https://www.cdc.gov/drugoverdose/epidemic/index.html

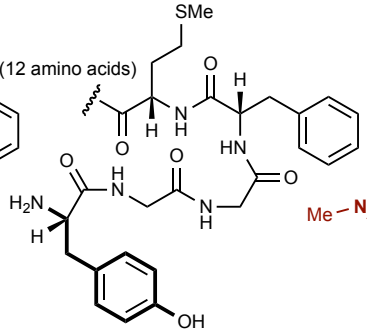
Buprenorphine (Subutex) and Naloxone (Narcan)



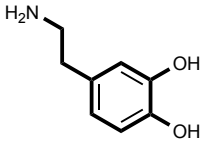
Opiates are believed to act at the μ-opiod receptor, with a conformationally restricted phenethylamine moiety (emphasized in bold) that mimics the *N*-terminal tyrosine residue found in enkephalin and endorphin neuropeptides (as well as neurotransmitters such as dopamine). The rise of synthetic opioids has revealed that the primary pharmacophore may actually be the phenyl-linked piperidine ring, with a conformationally restricted tertiary amine (highlighted in red).



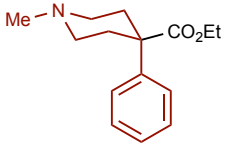
met-enkephalin



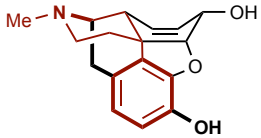
α,β,and γ-endorphins



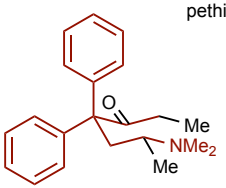
dopamine



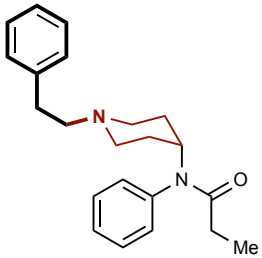
pethidine



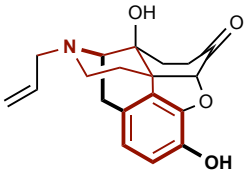
morphine



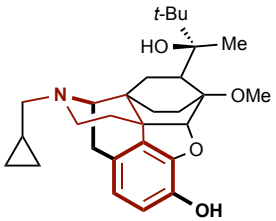
methadone



fentanyl



naloxone



buprenorphine

- Naloxone is a lipophilic, non-selective competitive μ-opioid receptor antagonist with excellent BBB penetration, and IC50 of 0.59 nM at MOR
- Buprenorphine is a partial MOR agonist with a low ceiling dose, above which there is no additional recreational or therapeutic benefit
- Naloxone is used intravenously to reverse acute opioid overdose, while buprenorphine is used for long-term therapy for addicts
- Naloxone has very poor oral bioavailability, and is often added to oral formulations of buprenorphine to discourage addicts from injecting it
- If naloxone is administered in the absence of concomitant opioid use, no functional pharmacological activity occurs, except the inability for the body to combat pain naturally.

Naloxone is absorbed so quickly and is so potent that catatonic patients can awake within seconds and experience dangerous withdrawal symptoms in minutes

"It's like waking the dead"

"It's like a fire extinguisher"

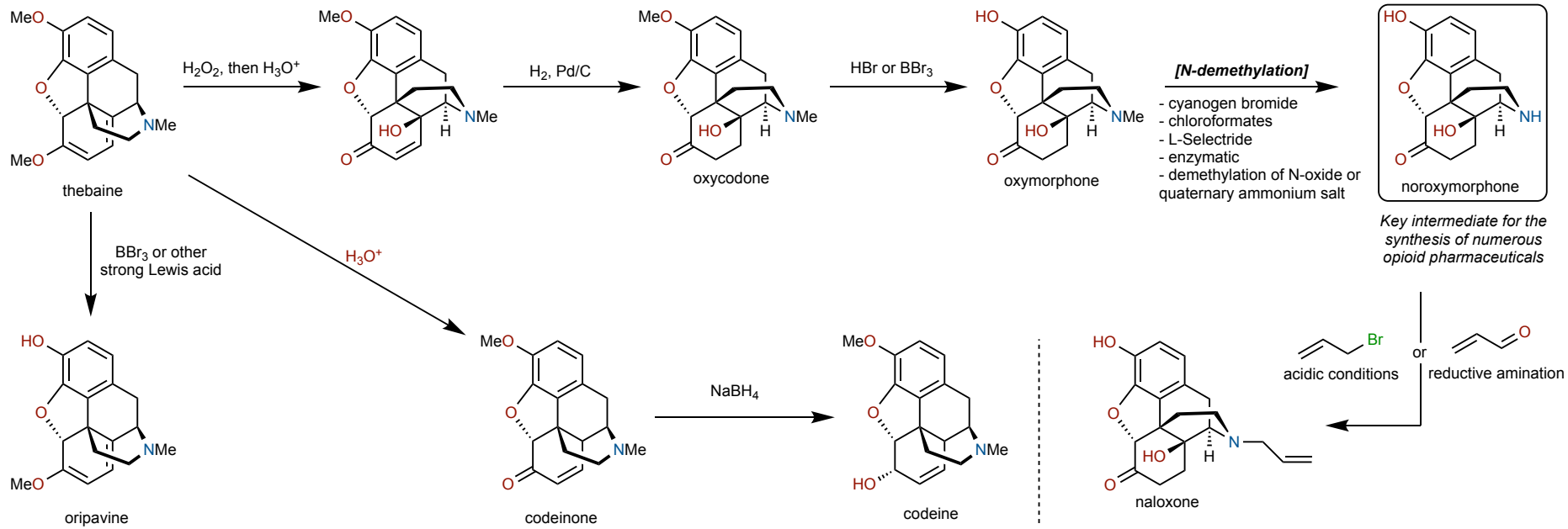
"It is not a pleasant experience. It takes all the drugs out, so you go into instant withdrawal. I can remember coming round and feeling really ill – cold, shivering, aching. But without it I would have died."

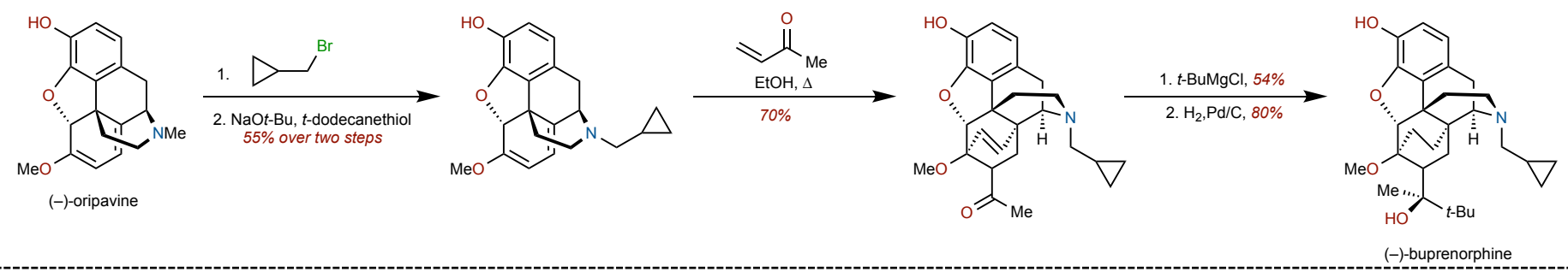
Currently 38 states have laws that make it possible for people to access naloxone without a prescription in specific circumstances

In 2015, the FDA approved a Narcan nasal spray, to allow family and friends of addicts to administer the drug without intravenous injection

Buprenorphine (Subutex) and Naloxone (Narcan)

Major product from crude opium





Theodor WB, and Roux L (2016) Improved method of manufacturing buprenorphine and analogues thereof from oripavine, Patent WO 2016/078833A1.