

# Opiophobia

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# Opium

From "opos," the Greek word for juice.

Papaver Somniferum  
(Opium Poppy)



# Opium

“Remedy to prevent excessive crying of children.”

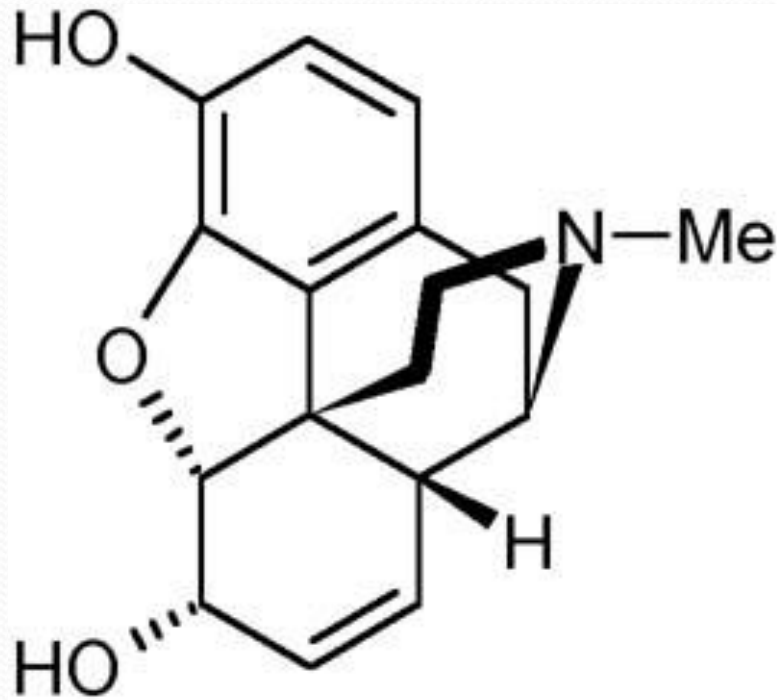
The Ebers Papyrus  
(ca.1500 B.C.)

“Presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow.”

The Odyssey, Homer  
(Eight century B.C.)



# Morphine

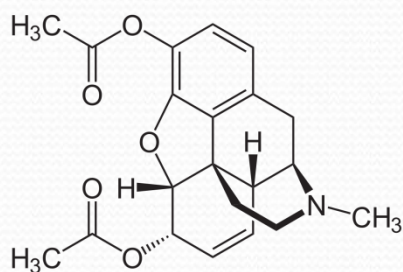


1806 - Friedrich Sertürner

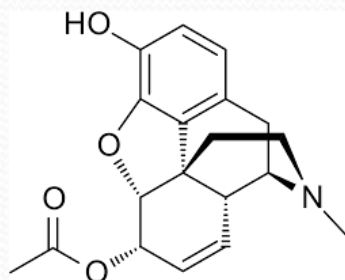
Morphine (Morpheus, the Greek god of sleep)

# Development of opioid analgesics

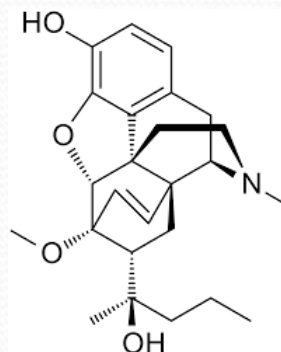
## Derivatives of morphine



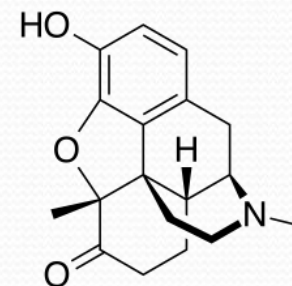
**Heroin**



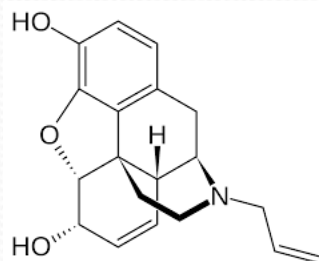
**6-Monoacetylmorphine**



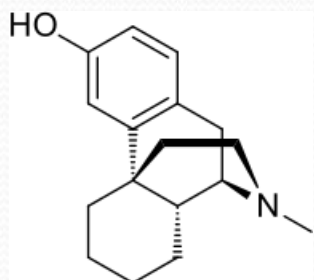
**Etorphine**



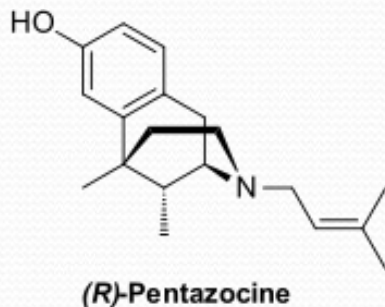
**Metopon**



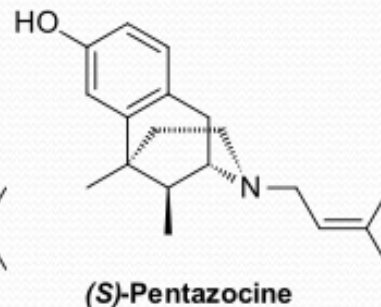
**Nalorphine**



**Levorphanol**

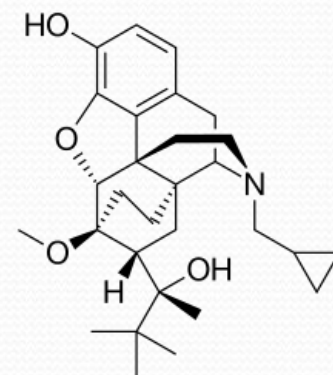


**(R)-Pentazocine**



**(S)-Pentazocine**

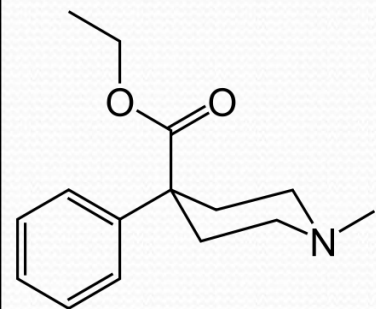
**Pentazocine**



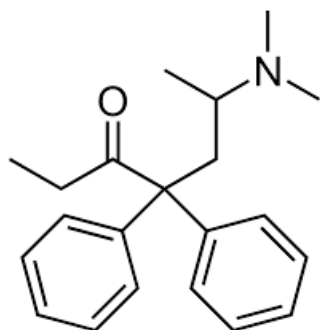
**Buprenorphine**

# Development of opioid analgesics

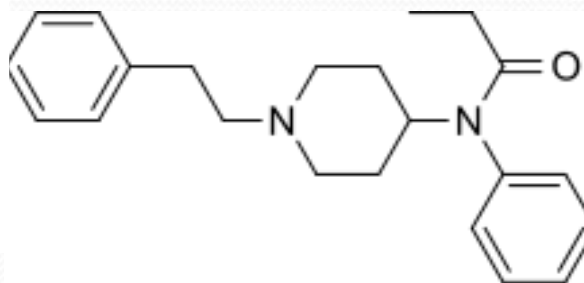
## Fully synthetic compounds



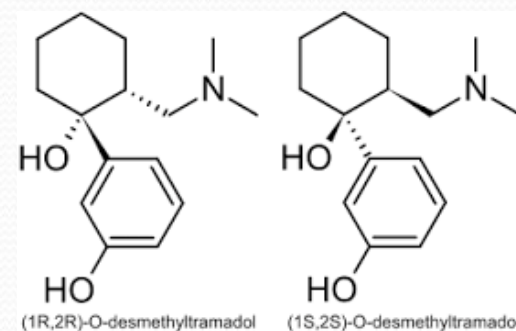
**Pethidine**



**Methadone**

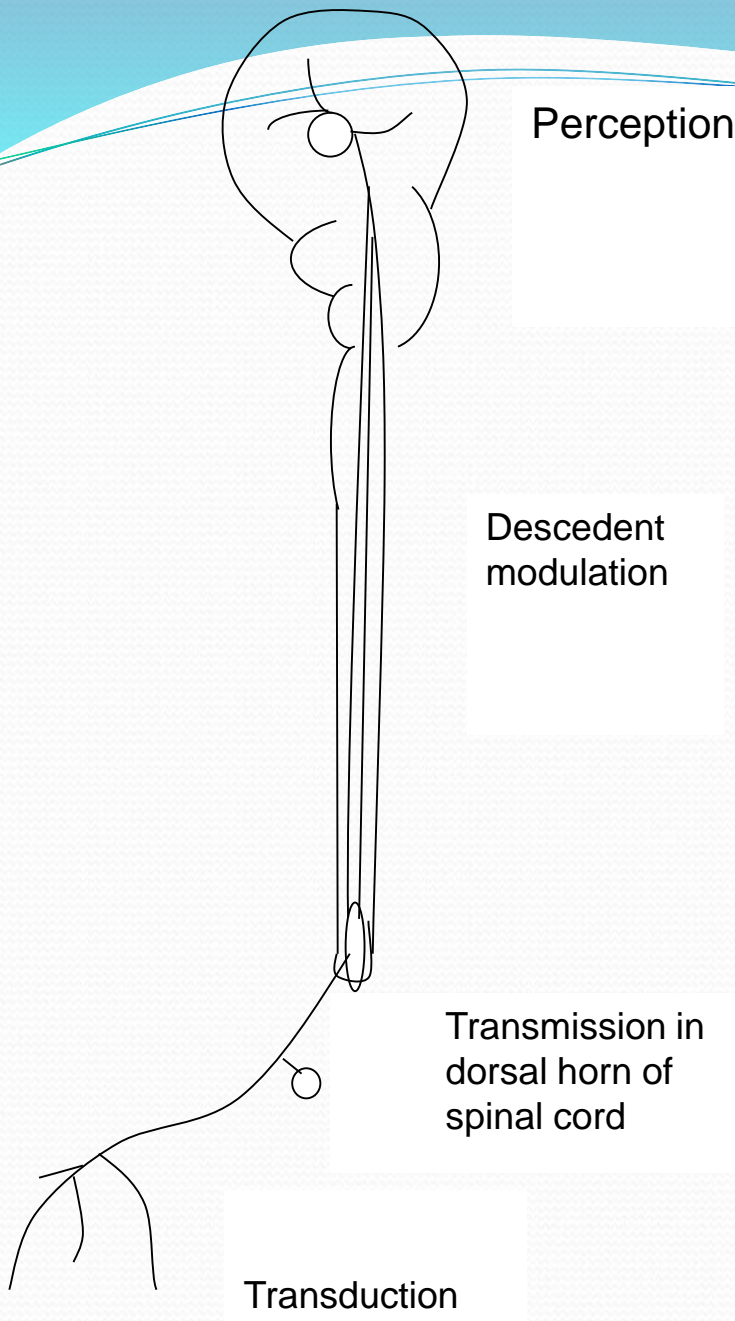


**Fentanyl**



**Tramadol**





# Opioid analgesics: mechanisms of action

Opioids acts through opioid receptors.

They work at multiple sites in pain pathways.

The most potent analgesics in general.

# Opioid analgesics: indications

Treatment of moderate to severe acute and chronic pain.

A favorable risk-benefit ratio in the treatment of

- acute pain (postoperative, trauma, *etc.*)
- cancer pain, and
- pain at the end of life.



# Clinical effects of opioids

Respiratory	Respiratory depression, cough reflex inhibition, histamine mediated bronchospasm.
Cardiovascular	Hypotension, peripheral vasodilatation, bradycardia, tachycardia.
Neurological	Analgesia, hyperalgesia, sedation, confusion, headache, dizziness, hallucinations, mood swings (euphoria/dysphoria), addiction, myoclonus, convulsions (eg. petidine, propoxyphene), psychomimetic effects, coma.
Gastrointestinal	Nausea, vomiting, constipation, reduced secretion in the gastrointestinal tract, increased pressure in the bile ducts.
Urogenital	Urinary retention, libido reduction, decreased ejaculate volume, decreased sperm motility, absence of ovulation, amenorrhea.
Ophthalmologic	Miosis, swelling, redness
Dermatological	Hives (histamine), rash, flushing, itching, sweating.
Endocrinology	Decreased release of antidiuretic hormone, increased prolactin secretion, decreased gonadotrophin release, decreased testosterone secretion, cortisol.
Bone-muscle	Rigidity of skeletal musculature (fentanyl).
Immune system	Reduced immune response.



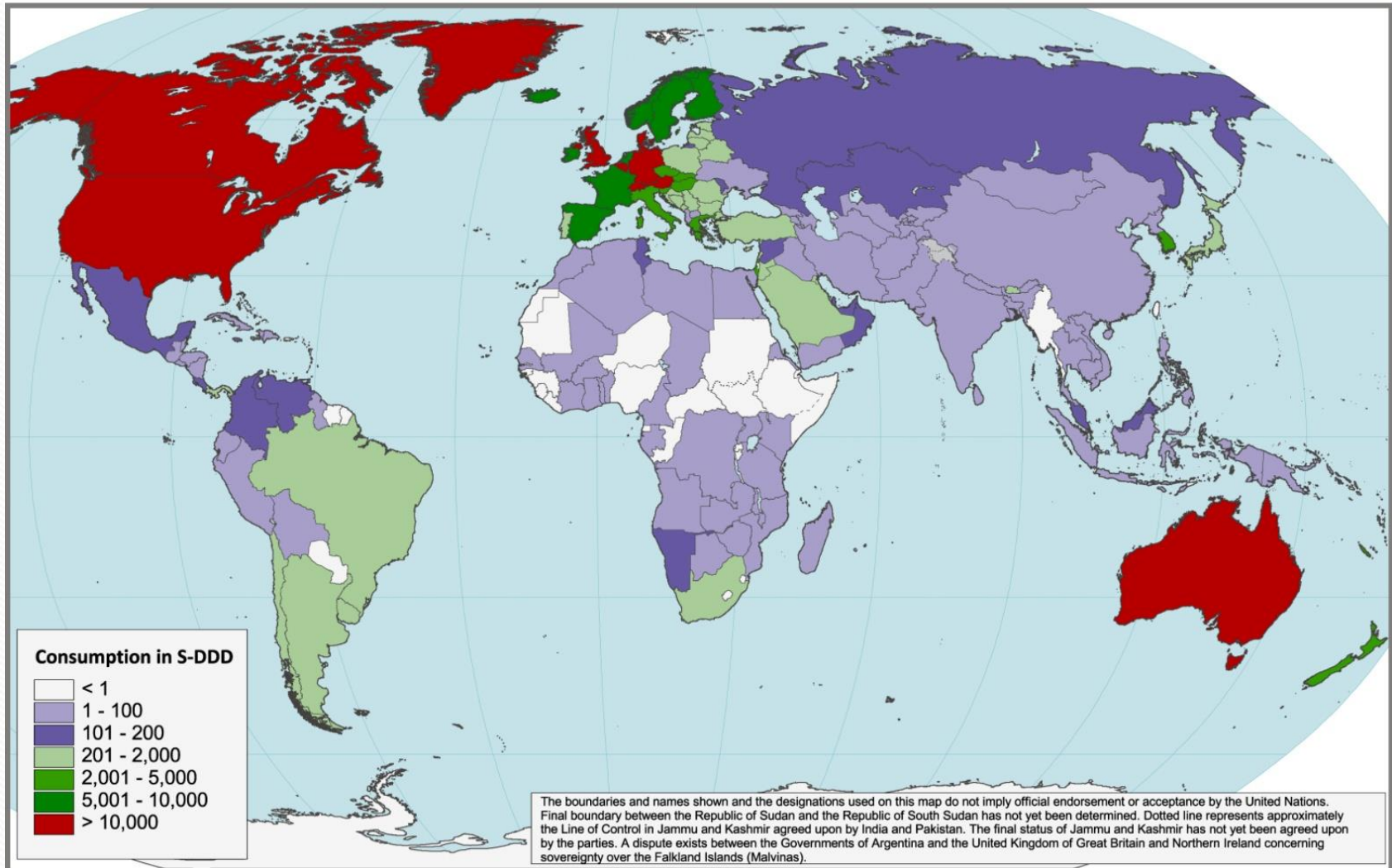
## **Single Convention on Narcotic Drugs, 1961, New York**

The Convention obligated the governments of the signatory countries:

1. To prevent the abuse of narcotics, and
2. To ensure their availability for the treatment of pain and the elimination of suffering.

# Availability of opioids\* for pain management (2010-2012 average)

(Consumption in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day)



\*Codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine and trimeperidine.





# The International Narcotics Control Board

highlights inequalities between high and low/middle income countries in the availability and access to controlled drugs including opioid drugs.

About 83% of the world's population, predominantly from low- and middle-income countries, has limited or no access to drugs containing narcotic drugs. They consume 8% of the world's morphine supplies.

More than 25 million people die annually in severe pain (Lancet Commission on Palliative Care and Pain Relief Study Group, 2017)

**Moderate to severe pain associated with trauma, surgery, cancer and palliative care is not effectively treated!**



# The International Narcotics Control Board

## Causes:

- Unnecessarily stringent regulation in most of the world that prevents the availability of opioid analgesics,
- The negative perception of opioids use by patients, families, lack of training or awareness among health workers,
- Limited financial resources, etc.



# Opiophobia

- Is unjustified fear of the therapeutic use of opioids (cancer pain, acute pain, etc.), primarily the fear of the development of iatrogenic dependence, tolerance, undesirable effects of opioids (eg. respiratory depression) and restrictive regulations controlling the prescription of opioids.
- May be present among health workers (doctors, nurses), patients and their families and health authorities.
- Is caused by: ignorance, prejudice, economic-marketing strategies and limited availability of opioids/morphine.





# Opioids: cancer pain

- ❑ In 1986, the World Health Organization (WHO) proposed a guide to pain therapy and advocated the widespread use of oral morphine and other opioid analgesics in patients with cancer pain.
- ❑ Opioids are key and irreplaceable drugs for the successful elimination of moderately strong and severe cancer pain.
- ❑ Non-prescribing opioids due to opiofobia is an important barrier to successful treatment of cancer pain.

# How to fight against opiofobia?

- ❑ Education of patients and members of their families.
- ❑ Multidisciplinary approach.
- ❑ It is necessary to explain how opioid analgesics work and how important they are in treating cancer pain, and that they are safe drugs when used properly.
- ❑ The education of doctors and other health professionals.



# Opioids: chronic non-cancer pain

- ❑ Chronic non-cancer pain is difficult to treat.
- ❑ It does not respond well to non-opioid analgesics.
- ❑ In the absence of effective alternative treatments for the treatment of chronic pain in the USA, doctors in the USA for the past two decades have opted for opioid pharmacotherapy, traditionally regarded as a medication for the acute pain and palliative care of cancer patients.



# Opioid crisis (epidemic): causes

- Publication of certain evidence, although weak and insufficiently scientifically based, that opioids can be safe in selected individuals with chronic pain.
- Pharmaceutical companies promoted the use of opioid analgesics (eg. OxycontinR) for the treatment of chronic pain by aggressive marketing campaigns.
- Liberalization of the law regulating the prescription of opioids for the treatment of chronic pain.
- Advocating doctors and other healthcare professionals against the prohibition of the prescription of opioids.
- Also, the consensus of professional associations for the treatment of pain emphasized that chronic pain was not sufficiently treated.

# What is opioid crisis?

- The quantity of opioids prescribed in the USA increased 4 times in the period from 1999 to 2010, although Americans did not report progress in the treatment of pain.
- Unused opioids have become increasingly available in American homes and communities, and therefore conditions have been created for redistribution of prescription drugs instead of medical, for non-medical use.
- This increased the incidence of adverse events, including abuse, dependence and increased mortality from opioid use.



# Opioid crisis: characteristics

- U.S. population, constituting less than 5% of the world's population consumed 83% of the world's oxycodone, and 99% of hydrocodone in 2008.
- During 2013, morphine consumption in the United States amounted to 57.3% of total world consumption, and in 2015, 29.3% of the total world consumption of fentanyl and 30% of the total global consumption of opioid analgesics was consumed in general.
- The rate of mortality from opioid overdose in US between 1999 and 2016 increased 5 times. Of all drugs, opioids are the most common (66%) cause of fatal outcome due to overdosage. On average, this is 115 deaths caused by opiates every day, which is more than those caused by firearms or traffic accidents.



# How US fight against opioid crisis?

- US limit the prescription of opioids.
  - The difficulty in supplying opioids to patients with chronic non-cancer pain,
  - The number of lethal overdoses with fentanyl and other synthetic opioids has more than doubled from 2015 to 2016.
- Prescription drug monitoring program (an electronic database) that use health information technologies and exchange data across a centralized platform provide promising results.
- In 2016, the Centers for Disease Control and Prevention in the United States published recommendations for the prescription of opioids for the treatment of chronic pain and are intended for doctors in the primary health care.

# **Opioid crisis promotes opiofobia!**

The measures against opioid epidemics may adversely affect the use of opioids in low-income countries.



# Are there opioid crisis in Europe?

- There is a fundamental concern that the epidemic from North America will spread to the rest of the world and become a pandemic.
- Prescription opioids in Europe today are responsible for three quarters of deaths due to overdose among people aged 15 to 39.
- Abuse of prescription drugs among adolescents in Canada, Australia and Europe at rates is similar to those of the same age in the United States.

# Opioid consumption in Serbia

- Opioid analgesics have been shown to be significantly less used in pain therapy compared to some countries in the region.
- In recent years there has been an increase in consumption of opioid analgesics.
- In Serbia, legislation related to opioids has been improved.
- According to the [report of the International Narcotics Control Board](#) for the period [2013-2015. year](#), Serbia is roughly at the level of [Bulgaria](#), and behind [Hungary, the Czech Republic, Croatia, Slovakia, Italy](#), and ahead of [Romania, Ukraine, Turkey, Belarus, Lithuania](#), etc.
- In [2012 and 2013](#) consumption in Serbia was [8.8 times lower than in Croatia](#). In [2015](#), this difference was reduced to [7.6](#) times. In both Croatia and Serbia, tramadol is used most frequently, followed by fentanyl, and morphine (Rančić et al., 2016).



# Opiophobia in Serbia

- Opiophobia is significantly present in Serbia.
- A research on the presence of opiophobia among patients was conducted at the Institute of Oncology and Radiology of Serbia (Bošnjak et al., 2009; Vujović et al., 2013). Approximately 93% of patients experienced opiophobia as follows:
  - Fear of addiction (about 84%),
  - Fear of opioid adverse reactions (about 58%),
  - Fear of tolerance (about 45%),
  - Fear that opioid use means that the terminal phase of the disease has occurred (about 35%),
  - Fear that others will think about him as coward.

# Opioid prescribing habits in Serbia

- There are few studies (Jovičić et al., 2015; Knezevic et al., 2018).
- Doctors in Serbia, compared to American doctors, are more cautious when they prescribe opioids to people with chronic non-cancer pain, which is in line with current guidelines.
- More research is needed.



# Conclusions

- There are two parallel crisis in the world regarding opioids use.
- The first crisis is undertreatment of pain due to poverty and/or opiofobia.
- The second crisis relates to opioid abuse, especially in America.
- At the heart of both crisis is inadequate or inaccurate understanding of opioid analgesics.
- More research and education on opioids may improve their use in pain management.

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# References

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