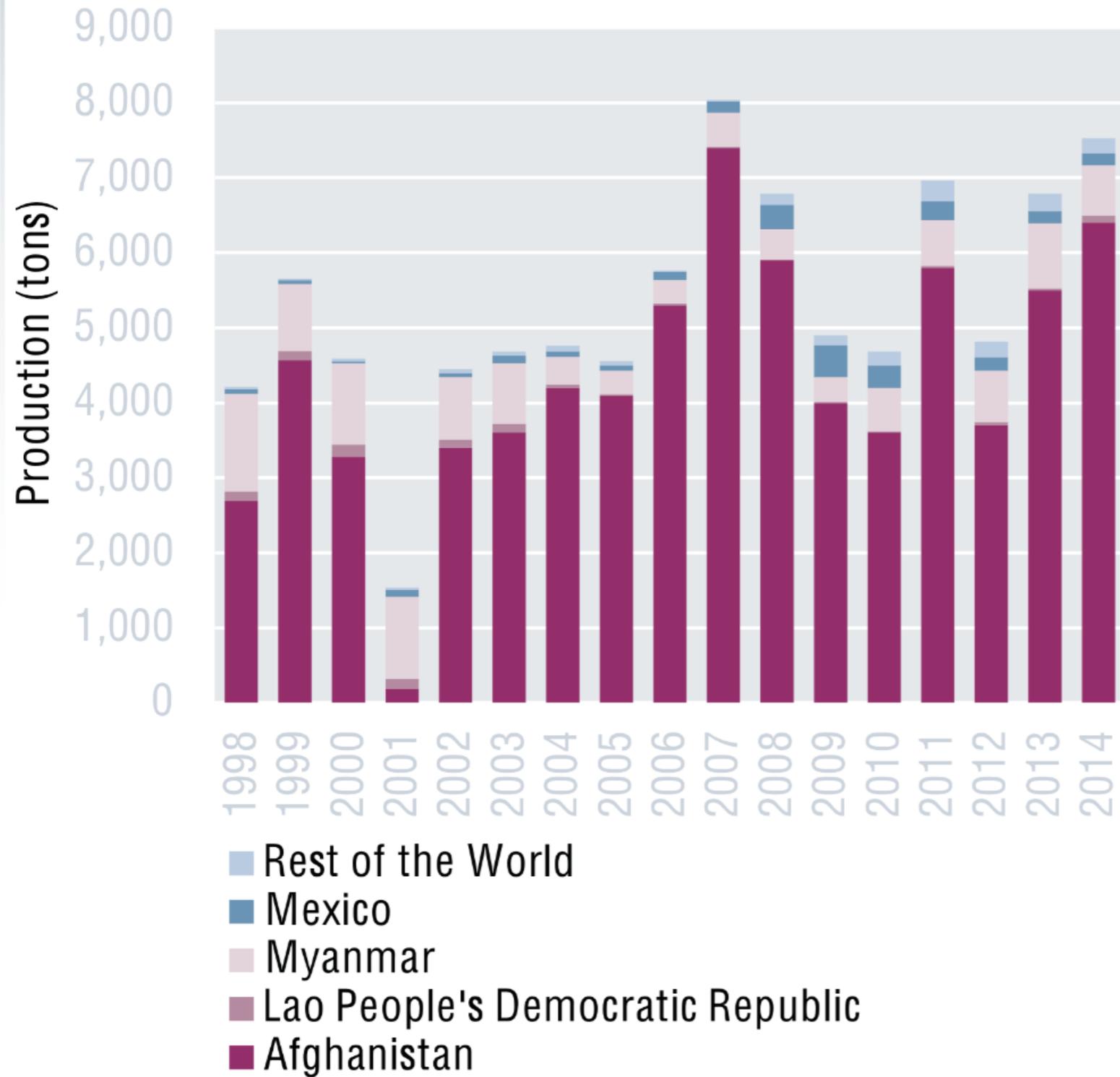


Opioid Use Disorder

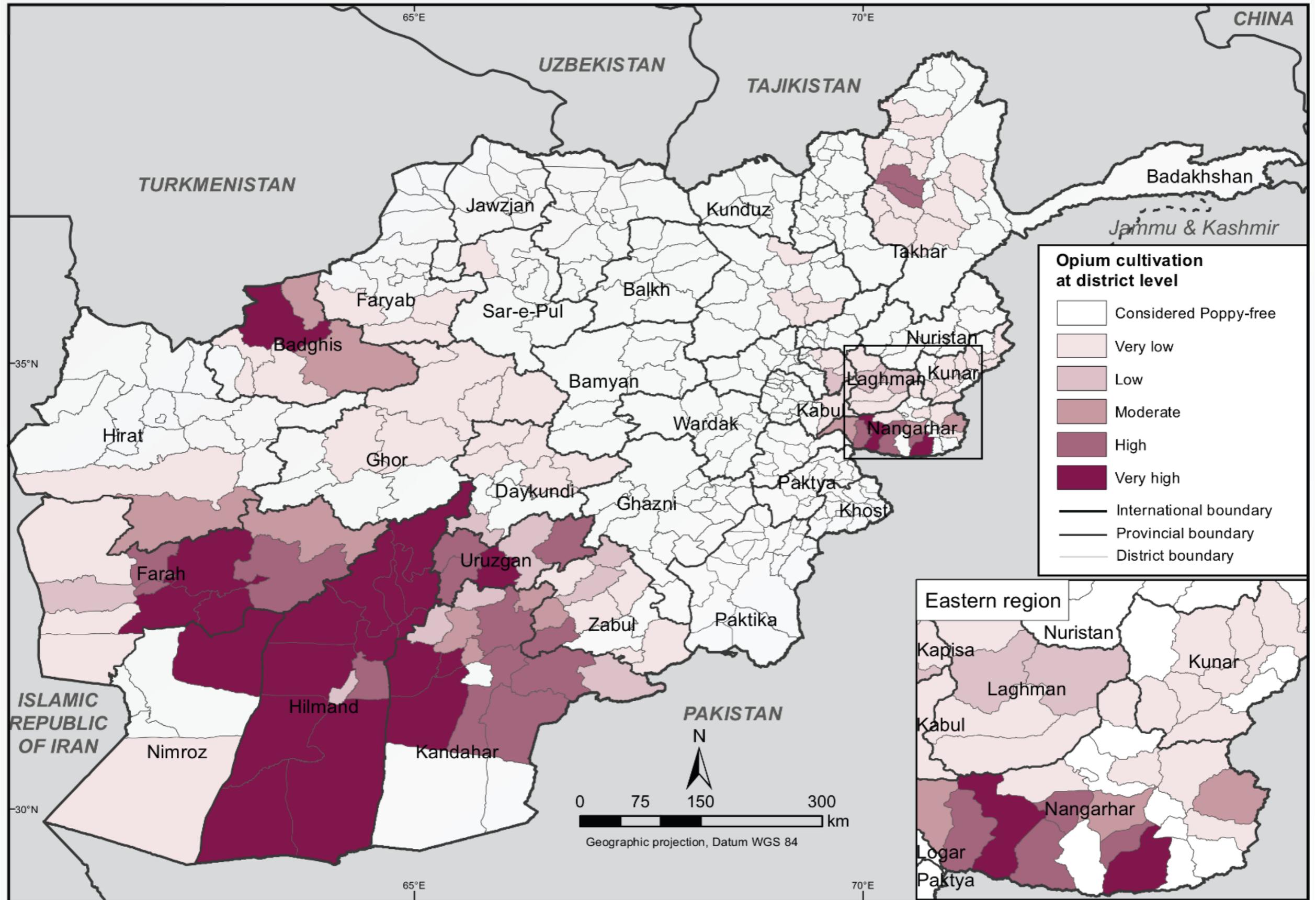
Daniel Duhigg, D.O., M.B.A.

FIG. 40. Global potential opium production, 1998-2014

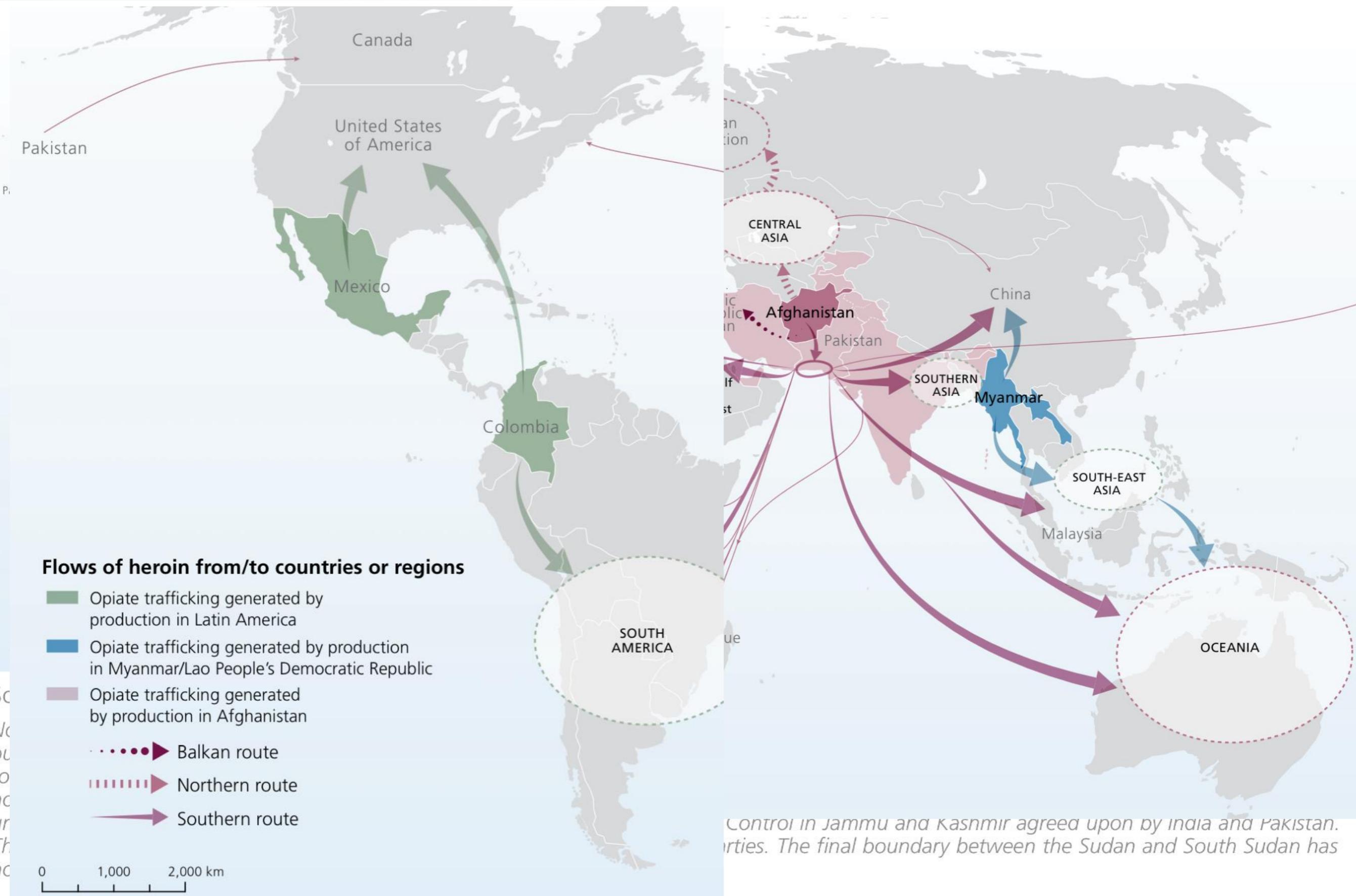


Source: Period 1997-2002: UNODC; since 2003: national illicit crop monitoring systems supported by UNODC.

Actual opium poppy cultivation, 2014

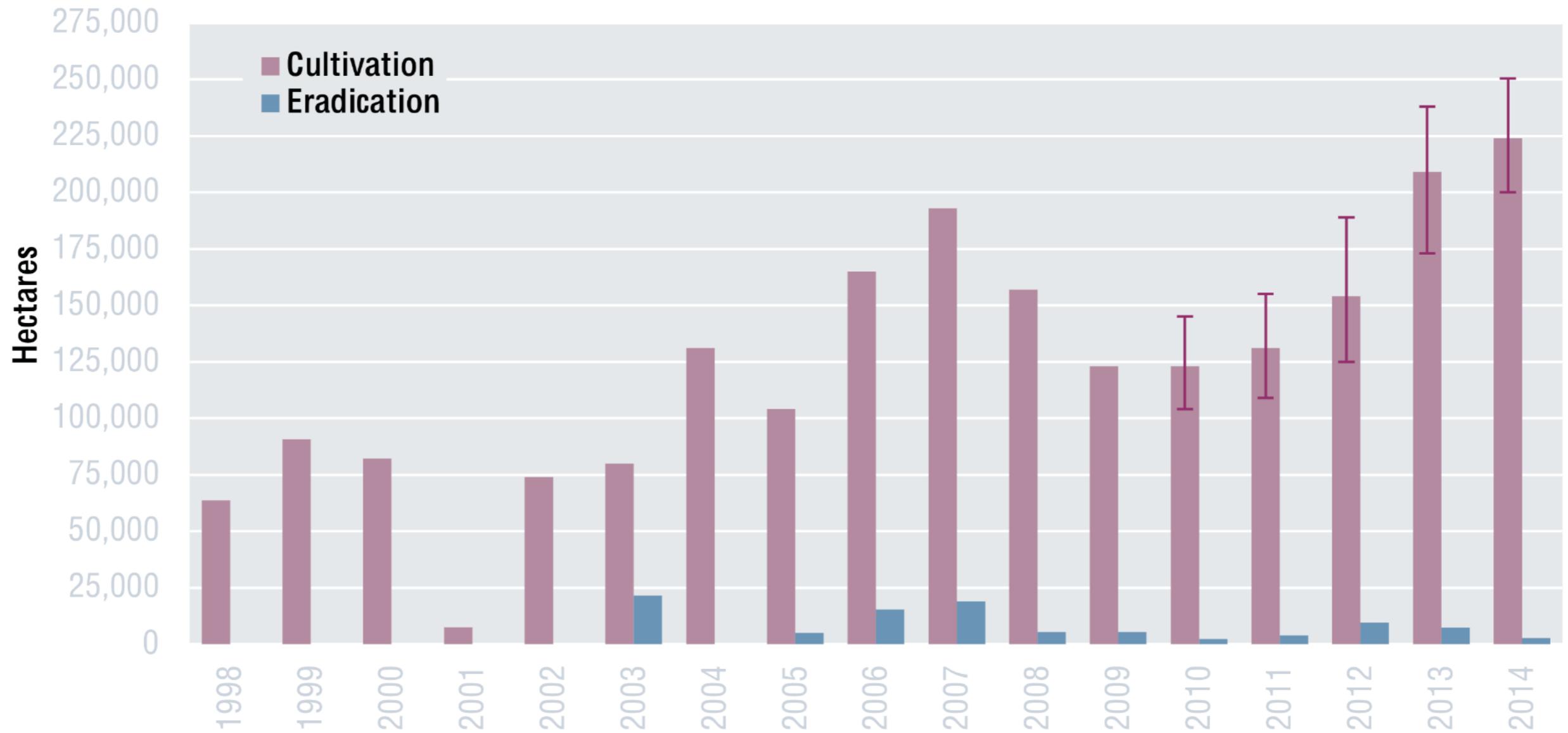


MAP 1. Main global trafficking flows of opiates



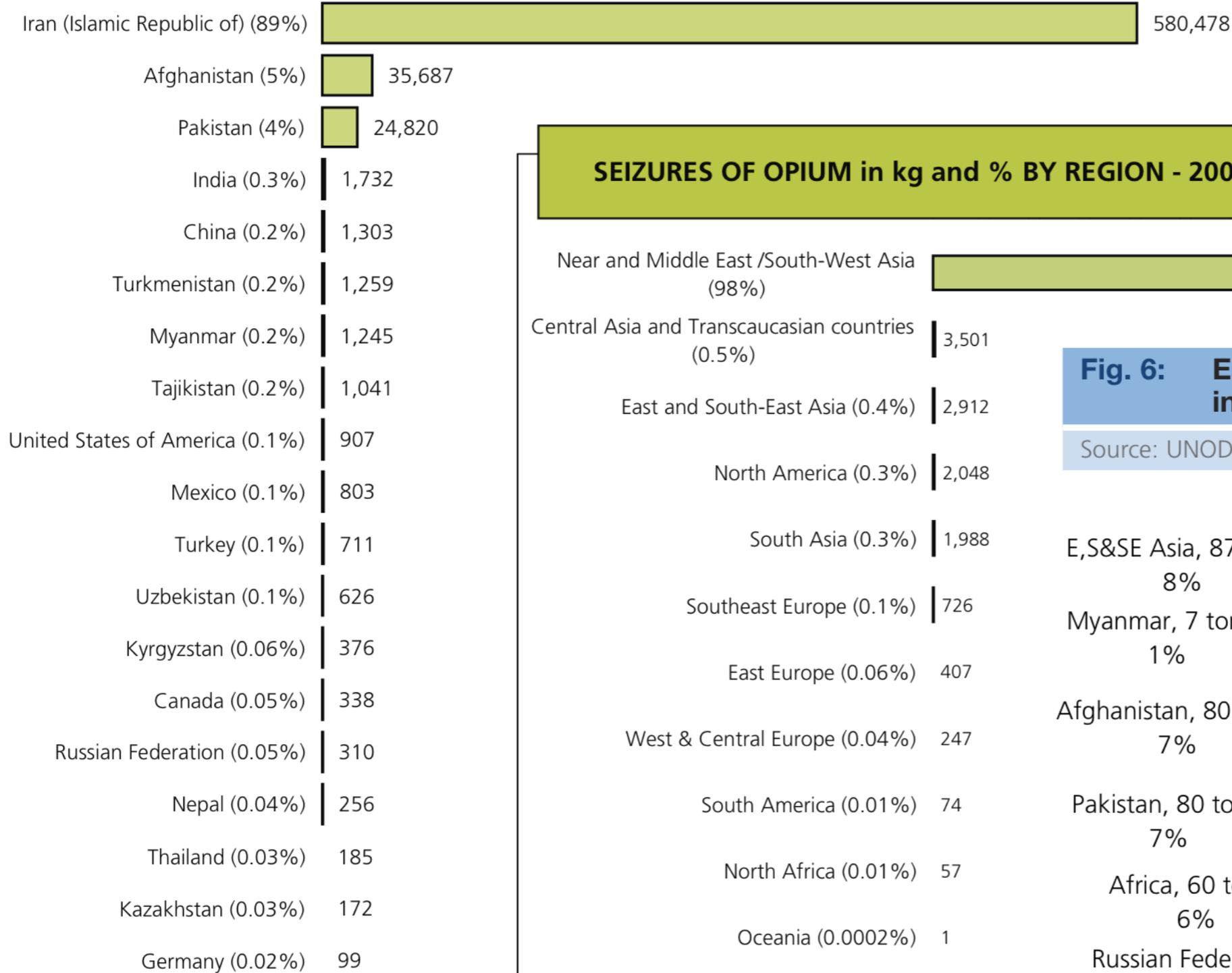
Control in Jammu and Kashmir agreed upon by India and Pakistan. The final boundary between the Sudan and South Sudan has

FIG. 39. Opium poppy cultivation and eradication in Afghanistan, 1998-2014



Source: Period 1997-2002: UNODC; since 2003: national illicit crop monitoring system supported by UNODC.

SEIZURES OF OPIUM as % of world total and in kg- HIGHEST RANKING COUNTRIES - 2009



SEIZURES OF OPIUM in kg and % BY REGION - 2009

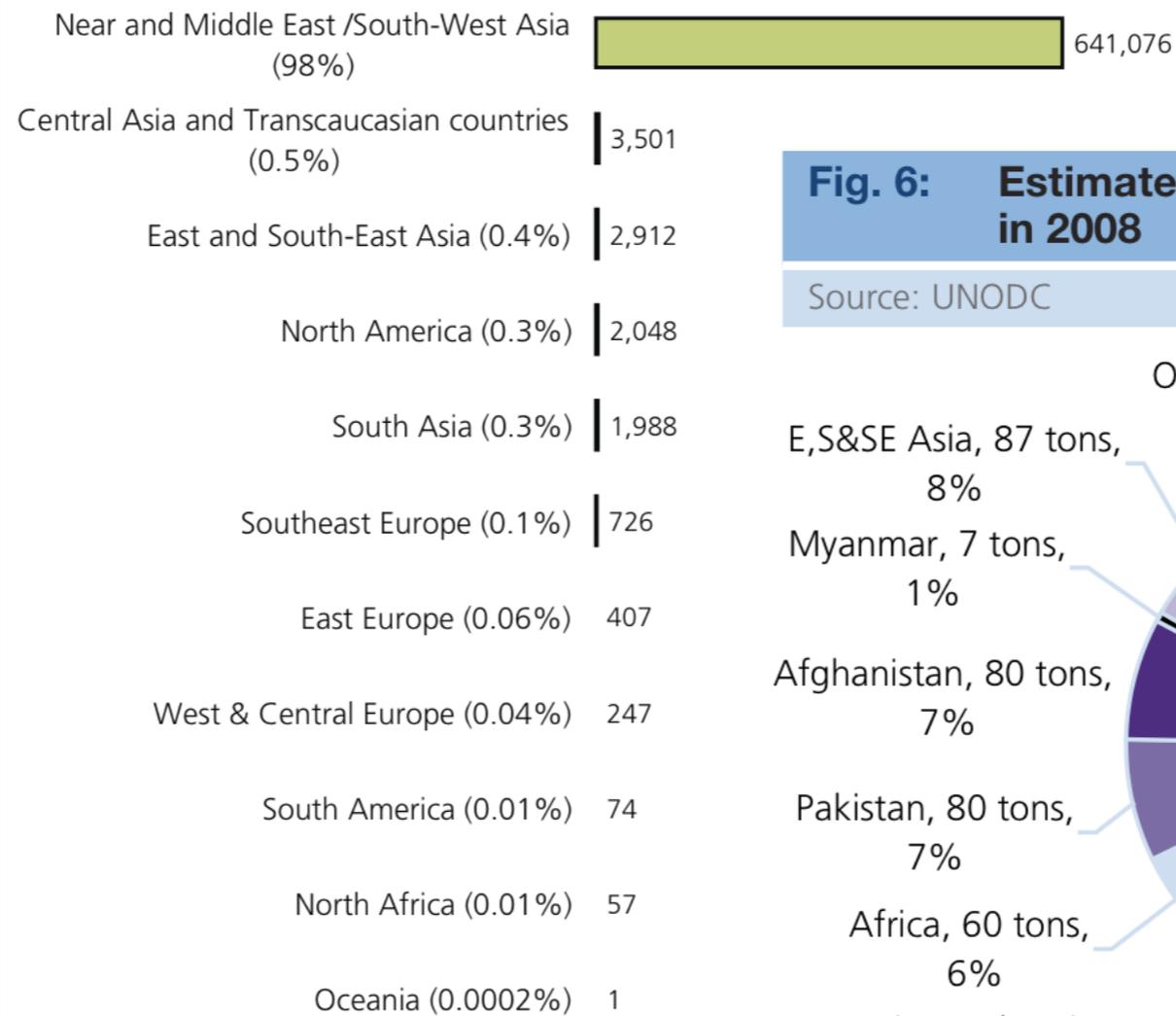


Fig. 6: Estimated global opium consumption in 2008

Source: UNODC

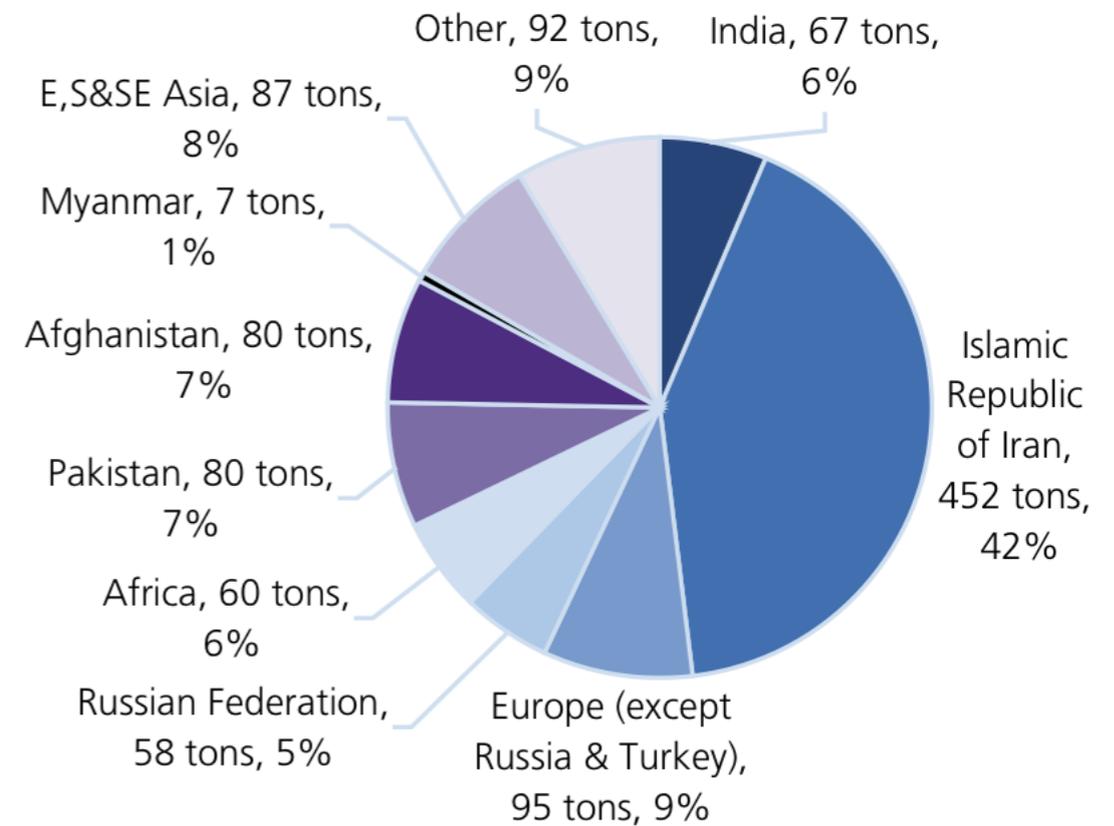


FIG. 41. Global quantities of heroin seized, by region and in selected countries, 2003-2013

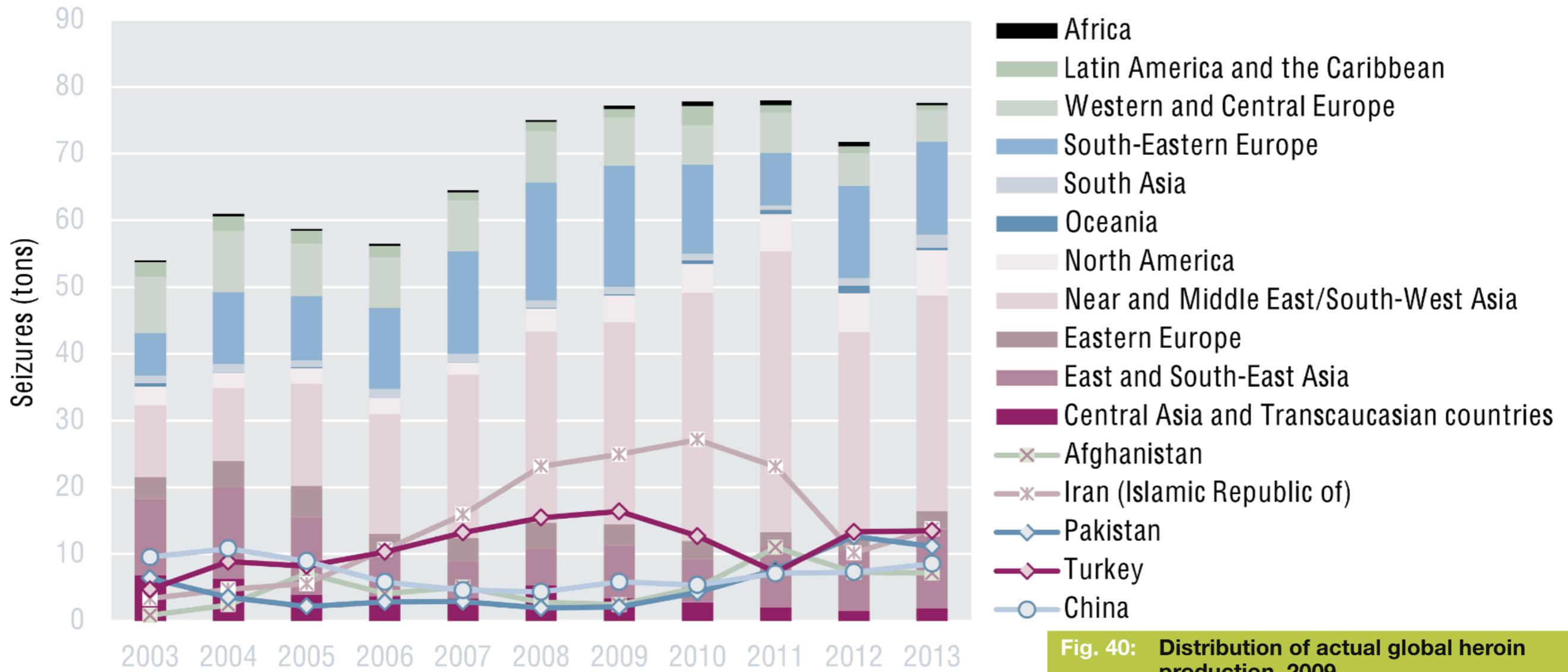
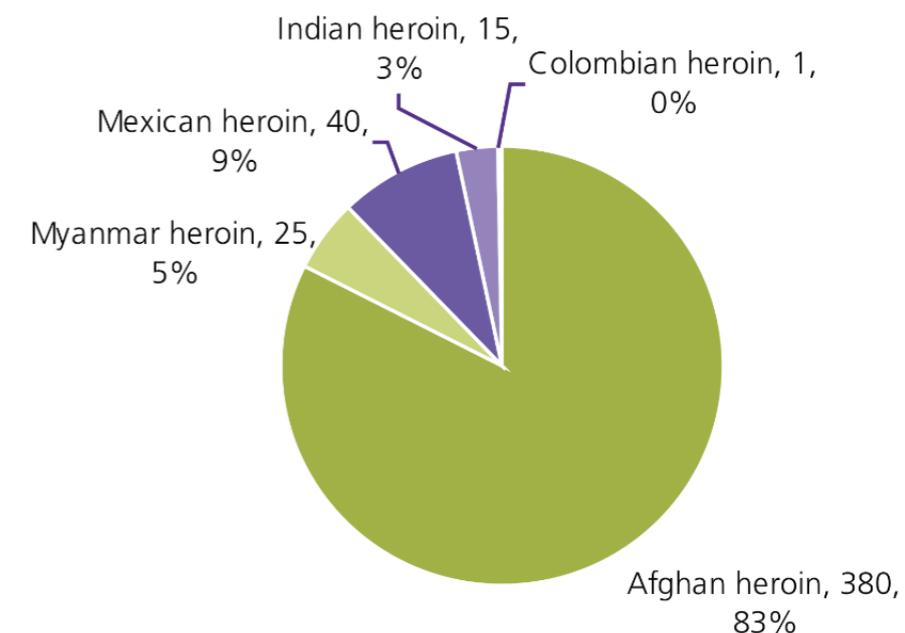


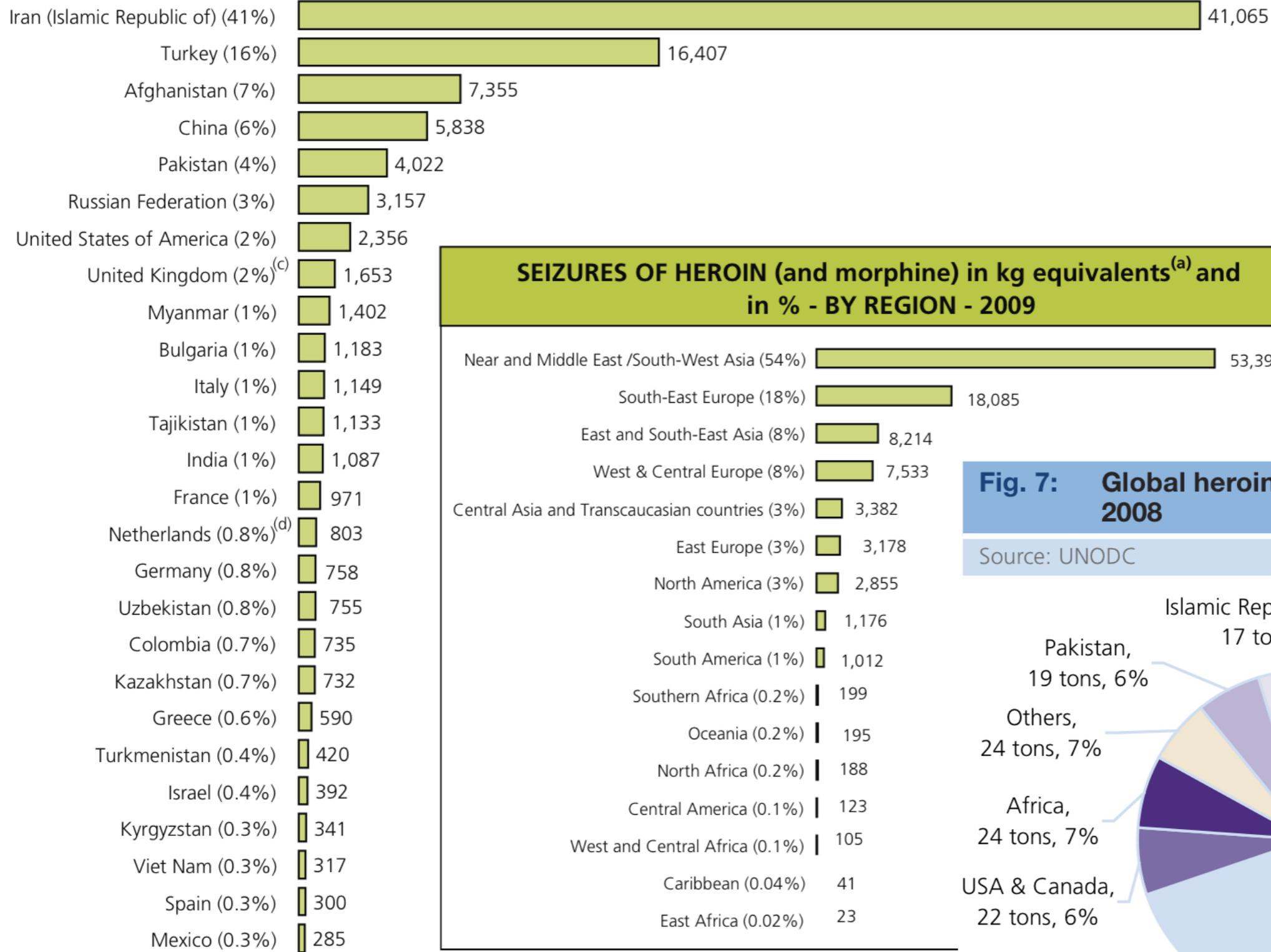
Fig. 40: Distribution of actual global heroin production, 2009

Source: UNODC.



Source: UNODC, responses to annual report questionnaire and other official sources.

**SEIZURES OF HEROIN (and morphine)^(a) as % of world total and in kg equivalents^(b)
HIGHEST RANKING COUNTRIES - 2009**



SEIZURES OF HEROIN (and morphine) in kg equivalents^(a) and in % - BY REGION - 2009

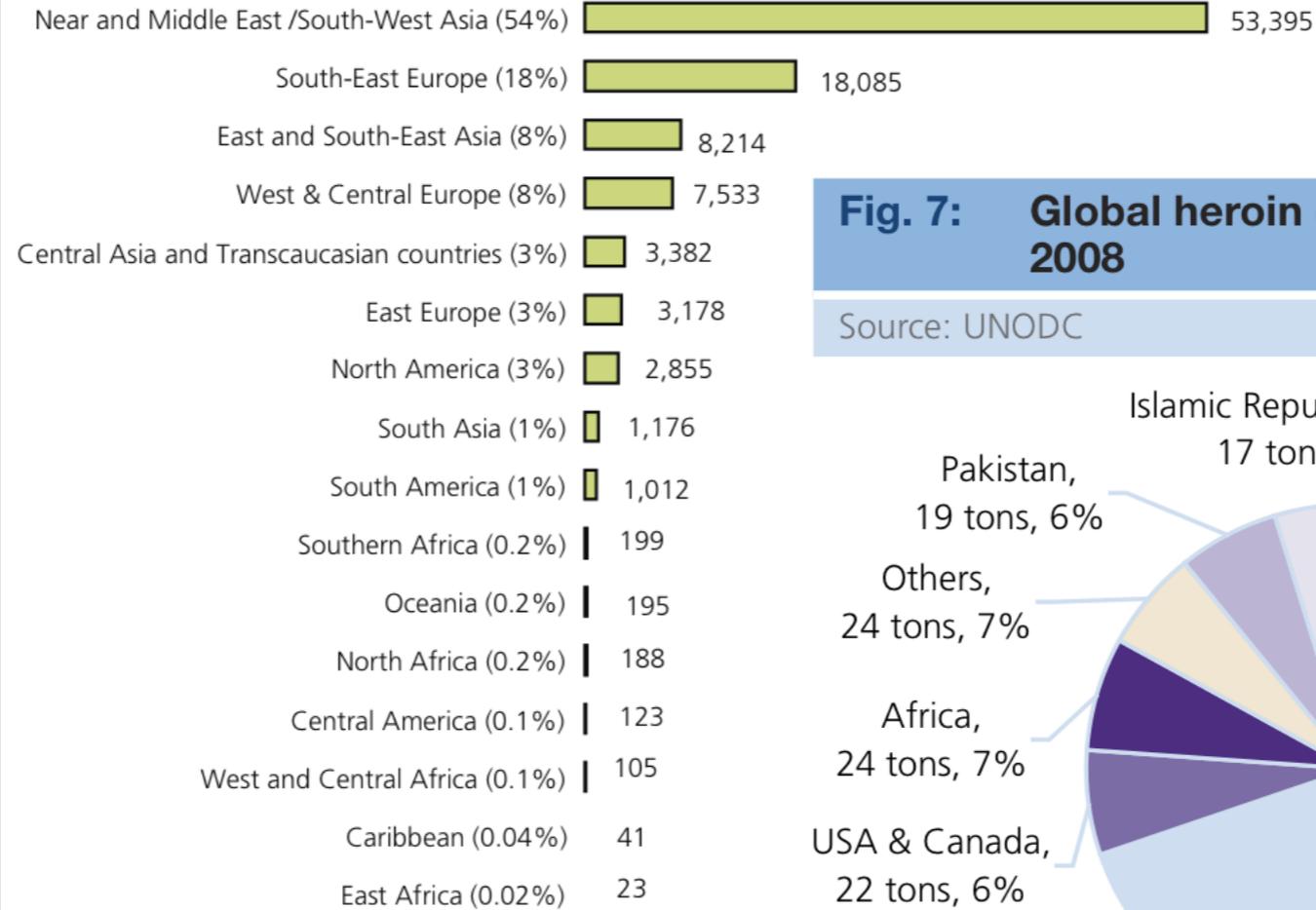


Fig. 7: Global heroin consumption (340 mt), 2008

Source: UNODC

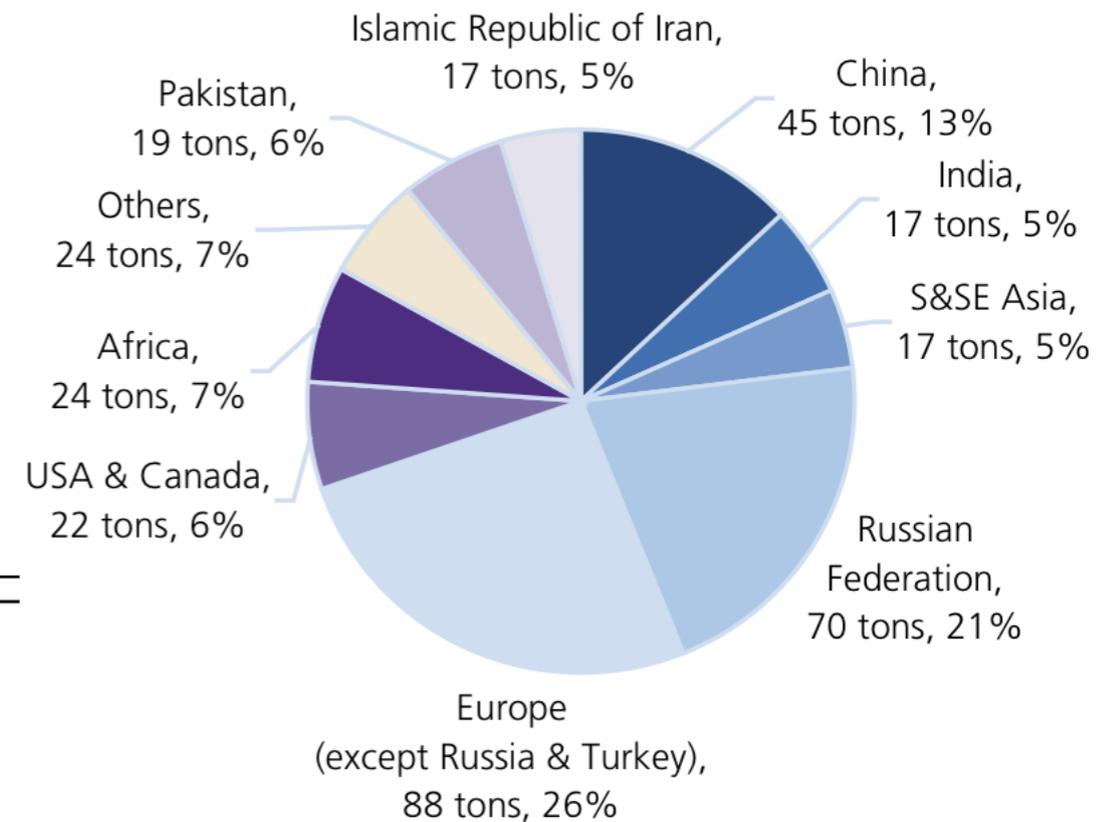
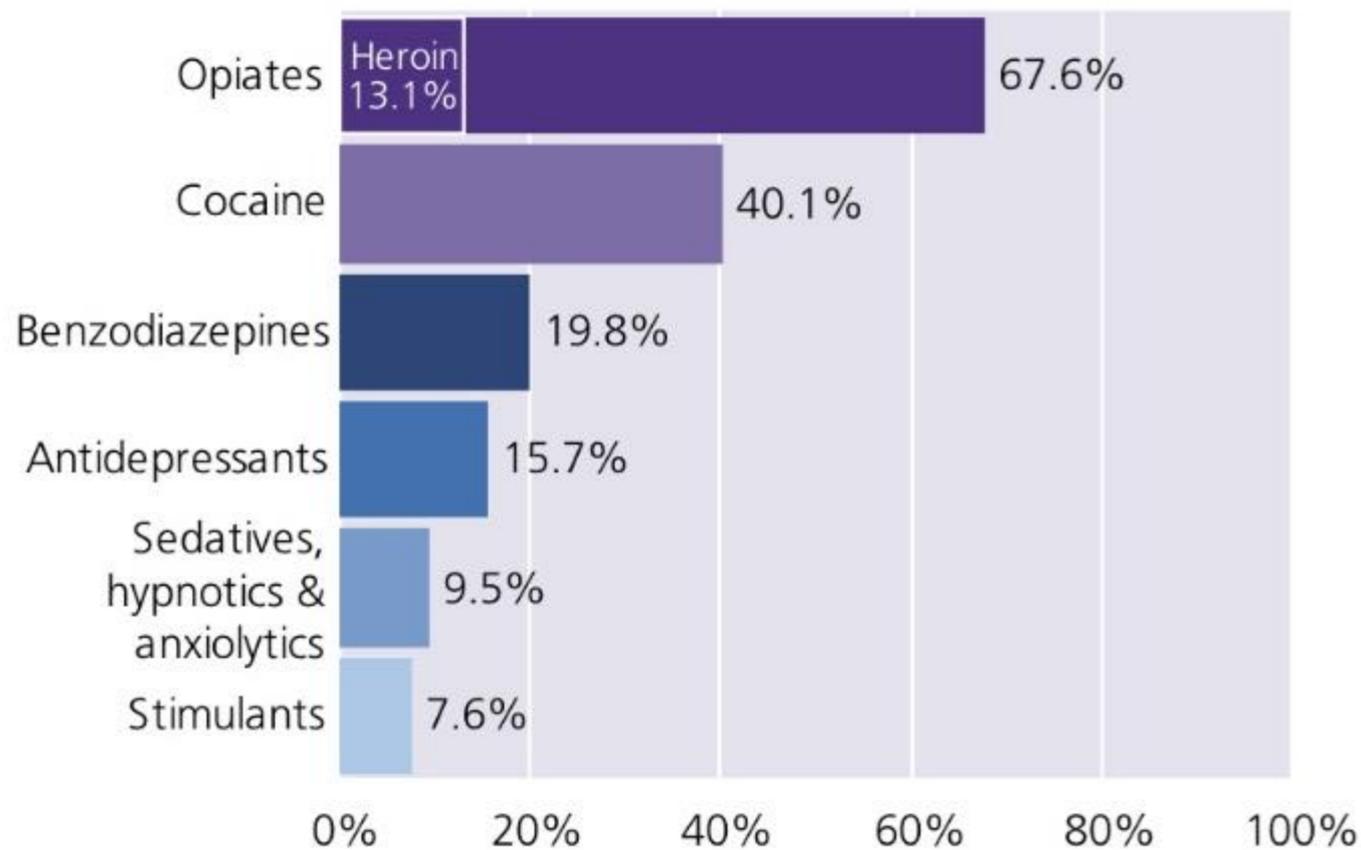


Fig. 41: Drug related deaths – by drug category – across 40 US metropolitan areas, 2007

Source: SAMHSA, *Drug Abuse Warning Network, 2007: Area Profiles of Drug Related Mortality, 2009*



The burden of
opioids in the US

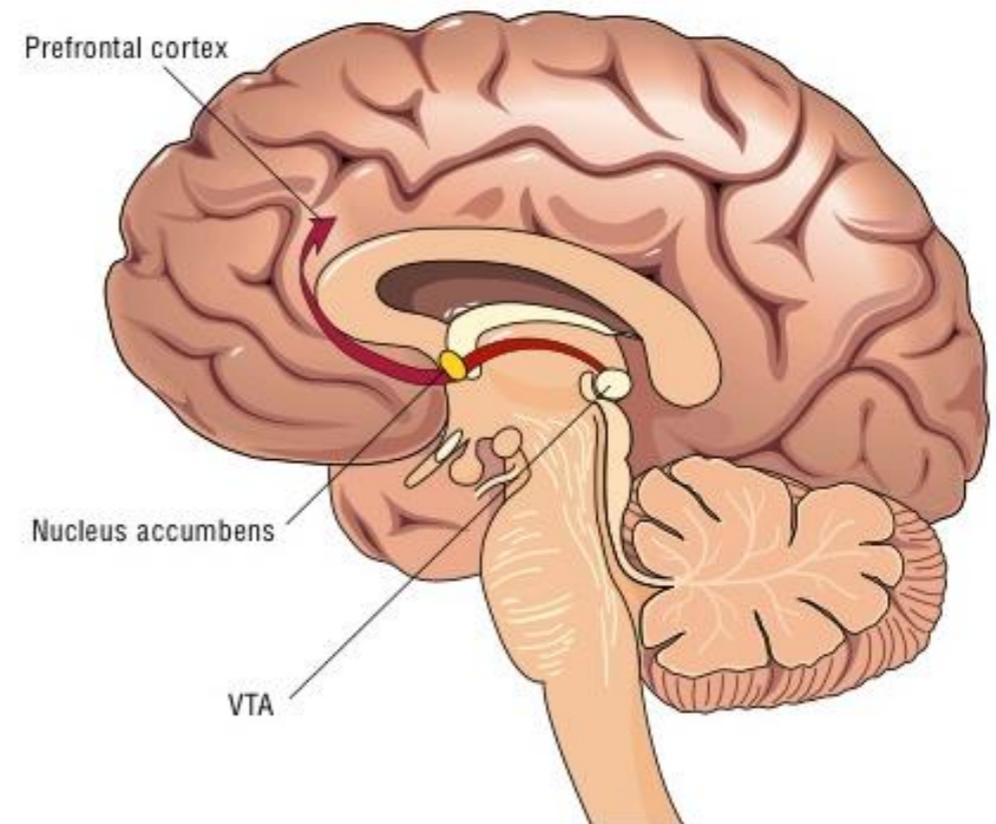
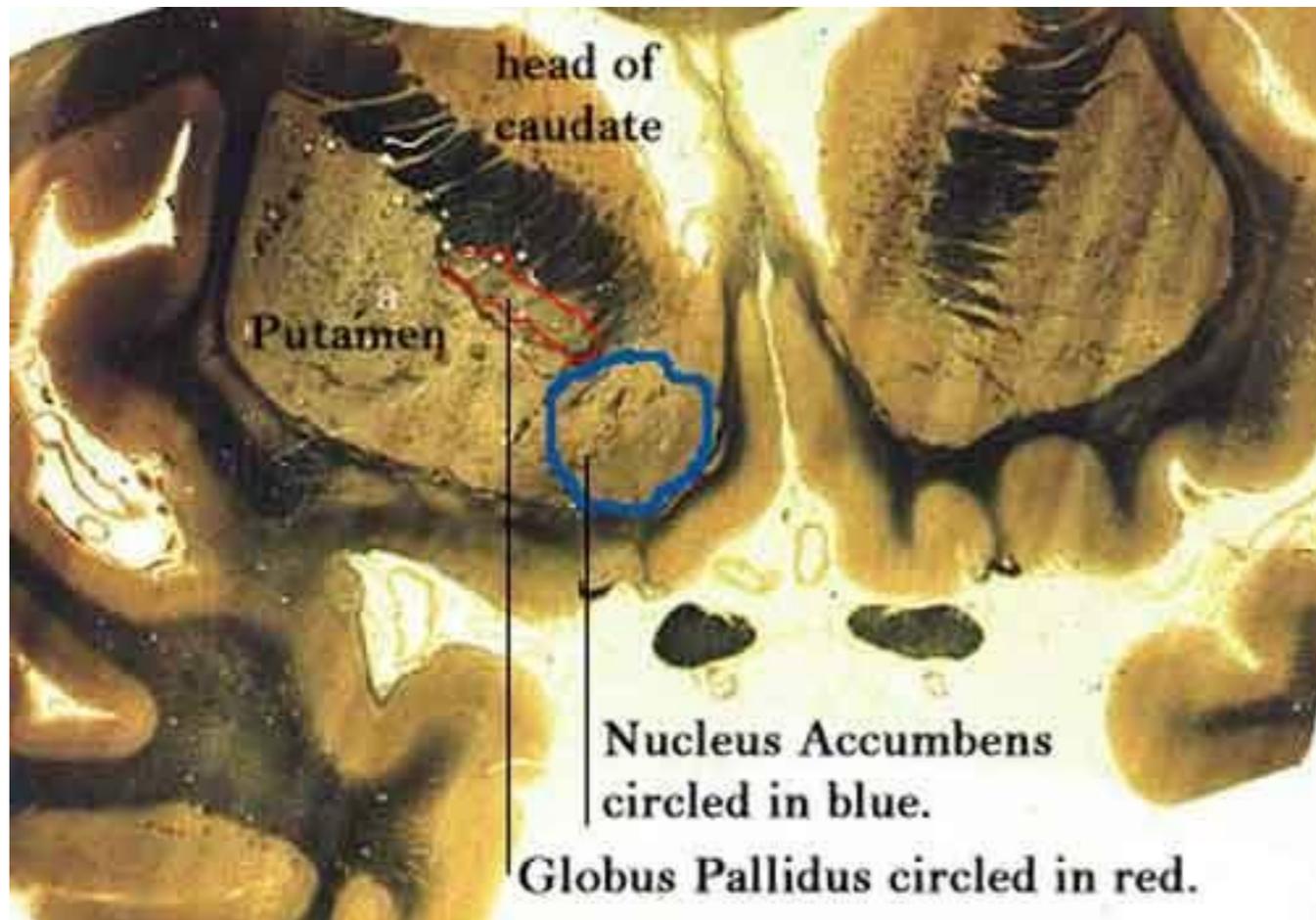
Opioid Use Disorder

DSM 5 Diagnostic Criteria

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent use in situations in which it is physically hazardous.
9. Use is continued despite a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by opioids.
10. Tolerance*
11. Withdrawal*

Nucleus Accumbens

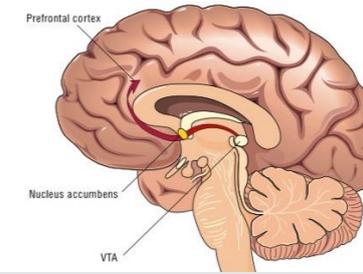


Source: National Institute on Drug Abuse (NIDA) website <http://www.drugabuse.gov/pubs/teaching/largegifs/slide-9.gif>

"They commonly report a feeling that something very interesting and exciting is going on."

Jaan Panskepp, describing the effect of stimulating the NAcc in conscious subjects

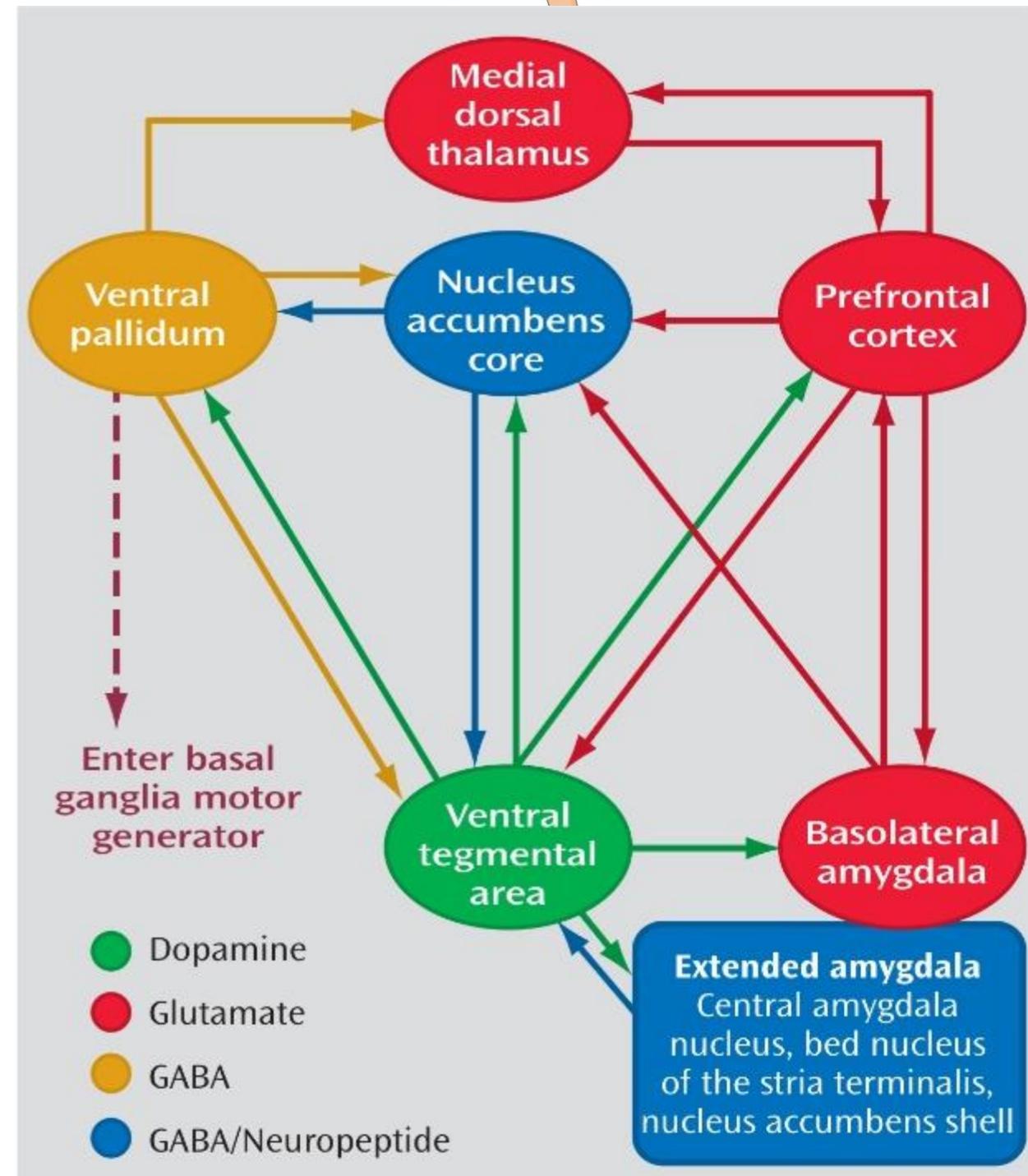
Mesolimbic Dopaminergic Pathway



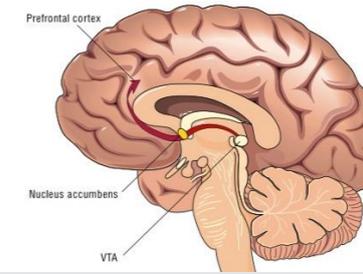
Activation of dopaminergic neurons in the VTA causes activation of the prefrontal cortex and the basolateral amygdala

These areas assign **salience** to a behavior or its associated cue

Salience is how important we feel something is at an emotional level



Mesolimbic Dopaminergic Pathway



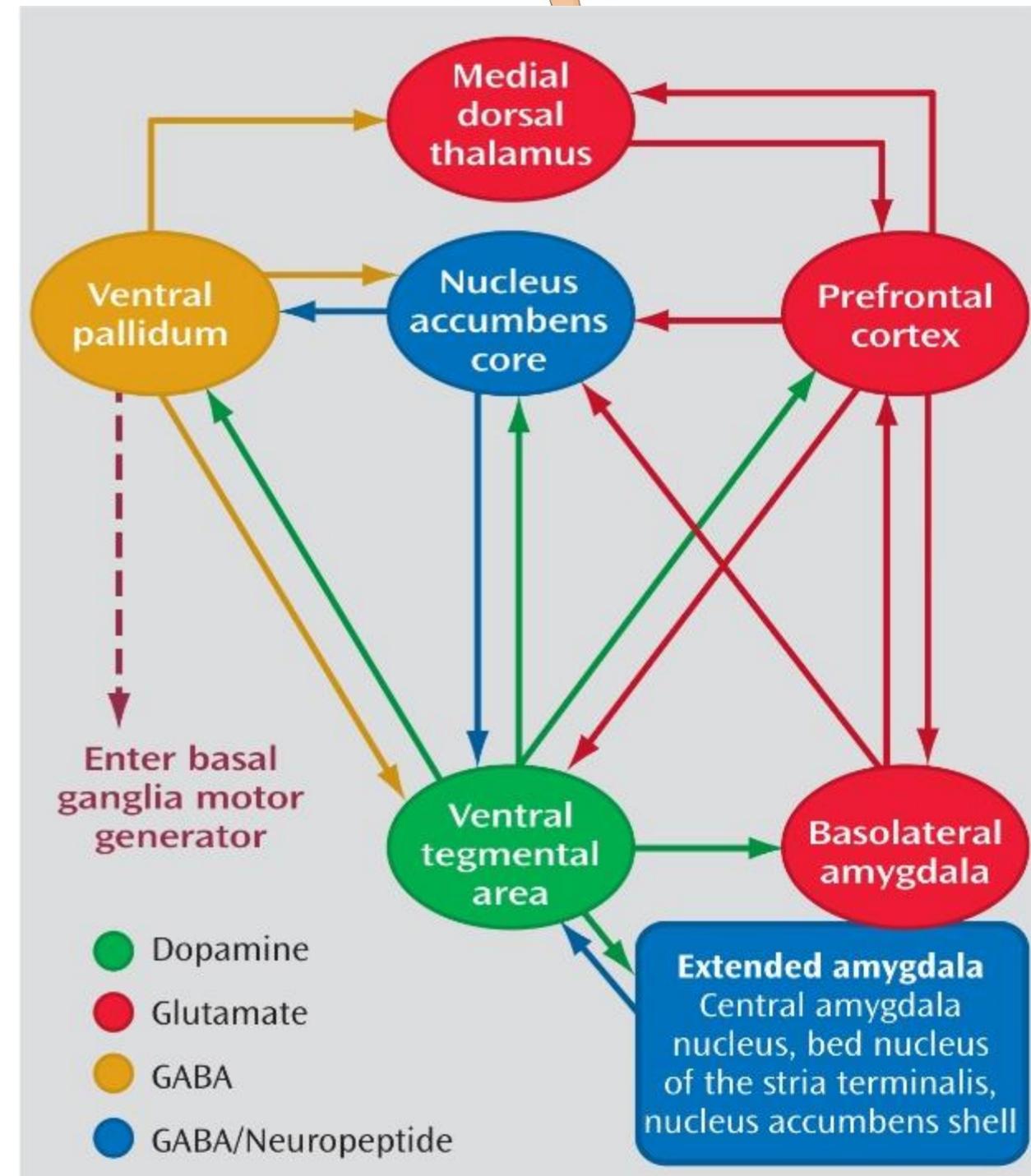
When something has a high positive salience, we want to do it again

The contrary is true with a high negative salience

This is the backbone of learning that promotes survival

This is the mechanism of classical conditioning, and is a key step in the development of an addiction

Any stimulus paired with these learned associations, in the context of substance use are called **triggers**



Nucleus Accumbens

The shell vs. The core

The NAcc is functionally separated into 2 parts: the outer shell and the inner core

The shell receives DA input from the VTA in response to novel stimuli, and moderates the development of salience in learning associations between environmental stimuli and motivationally relevant events

The core projects to the orbitofrontal cortex and anterior cingulate, and moderates learned behaviors in response to stimuli that predict a motivationally relevant event. This is not mediated by DA, but by glutamate from the prefrontal cortex

DiCiano, et al. Journal of Neuroscience, 2001;21:9471-9477

DiCiano, et al. Neuropsychopharmacology, 2001;25:341-360

Sellings, et al. Journal of Neuroscience, 2003;23:6295-6303

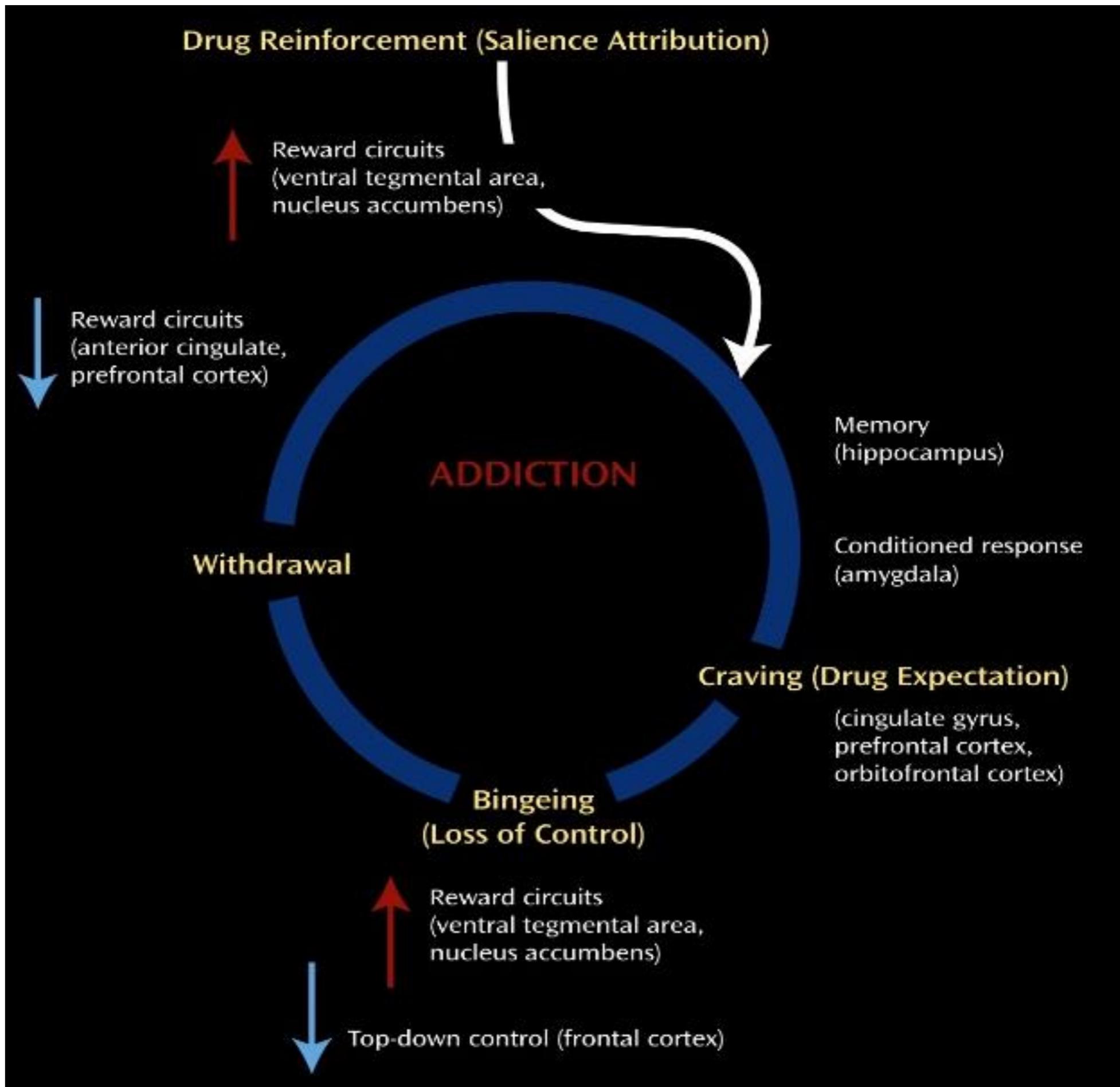
Nucleus Accumbens Core

The glutamatergic afferents from the prefrontal cortex to the NAcc Core appears to be necessary for the development of drug-seeking behaviors
(which are learned behavioral responses)

Substance dependence manipulates this system so strongly that it is reorganized to the point that orbitofrontal cortex and anterior cingulate activity is (relatively) blunted in response to non-drug stimuli associated with survival (sexual cues) I.e.
Drugs become valued more than sex and food.

McFarland, et al. Journal of Neuroscience, 2004;24:1551-1560

Garavan, et al. American Journal of Psychiatry, 2000;157:1789-1798



Acute Opioid Intoxication

Apathy

dysphoria/euphoria

psychomotor retardation

dysarthria

pin point pupils

respiratory depression

coma

Physical Findings
Specific to Opioid
Use

Detoxification

Rationale:

- Overcome the acute physiologic dependence of chronic opioid use
- Diminish the discomfort of acute opioid withdrawal
- Provide humane structure early in treatment
- Identify medical comorbidities that were masked by chronic opioid use
- Begin educating the patient about health, relapse prevention

Detoxification can be humane or not, depending on the approach taken by the practitioner

Opioid Withdrawal

Symptomatic Support

Clonidine 0.1 mg Q4H prn for SBP>150, DBP>90, HR>150
(Give for 10 Days)

NSAIDs or Tylenol prn for pain, fever

Loperamide 2mg Q4H prn diarrhea, not to exceed 16mg/24
hours

Dicyclomine 10mg Q6H prn Cramps

When can you give an opioid?

Opioids for opioid withdrawal



Drug Addiction Treatment Act 2000

Narcotic Addiction Treatment Act 1974

Methadone can be started ONLY by a federally approved
methadone treatment center

Schedule III, IV, V drugs to treat addiction require a special DEA
waiver (E.g. Buprenorphine)

Can continue opioid-agonist if started prior to admission

Can Administer 3 Days Worth Without Waiver

Title 21, Code of Federal Regulations, Part 1306.07(b)

Laws, laws, and more laws

The Narcotic Addict Treatment Act (NATA) of 1974, Code of Federal Regulations, Title 42, Part 8 allows C-III,IV,V medications to be used to treat opioid dependence in federally approved Opioid Treatment Programs, and makes it a federal offense to do so in other out-patient settings

The Drug Addiction Treatment Act (DATA) of 2000 allows a qualifying physician (not a mid-level or prescribing psychologist) to apply for a waiver to CFR 42(8) in order to use buprenorphine to treat opioid dependence in any medical setting

Setting For Detoxification

Out-Patient:

Pros: Inexpensive, can continue to work, forced to confront environmental cues

Cons: Immediate access to drugs when craving, largely unmonitored by a practitioner (can miss medical comorbidities), low success rate

In-Patient:

Pros: Access to drugs & triggers is minimized, closer medical observation, program can begin work on psychosocial barriers to success

Cons: Expensive, disrupts ability to work

Partial Hospitalization:

Pros: Less expensive than in-patient, allows medical monitoring, patient may be able to work part-time

Cons: Rarely available, rarely covered by insurance

Detoxification with methadone

Only in a methadone
clinic!

1. Dosing:

- Equianalgesic charts for methadone should NEVER be used to start methadone
- Start with ≤ 30 mg/day to avoid fatal overdose in nontolerant patients
 - Titrate the dose to eliminate withdrawal symptoms, as tolerated

2. Duration

- Wean by 5-10 mg/24 H until discontinued
- If weaning from chronic methadone use, wean by 5-10 mg/week

Detoxification with buprenorphine

Must have DATA
2000 waiver!

1. Dosing

- Use whatever dose controls symptoms of withdrawal
 - Typically: 8-16 mg on day 1
- Repeat after 1 hour, based on severity of symptoms

2. Duration

- Evidence is insufficient to determine optimal duration
 - Range is from a single dose to a 6-week wean

Opioid Replacement

Detoxification alone leads to a 90% relapse rate

Methadone Maintenance Therapy (MMT)
Buprenorphine Maintenance Therapy

Methadone Maintenance Treatment

80mg - 120mg / day is typically needed to:

Control cravings
Prevent withdrawal

In a pinnacle study funded by the state of New York, MMT led to:

- A drop in arrest rates from 201 per 100 person-years to 1.24 per 100 person-years
- The death rate of those who left treatment was 28.2 per 1000 compared to 7.6 per 1000 for those in treatment

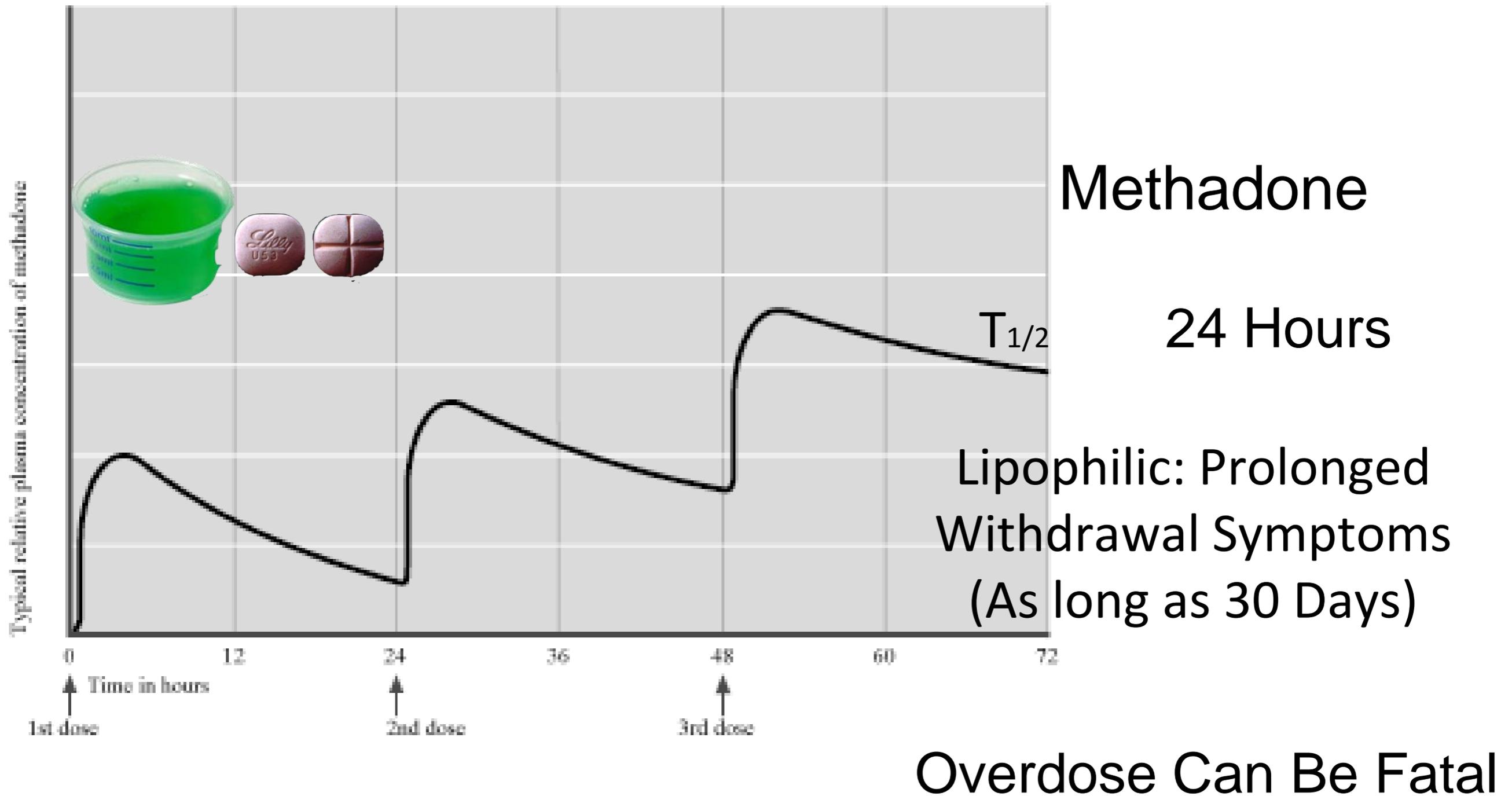
A prospective study on HIV seroconversion in heroin users and MMT showed:
3.5% seroconversion in MMT patients and 22% in non-MMT patients

Metzger, et al. JAIDS, 1993;6:1049-1056

Gearing & Schwietzer, American Journal of Epidemiology, 1974;100(2):101-112

Dole & Nyswander, JAMA, 1965;193(8):80-84

Opioids for opioid withdrawal



Methadone and Pregnancy

- Use of short-acting opiates during pregnancy increases the risk of experiencing acute opioid withdrawal, which can cause fetal distress and miscarriage
 - MMT provides a steady serum concentration, and also decreases the risks associated with parenteral drug use
- MMT doses need to be increased in the 3rd trimester due to increased metabolic needs, then decreased post-natally
 - Newborn infants may experience opioid withdrawal in the 72 hour post-natal period
- Methadone concentrations in the breast-milk are not high enough to dissuade breast-feeding
 - Exposure to MMT *in utero* does not cause cognitive deficits

Methadone is metabolized via CYP 3A4

3A4 Inhibitors (increase methadone levels)

Amiodarone
Clarithromycin
Erythromycin
Fluconazole
Grapefruit Juice
Indinavir
Itraconazole
Ketoconazole

Metronidazole
Nicardipine
Omeprazole
Paroxetine
Sertraline
Verapamil
Zifirlukast
Zileuton

3A4 Inducers (decrease methadone levels)

Carbamazepine
Dexamethasone
Efavirenz
Phenobarbital
Phenytoin
Primadone
Rifampin

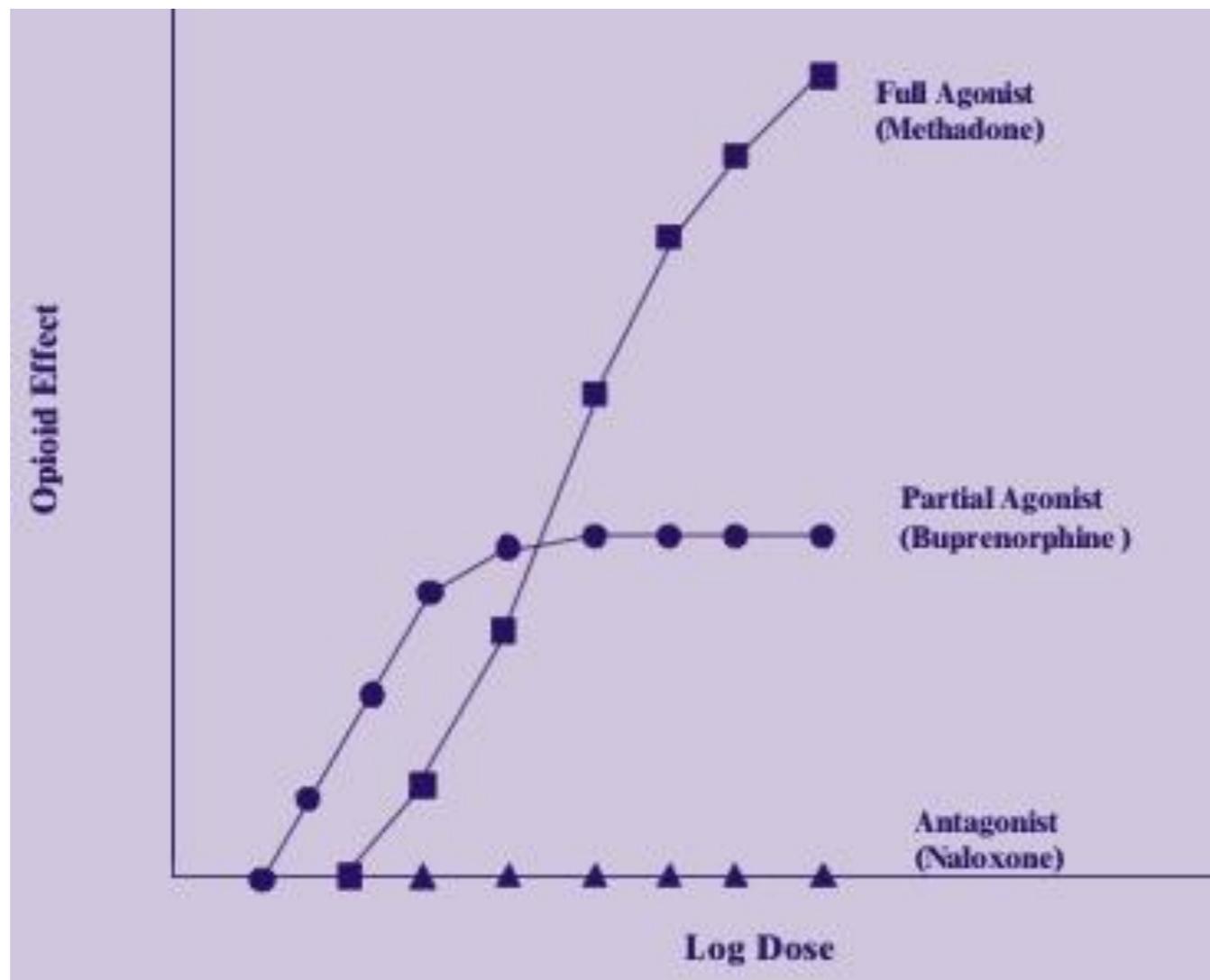
Buprenorphine Maintenance Therapy

The extremely high level of regulation regarding MMT has been criticized as a significant barrier to access to treatment
DATA 2000 and the approval of buprenorphine for use in the out-patient office setting was the FDA's response

Subutex - buprenorphine

Suboxone - buprenorphine/naloxone (4:1)

Buprenorphine Pharmacology



Buprenorphine alone does not cause respiratory depression, given the ceiling effect of partial agonism

However, there are case reports of respiratory depression when combined with benzodiazepines

Buprenorphine Maintenance Therapy

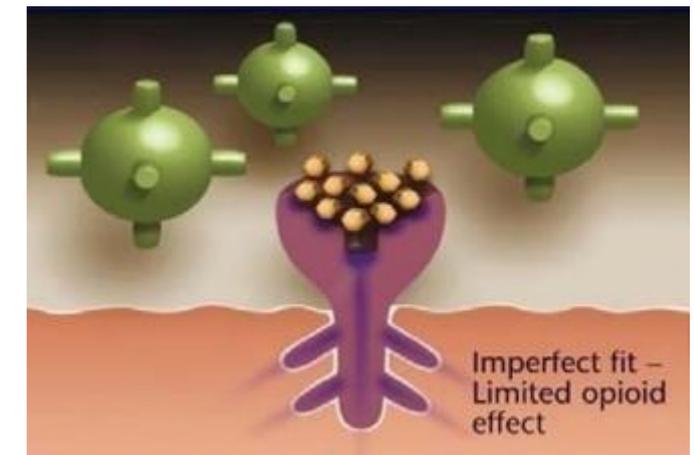
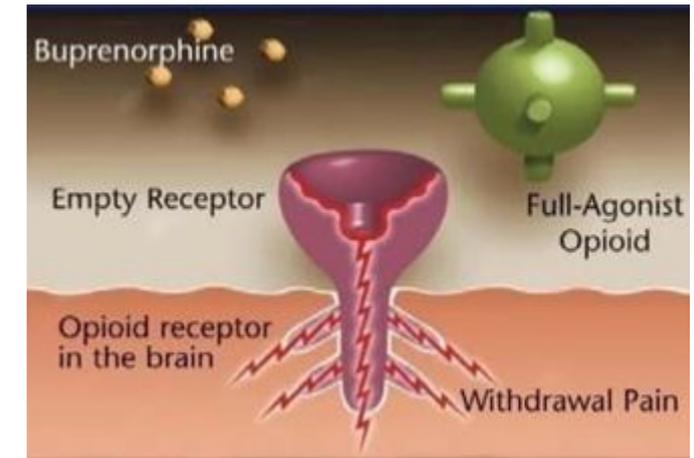
Subutex - buprenorphine

Suboxone - buprenorphine/naloxone (4:1)

Buprenorphine has high affinity for the mu-opioid receptor, dissociates very slowly, and has a ceiling effect, where higher doses do not increase its action

This makes it a long-acting partial agonist

Its affinity is high enough that it will displace other opiates at the receptor, which is how it can precipitate withdrawal



It has very poor GI absorption, and so is taken sublingually

The naloxone is eliminated via first-pass metabolism, and thus will not antagonize mu-receptors unless injected parenterally

Buprenorphine Induction

Because buprenorphine can precipitate acute opioid withdrawal via competitive binding of the mu-opioid receptor, the following should be kept in mind:

If the patient is dependent on **short-acting** opioids, induction should occur 12-24 hours after the last use. The best results occur when the patient is experiencing acute opioid withdrawal (COWS>11), since administration of buprenorphine will eliminate those symptoms

If the patient is dependent on **long-acting** opioids (methadone), then wean to a 30mg daily dose before converting to buprenorphine to avoid precipitating withdrawal

Buprenorphine Induction

Guidelines initially suggested:

Day 1: 4/1 - 8/2 mg suboxone

Day 2: titrate dose to 12/3 -16/4 mg, as tolerated, and depending on severity of withdrawal symptoms

Day 3+: continue at effective dose, or continue to titrate, up to a maximum daily dose of 32/8 mg

Updated guidelines suggest: Use whatever dose on day 1 that controls symptoms

Buprenorphine without naloxone (Subutex) should be used in pregnant women. Otherwise, unless there is a well documented allergy to naloxone, Suboxone is recommended for all out-patients due to the diversion liability of Subutex

Buprenorphine is metabolized via CYP 3A4

3A4 Inhibitors (increase buprenorphine levels)

Amiodarone
Clarithromycin
Erythromycin
Fluconazole
Grapefruit Juice
Indinavir
Itraconazole
Ketoconazole
Metronidazole

Nicardipine
Omeprazole
Paroxetine
Sertraline
Verapamil
Zifirlukast
Zileuton

3A4 Inducers (decrease buprenorphine levels)

Carbamazepine
Dexamethasone
Efavirenz
Phenobarbital
Phenytoin
Primadone
Rifampin

Antagonist Treatment

Naltrexone is FDA indicated for the treatment of opioid dependence

MOA: antagonism of the mu-opioid receptor prevents opioid binding

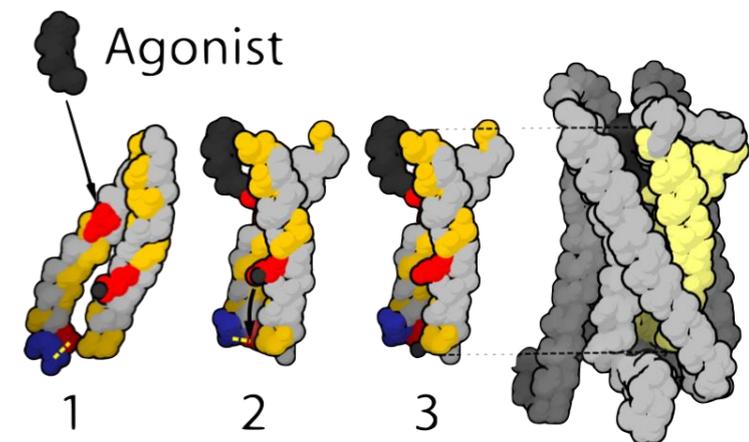
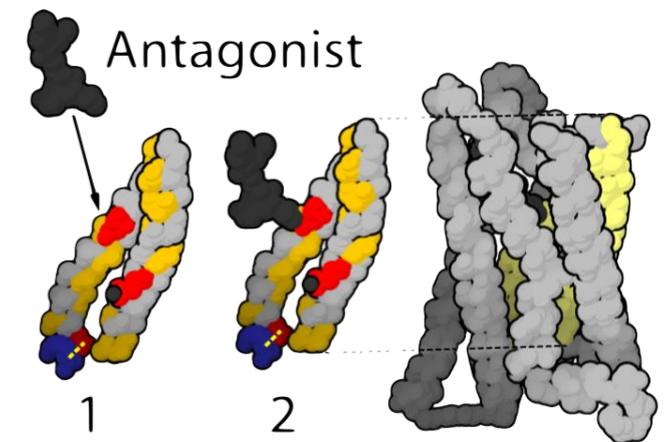
P.O. Dosing (ReVia):

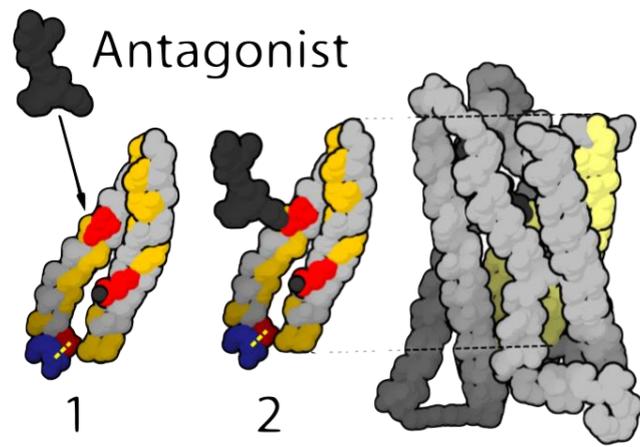
50mg daily, 100mg EOD, 150mg q3 days

I.M. Depot (Vivitrol):

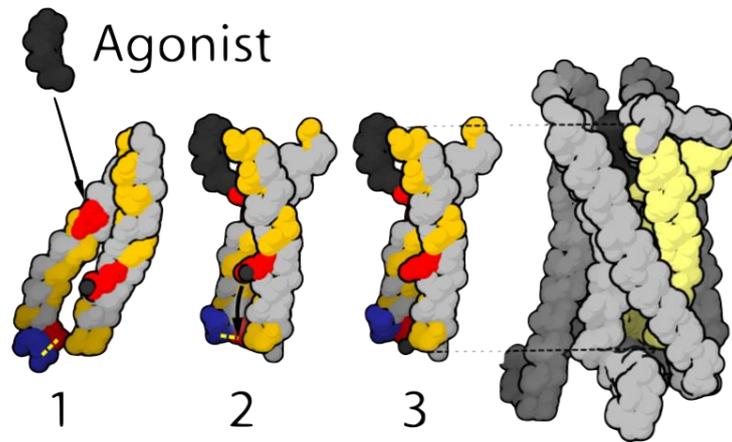
380 mg q4wk

Caution: if any opioids are bound, this will precipitate withdrawal





What About Antagonists in the hospital?



Indication:

Respiratory Compromise with an unstable airway, and no chance of immediate intubation

Reversal Agents antagonize these receptors, and may result in:
A very angry person just taken out of their high
A very angry person in a lot of pain

What About Antidotes?

Naloxone: 0.4 - 2mg IV/IM Q2-3 minutes

Reverses μ -receptor binding by opioids

T1/2: 64 minutes

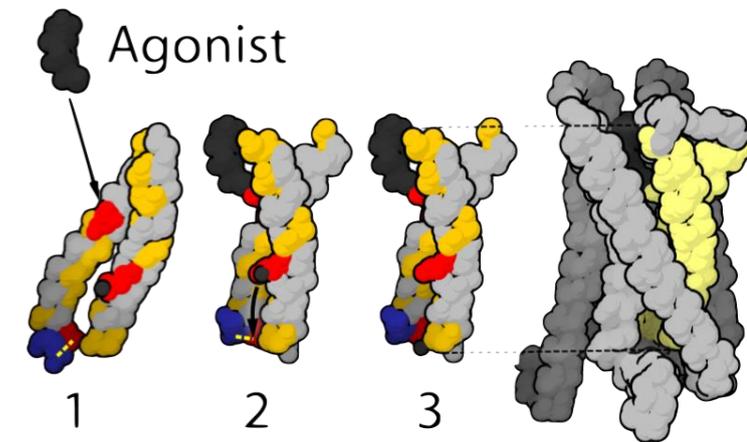
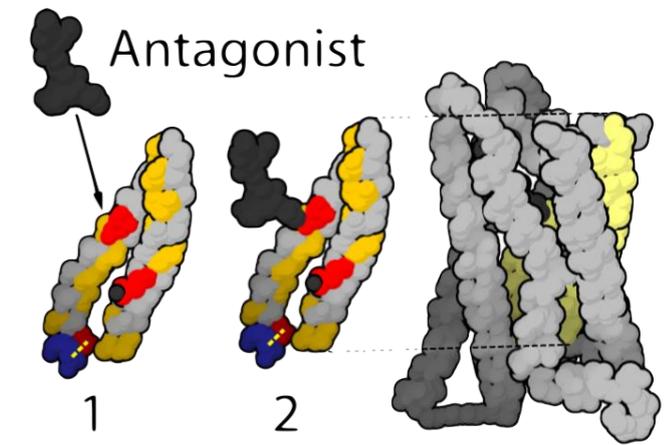
Flumazenil: 0.2mg IV x 1, wait 30sec, then

0.3mg IV prn, wait 30sec, then 0.5mg IV

Qminute prn up to 6x

Reverses GABAA bound substances only (not
ETOH, barbiturates)

T1/2: 54 minutes



Opioid Use Disorder and Pain

Do's and Don'ts

1. Consider the possibility that the opioid use may be the cause of the pain (opioid induced hyperalgesia)
2. It is a federal offense to treat opioid use disorder with methadone in an outpatient clinic that is not a federally approved Opioid Treatment Program (OTP)
3. For acute pain, short-acting opioids can be used, but higher doses may be needed to achieve analgesia
4. During a prolonged hospital stay, buprenorphine can be discontinued temporarily, and then re-induced when analgesia is no longer needed
5. For chronic pain, methadone scheduled multiple times a day is recommended, optimally in partnership with an OTP. Suboxone is a safer option.
6. Communicate with OTP clinic, and refer patients/consult with colleagues and document doing so