



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

THE PATHOPHYSIOLOGY OF ADDICTION

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*And thanks to CNS
Productions for use of
their Uppers Downers
All-Arounders PPTs*

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

RIES CONFLICT OF INTEREST STATEMENT

Richard Ries, MD has no financial relationships with an ACCME defined commercial interests.

But does grant funding around addiction and/or suicide from

- NIH (NIDA, NIAAA)
- SAMHSA
- Dept of Defense
- Washington State

Psychoactive Drugs

Uppers (stimulants)

Downers (depressants)

All Arounders (psychedelics)

Other Drugs (inhalants, sports drugs, psychiatric drugs)

Compulsive Behaviors (e.g., gambling, eating disorders, Internet addiction)

Uppers (stimulants)

- Cocaine (hydrochloride, crack, freebase)
- Amphetamines (speed, meth, “ice”)
- Amphetamine congeners (Ritalin[®], diet pills, e.g., fen-phen)
- Plant stimulants (khat, betel nut, yohimbe)
- Caffeine (coffee, tea, soft drinks, OTC meds)
- Nicotine (cigarettes, cigars, smokeless tobacco)

Downers (depressants)

Opiates/Opioids

opium, codeine, morphine, heroin,
methadone, Darvon[®], codeine

Sedative-Hypnotics

benzodiazepines, e.g., Xanax[®], Valium[®],
barbiturates, e.g., Seconal[®],
others, e.g., Rohypnol[®], Miltown[®]

Alcohol

beer, wine, hard liquor

Others

antihistamines, skeletal muscle relaxants,
OTC downers, lookalike downers

All Arounders (psychedelics)

- LSD, psilocybin mushrooms, & other indole psychedelics)
- Mescaline (peyote), ecstasy, & other phenylalkylamine psychedelics
- Belladonna, mandrake, & other anticholinergic psychedelics
- Ketamine, PCP, amanita mushrooms, nutmeg, mace, kava
- Marijuana (grass, hashish) & other cannabinols

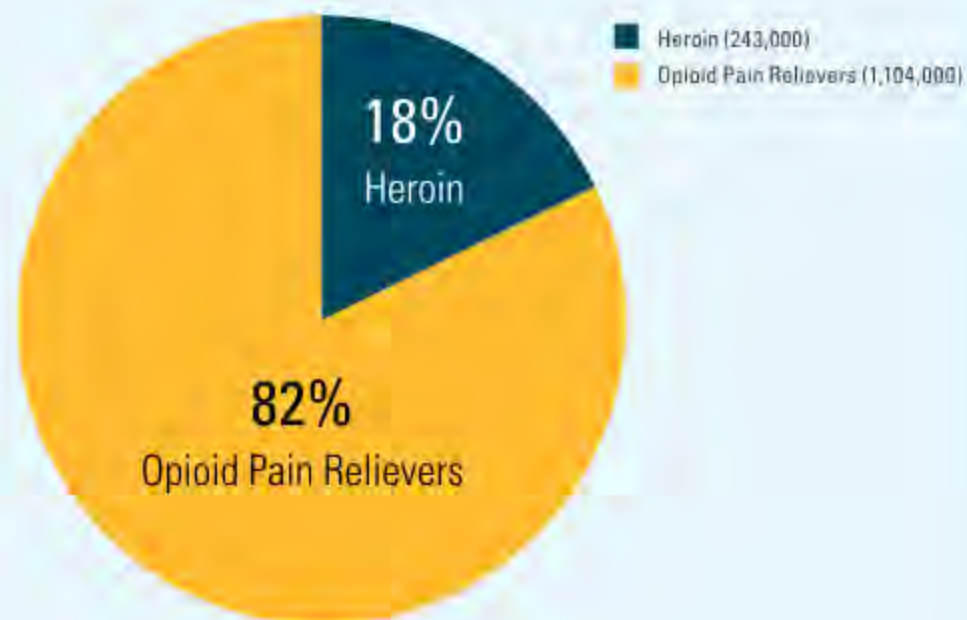
2001 U.S. Drug Use in Past Month

Alcohol	48.3%	108.9 million
Cigarettes	24.9%	60.4 million
Marijuana	5.4%	12.2 million
Ecstasy	3.6%	8.1 million
Cocaine	0.7%	1.7 million
Heroin	0.1%	123 thousand

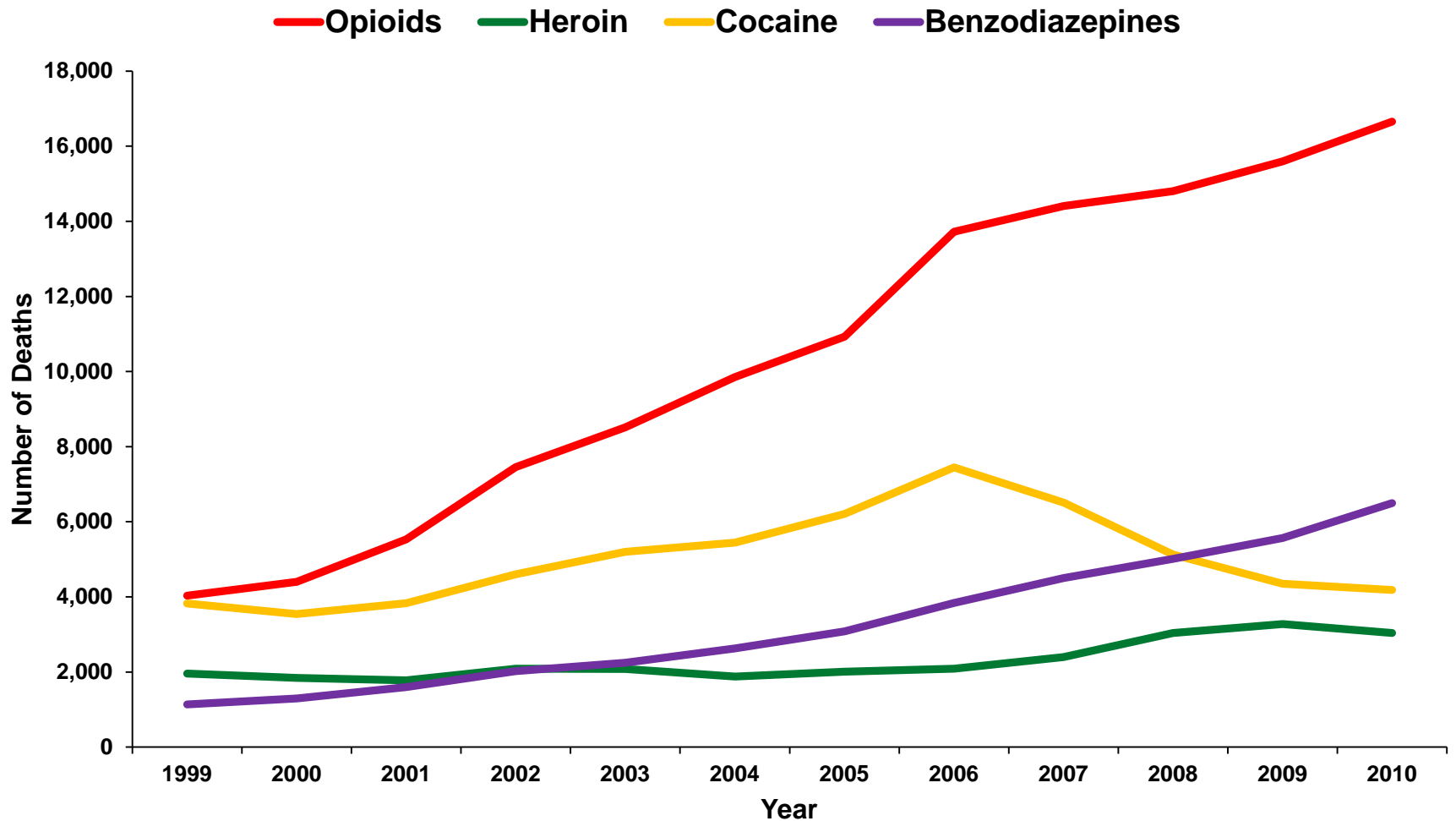
Prevalence of Opioid Dependence

More than 1.3 million American adults were dependent on opioids in 2008

82% of Opioid-Dependent Individuals Are Dependent on Prescription Opioid Pain Relievers



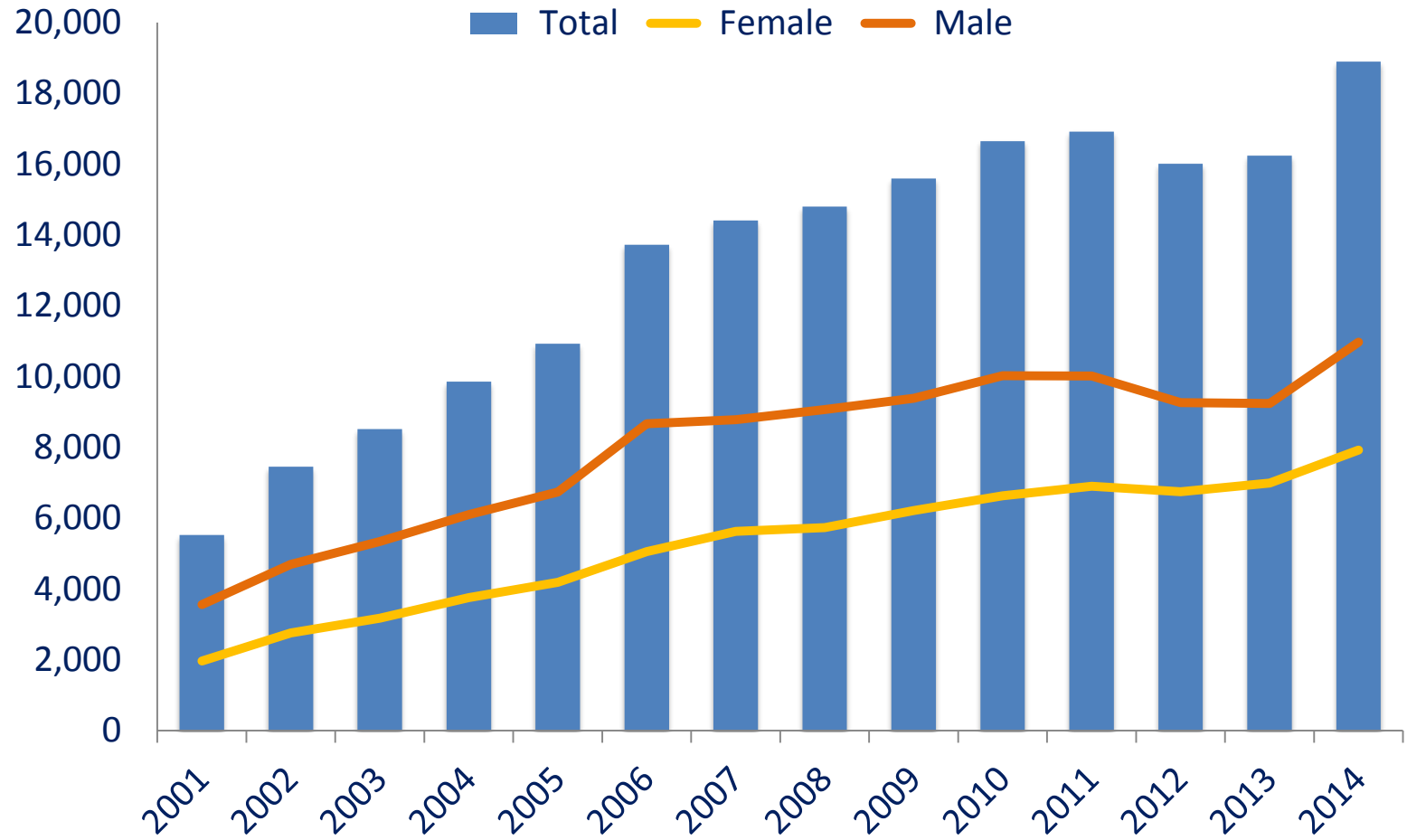
DRUG OVERDOSE DEATHS BY MAJOR DRUG TYPE, US, 1999-2010



CDC/NCHS National Vital Statistics System, CDC Wonder. Updated with 2010 mortality.

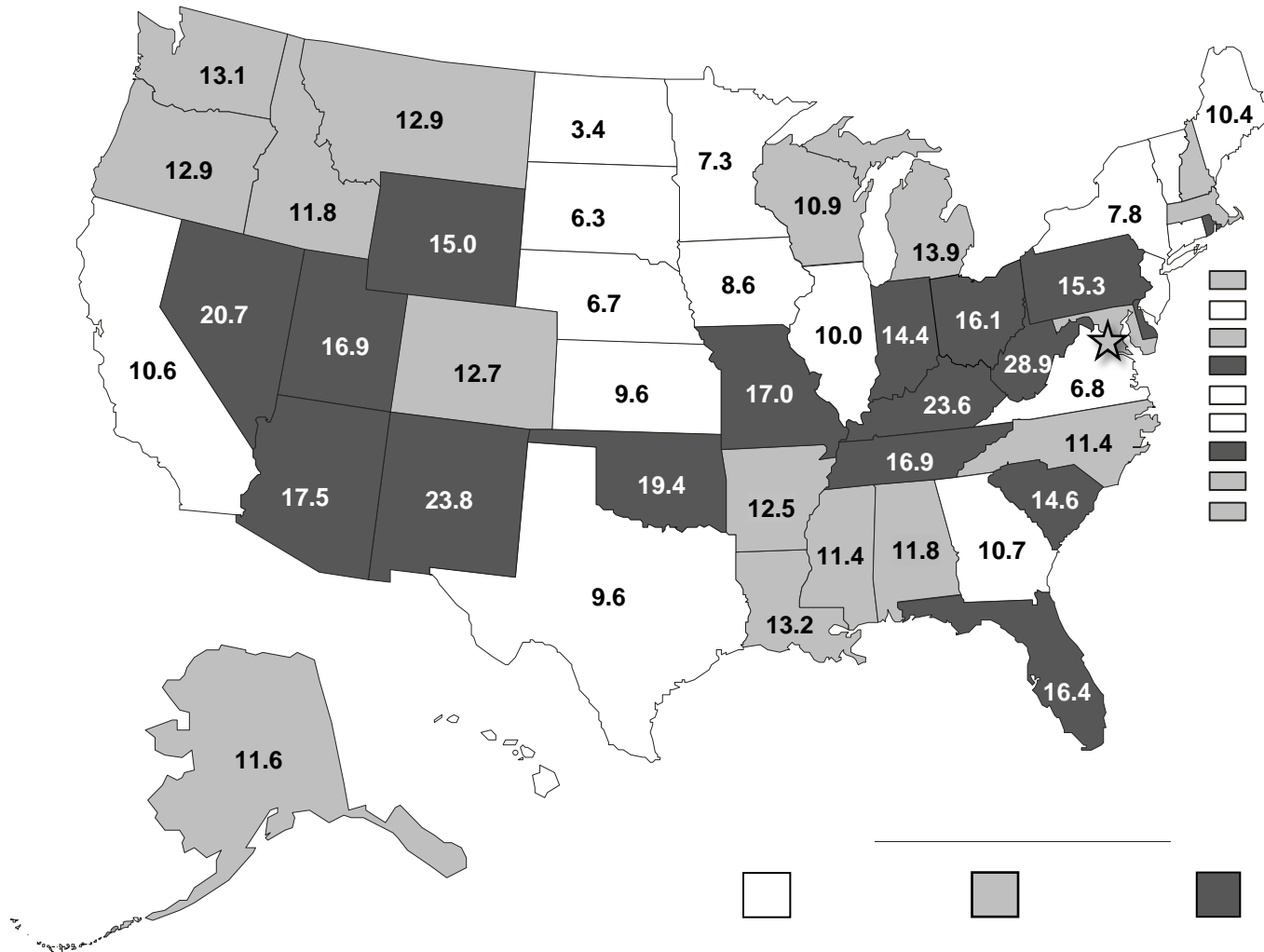
NATIONAL OVERDOSE DEATHS

NUMBER OF DEATHS FROM PRESCRIPTION OPIOID PAIN RELIEVERS



Source: National Center for Health Statistics, CDC Wonder

Death Rates for Drug Overdose by State, 2010



HOW DO DRUGS WORK ?

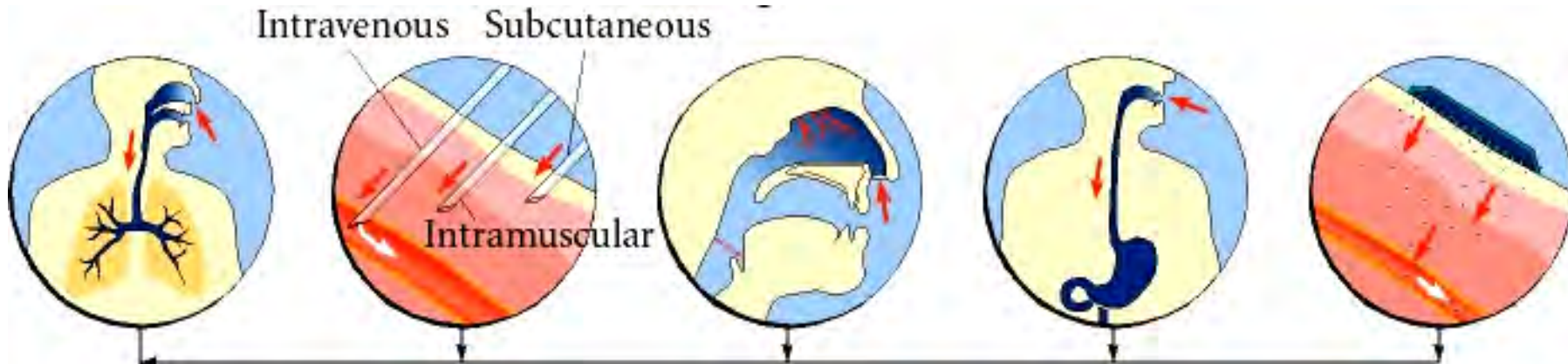
Inhaling

Injecting

Snorting

Orally

Transdermal

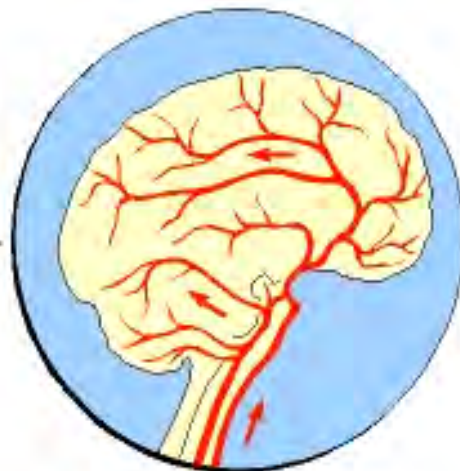
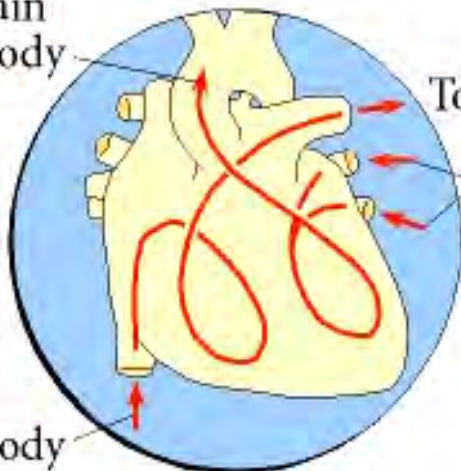


To brain and body

To lungs

From lungs

From body



Blood circulation

Drug delivered to the brain by blood

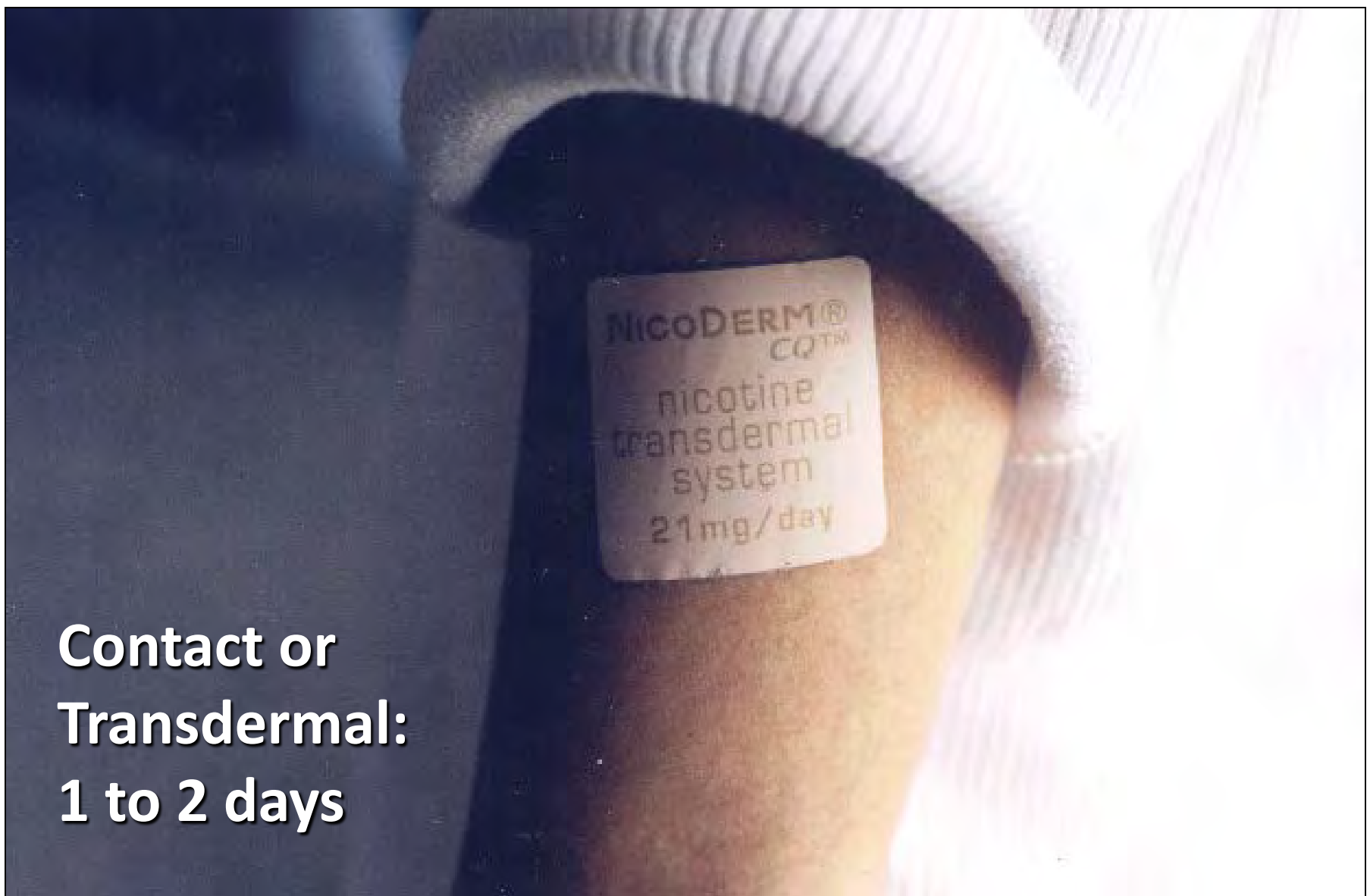
Inhaling: 7 to 10 seconds

Intravenous (IV)	15 – 30 seconds
Intramuscular (IM)	3 – 5 minutes
Subcutaneous	3 – 5 minutes

Snorting or Mucosal Exposure: 3 to 5 minutes

Oral use (ingesting): 20 to 30 minutes

**Contact or
Transdermal:
1 to 2 days**



NICODERM®
CQ™
nicotine
transdermal
system
21mg/day

WHAT ABOUT NEURO- TRANSMITTERS ?

Reward System of the Brain

Prefrontal cortex

Nucleus accumbens

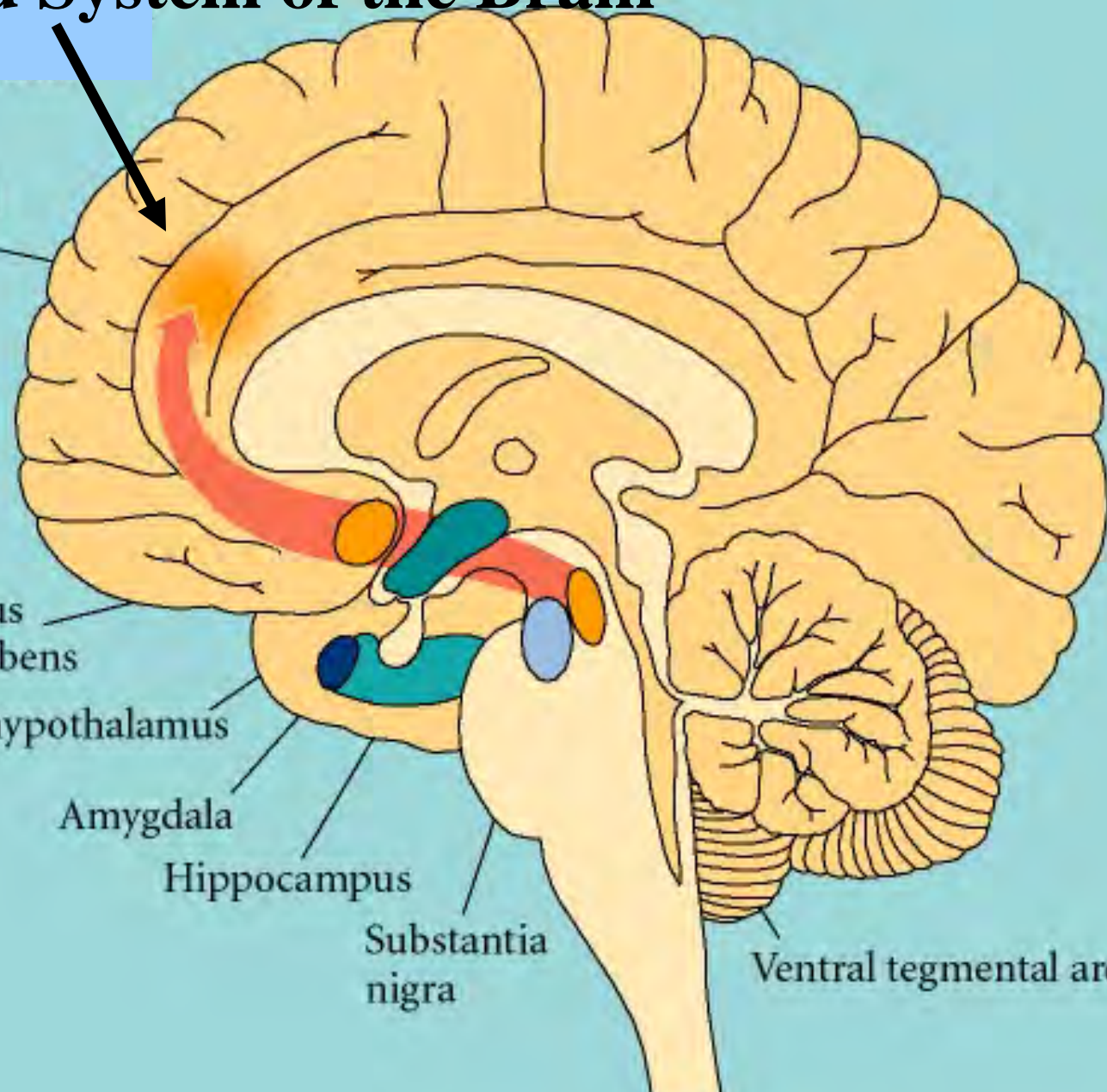
Lateral hypothalamus

Amygdala

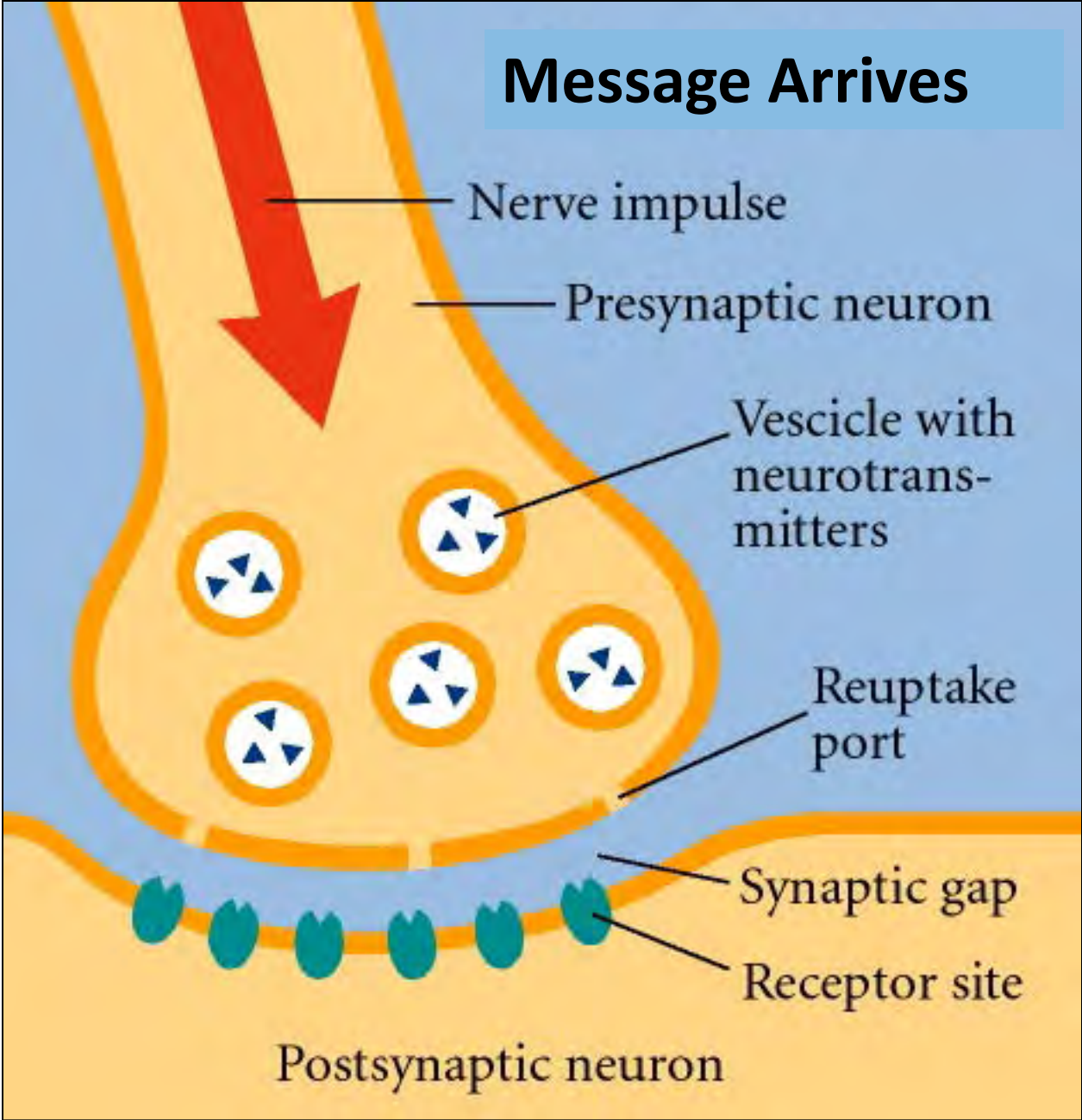
Hippocampus

Substantia nigra

Ventral tegmental area

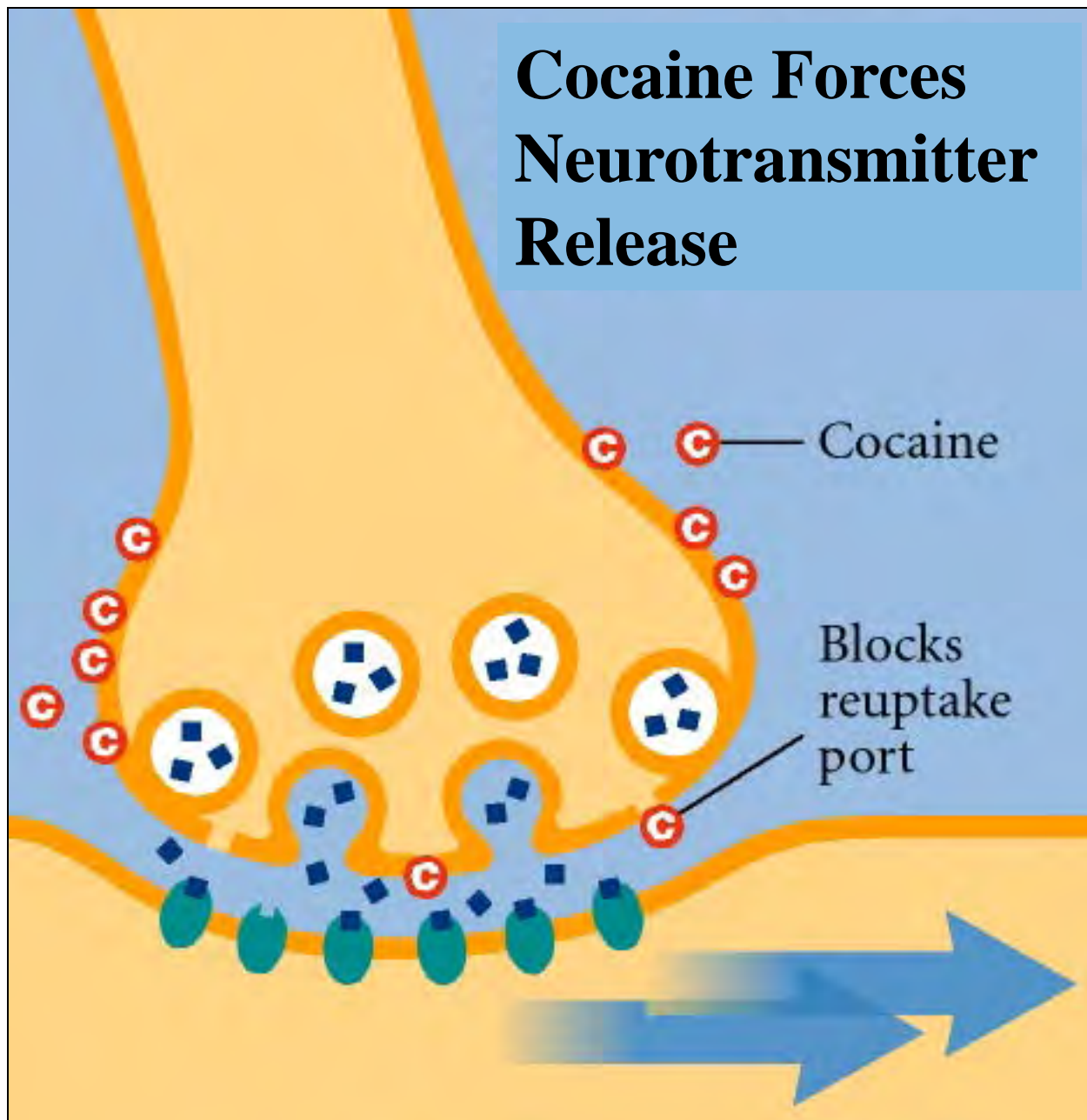


Message Arrives



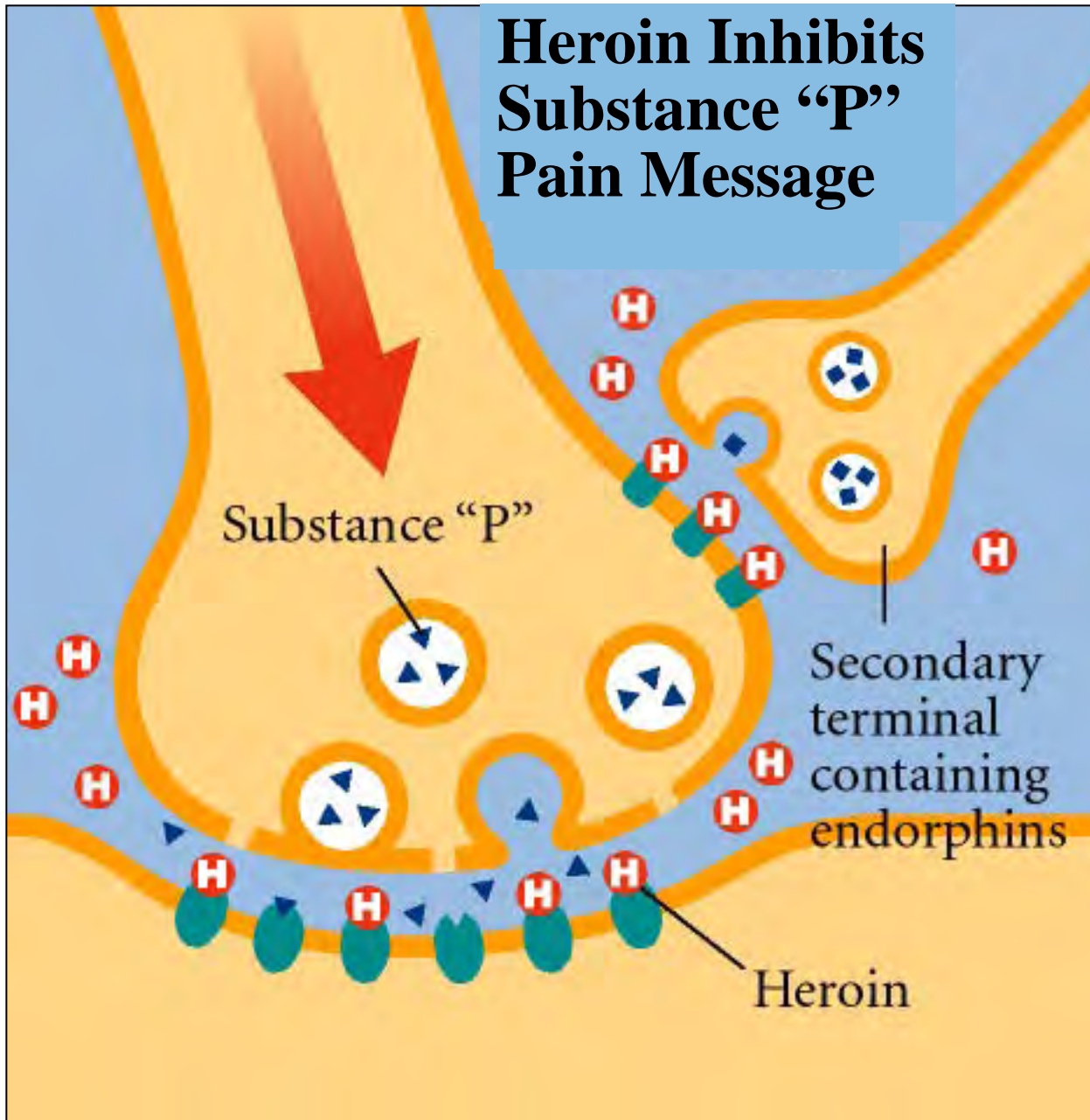
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Cocaine Forces Neurotransmitter Release



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Inc.

Heroin Inhibits Substance "P" Pain Message



Neurotransmitters

Acetylcholine

Substance "P"

Norepinephrine Anandamide

Epinephrine

Glycine

Dopamine

Histamine

Endorphin

Nitric oxide

Enkephalin

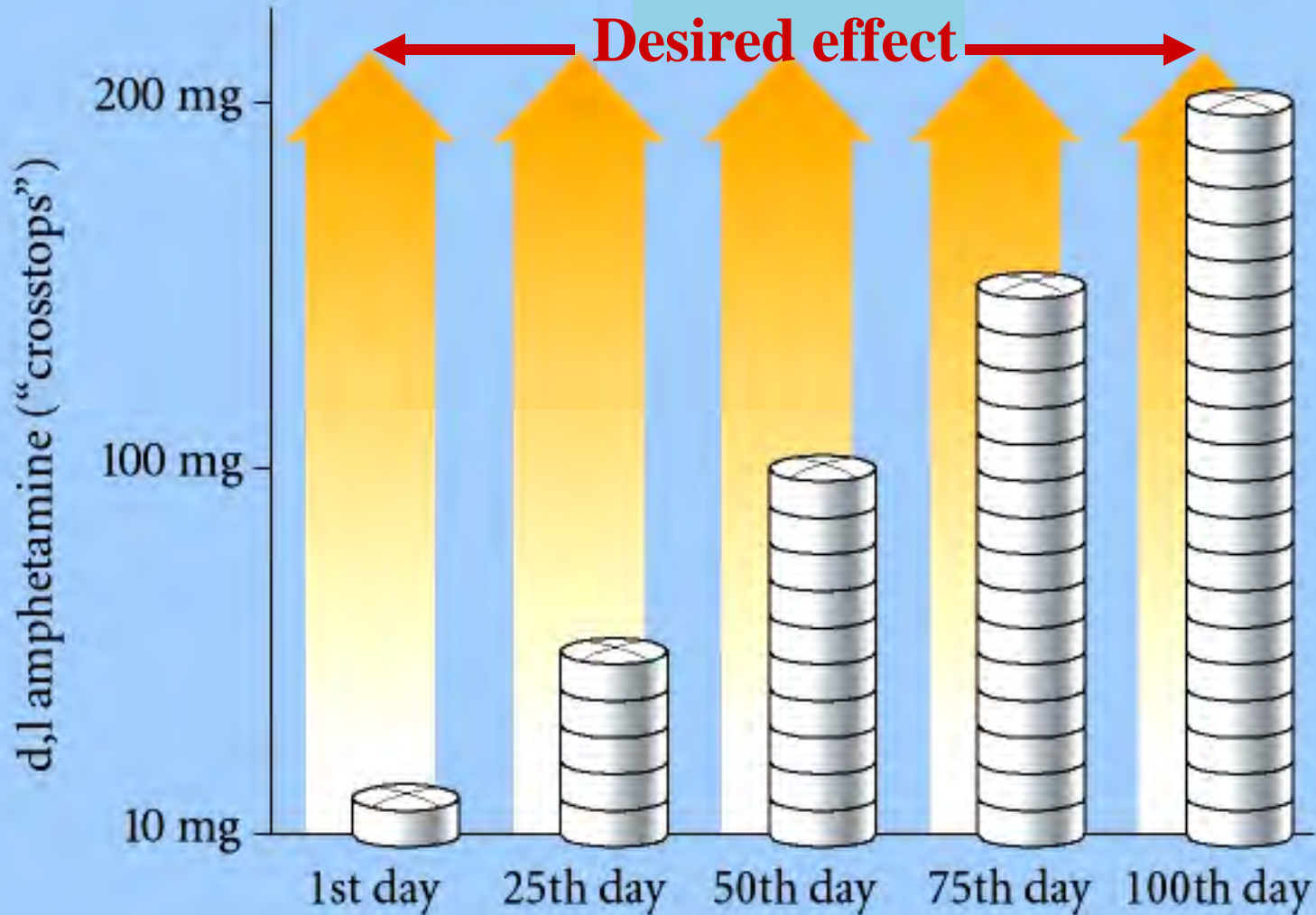
Glutamic acid

Serotonin

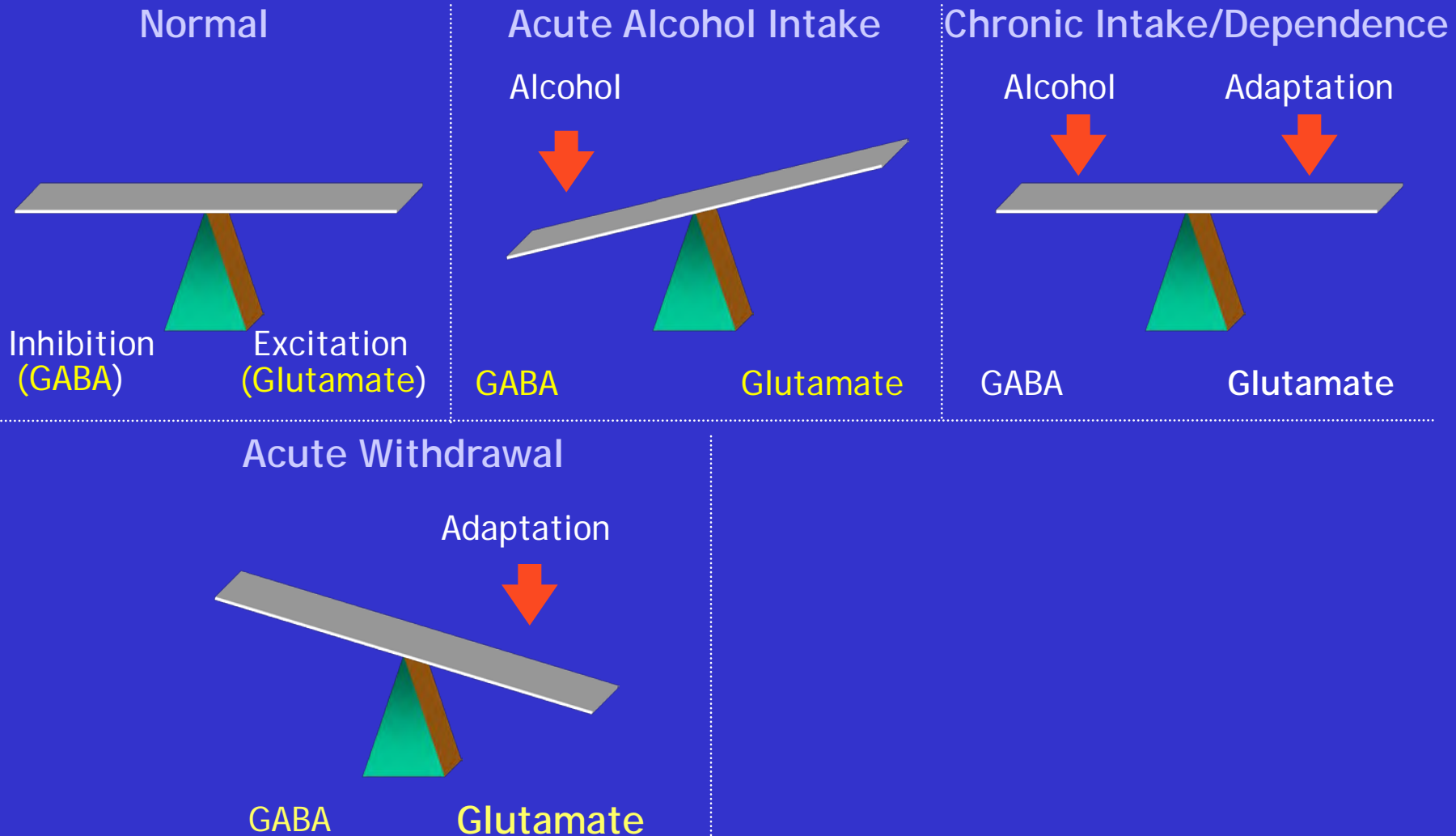
Cortisone

GABA

Development of Amphetamine Tolerance Over Time



Alcohol Tolerance and Withdrawal on Neurochemical Balance



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Levels of Use

Abstention

Experimental

Social/Recreational

Habitual

Abuse

Addiction

Addiction

- Practices addiction most of the time
- Continues use despite adverse consequences
- Denies there's a problem
- After withdrawal has a strong tendency to relapse
- Has lost control
- Has altered brain chemistry

Uppers (stimulants)

Cocaine (hydrochloride, crack, freebase)

Amphetamines (speed, meth, “ice”)

Amphetamine congeners (Ritalin[®], diet pills, e.g., fen-phen)

Plant stimulants (khat, betel nut, yohimbe)

Caffeine (coffee, tea, soft drinks, OTC meds)

Nicotine (cigarettes, cigars, chewing tobacco)

Initial Effects of Stimulants

Increased energy

Increased heart rate, blood pressure, breathing, & reflexes

Restlessness & excessive talking

Hypersensitivity

Dilated pupils

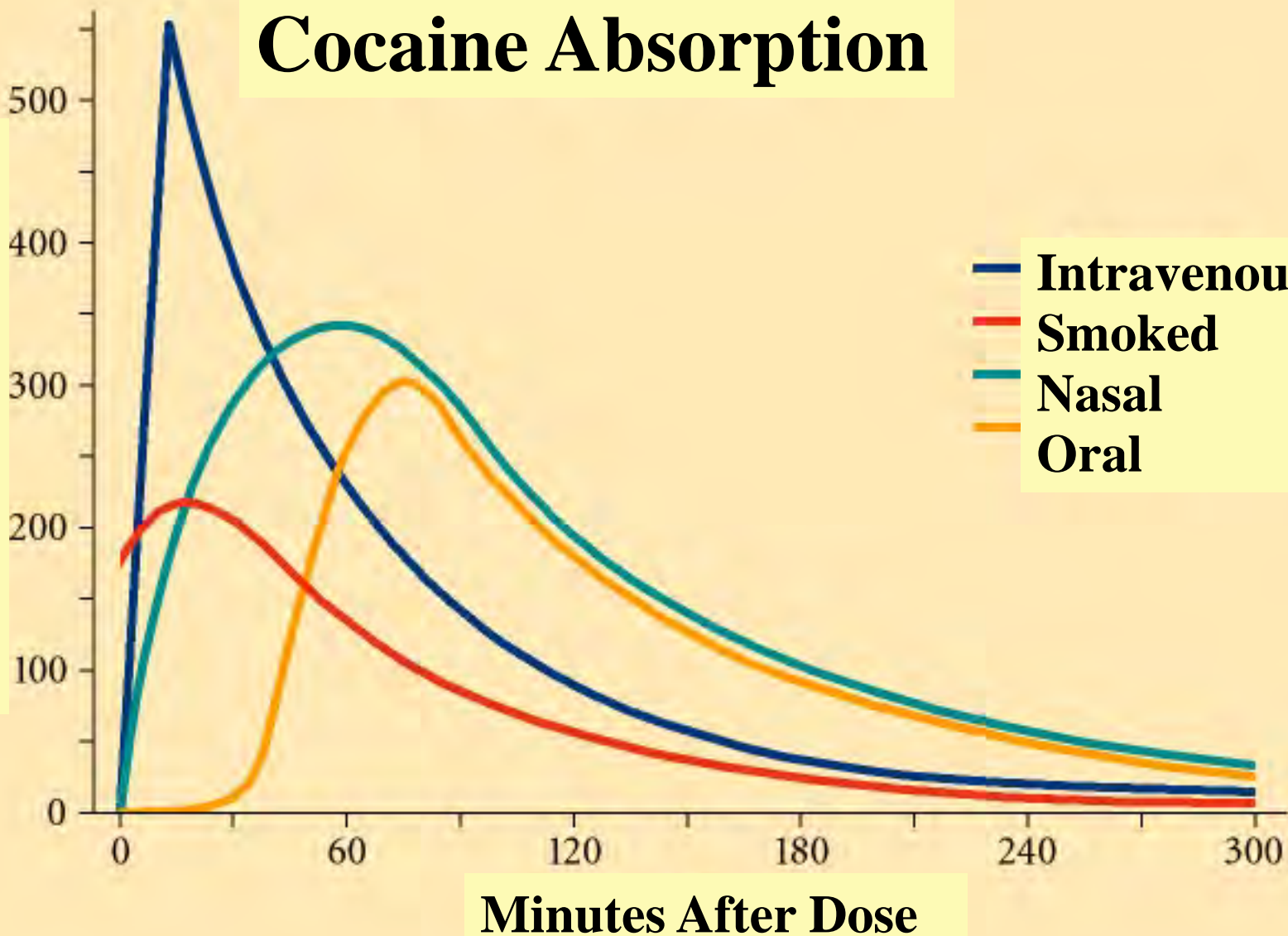
Little appetite or thirst

Overconfidence

Euphoria

Cocaine Absorption

Plasma Levels of Cocaine
(nanograms per milliliter)



- Intravenous
- Smoked
- Nasal
- Oral

Smokable cocaine (freebase, crack, paste)

Crack pipes

Amphetamines

d,l amphetamine (e.g., benzedrine, “crosstos,” “black beauties,” “bennies”)

Methamphetamine (e.g., methedrine, “crank,” meth, “crystal”)

Dextroamphetamine (e.g., dexedrine, “dexies,” “beans,” “Christmas trees”)

Dextromethamphetamine (“ice,” “glass,” “batu,” “snot”)

Methamphetamines

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“Ice- a form of Meth”

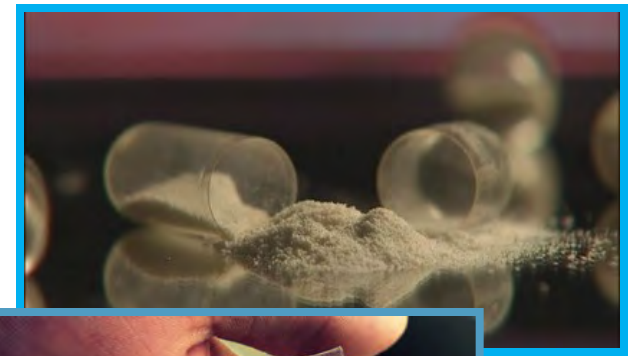
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MDMA (ECSTASY)

- 3, 4-methylenedioxy-methamphetamine
- Street terms: Adam, E, X, XTC, love drug, Molly
- A synthetic, psychoactive drug with both stimulant and hallucinogenic properties similar to methamphetamine and mescaline
- Adverse effects: enhanced physical activity, sweating, lack of coordination, mental confusion, jaw clenching, hyperthermia, and agitation

WHAT IS “MOLLY”?

1. Ecstasy pills with little MDMA and lots of caffeine, meth, assorted drugs? OR
 2. A pure crystalline form of MDMA, most often sold as a powder filled capsule? OR
 3. Methylone? Bath salts?
- Reports of desired effects of euphoria, but also increased paranoia, agitated delirium, scary hallucinations, psychotic episodes, violent or destructive self-harm behavior, including death
 - Bottom line - Molly usually is not a pure form of MDMA, but may be a drug that can be very dangerous since its contents are unknown

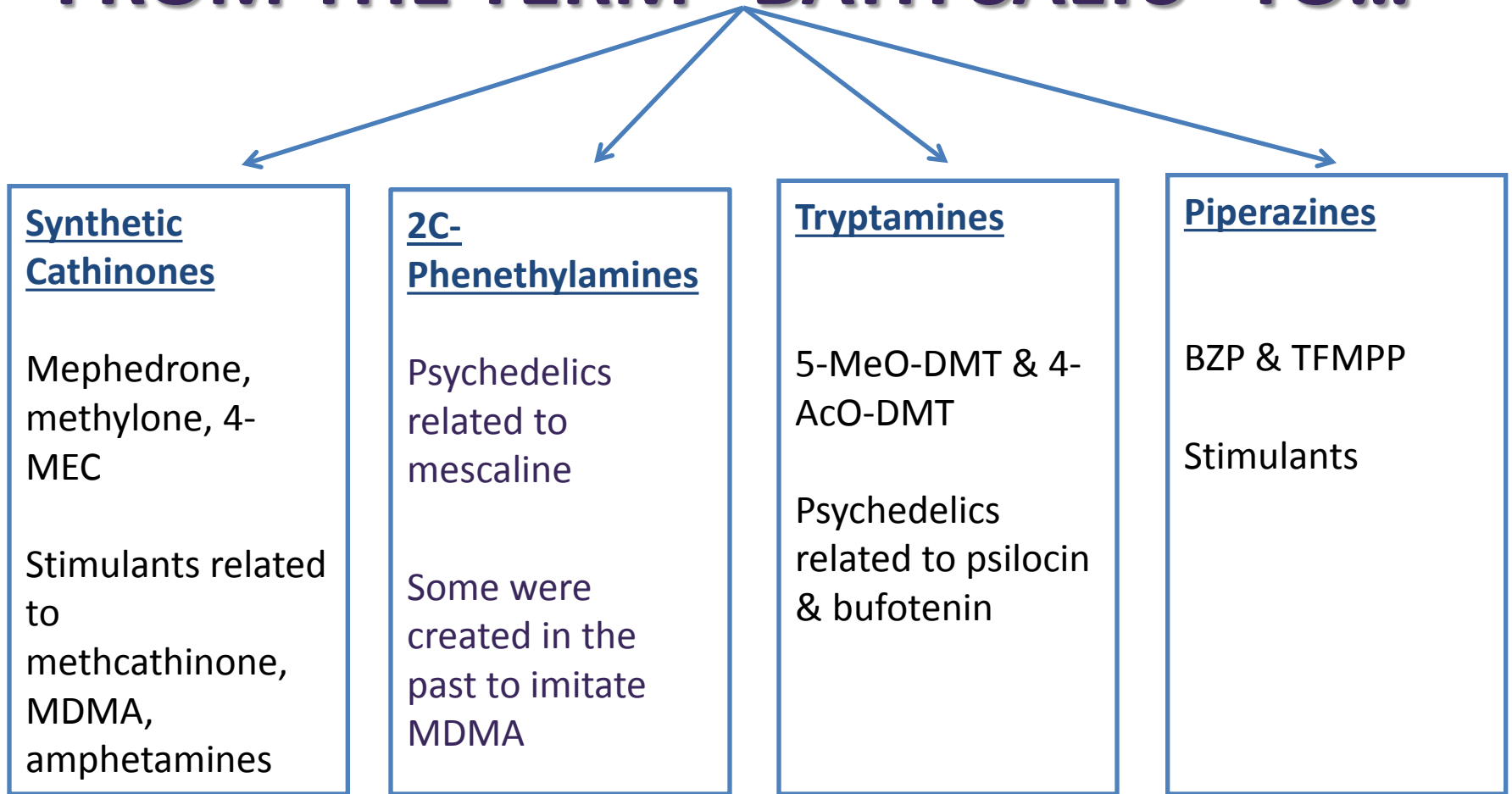


Synthetic Drugs



- “Spice,” “Bath Salts,” main names
- Chemically-based; not plant derived
- Complex chemistry
- Constantly changing to “stay legal”
- Need to prove “intended to use” to convict in some areas

FROM THE TERM “BATH SALTS” TO...



And **Dissociatives** related to ketamine and PCP and **Opioids** related to morphine, fentanyl, and heroin.

Downers (depressants)

Opiates/Opioids

Opium, codeine, morphine, heroin

Vicodin[®], OxyContin[®]

Heroin laced fentanyl

Sedative-Hypnotics

Benzodiazepines, e.g., Valium[®]

Barbiturates, e.g., Seconal[®]

Others, e.g., Rohypnol[®],
Miltown[®]

Alcohol

Beer, wine, hard liquor

Others Downers

Antihistamines

Skeletal muscle relaxants

Over-the-counter downers

Lookalike downers

Opiates/Opioids

From Opium

opium

morphine

(Vicodin[®])

codeine

thebaine

Semisynthetic

heroin

hydrocodonepropoxyphene

(Darvon[®])

hydromorphone

(Dilaudid[®])

oxycodone

(OxyContin[®])

Synthetic

methadone

meperidine

(Demerol[®])

fentanyl

(Sublimaze[®])

Effects: Opiates/Opioids

Pain suppression

Pinpoint pupils

Lowered heart rate, blood pressure, respiration

Constipation

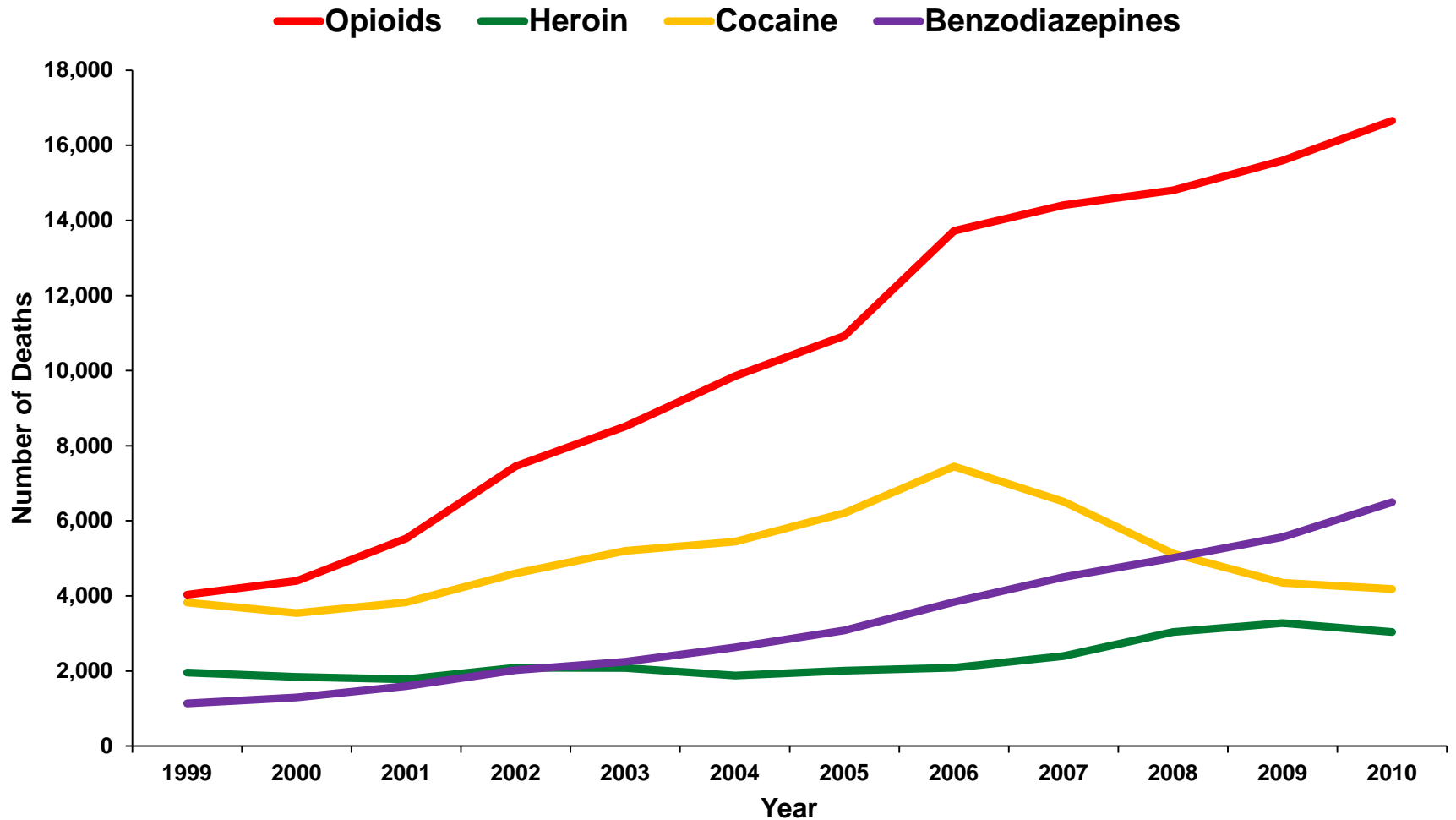
Cough suppression

Lax muscle tone

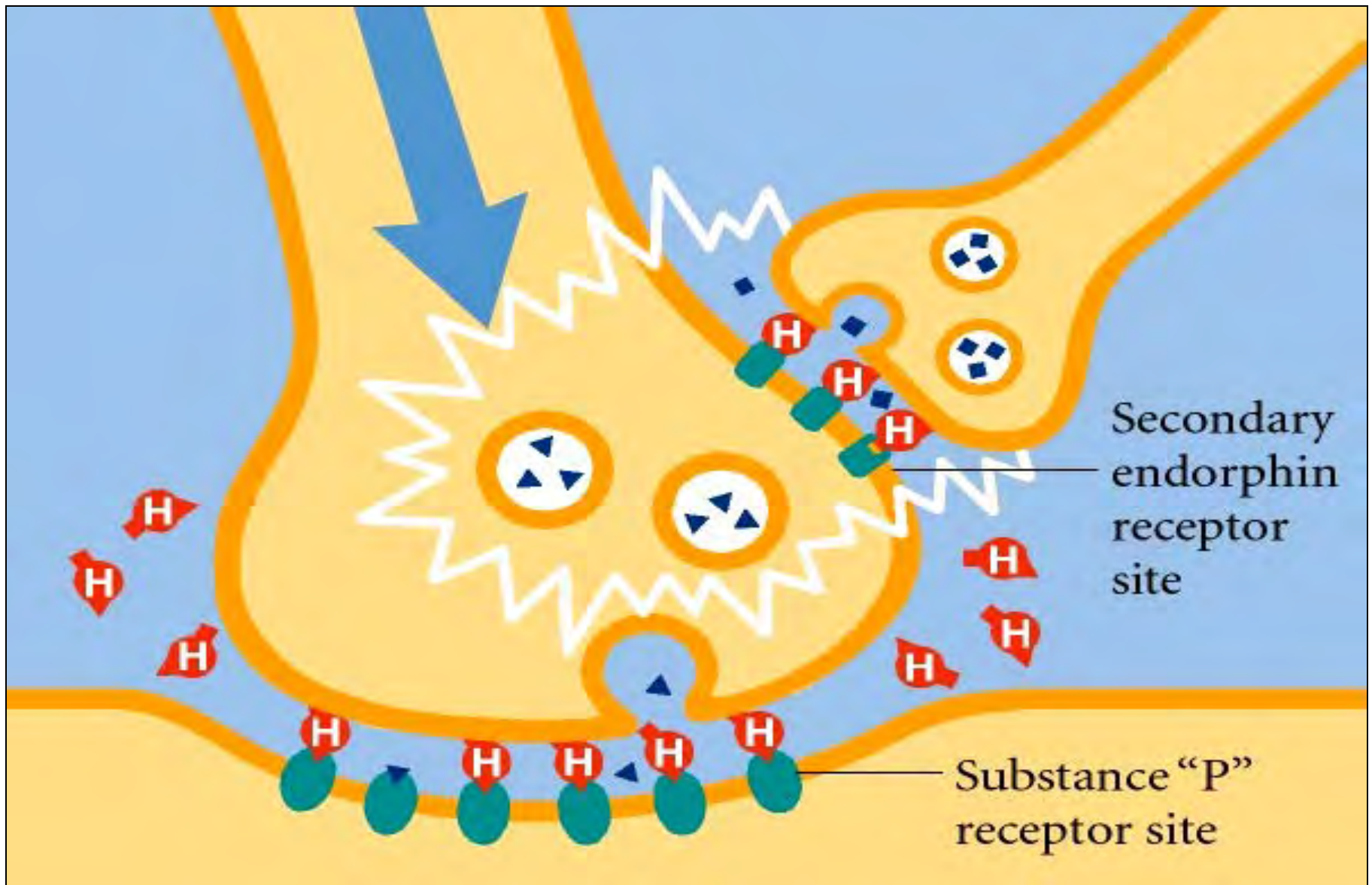
Dryness of mouth

Euphoria

DRUG OVERDOSE DEATHS BY MAJOR DRUG TYPE, US, 1999-2010



CDC/NCHS National Vital Statistics System, CDC Wonder. Updated with 2010 mortality.



Artificial Pain Suppression

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Black Tar Heroin

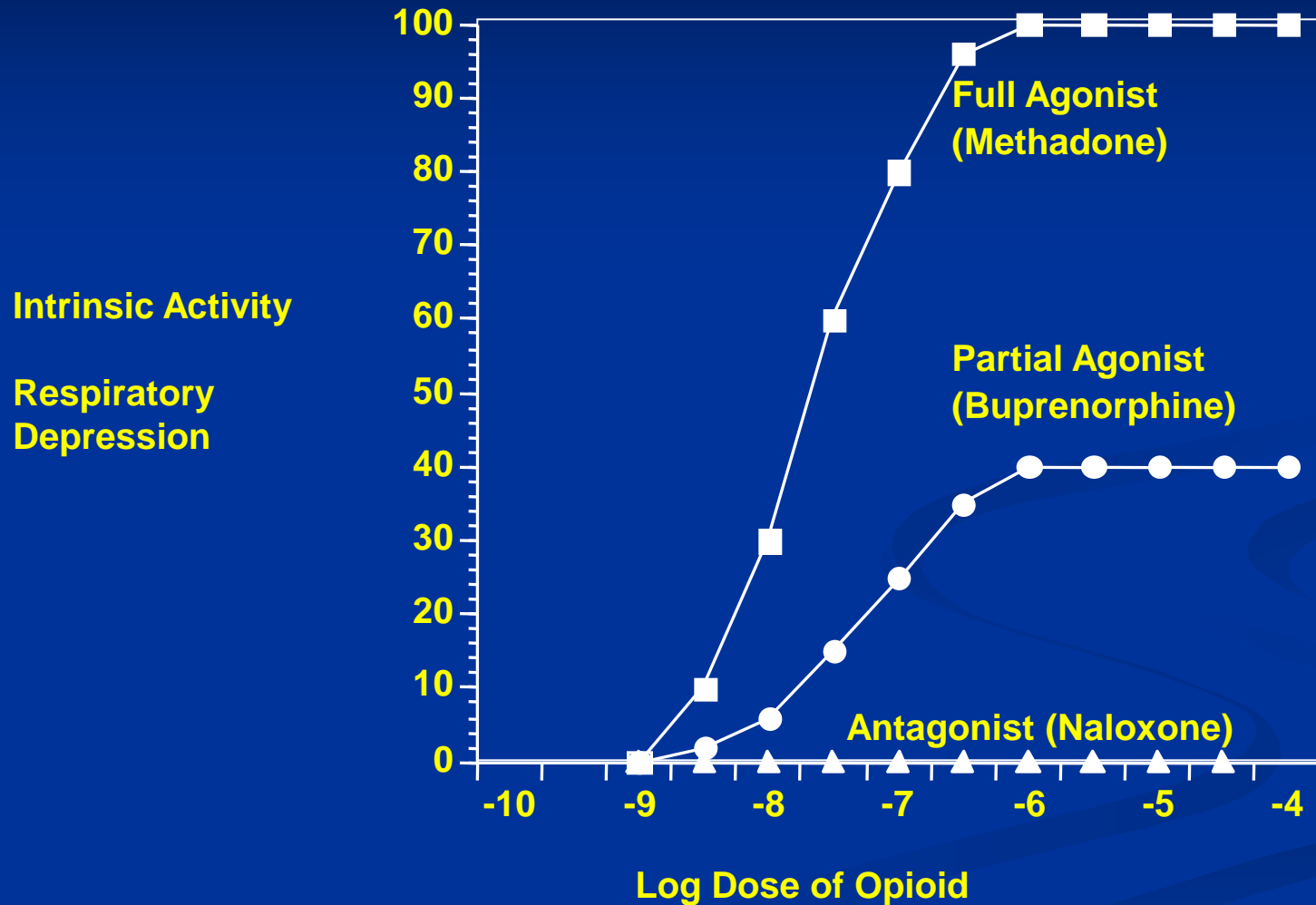
CHANGING HEROIN MARKET

- 1920's to 90's mostly Asian White
 - Low %
 - Concentrated in large Urban areas
- Later 90's- now--Black Tar from Mexico
 - More concentrated,
 - Different Biz model- middle/smaller towns
 - Deliver via cell phone
- NOW and Future---Fentanyl/Su and Car-Fentanyl
 - 10-100 x stronger, synthetic, cheaper
 - More deadly, resists naloxone block

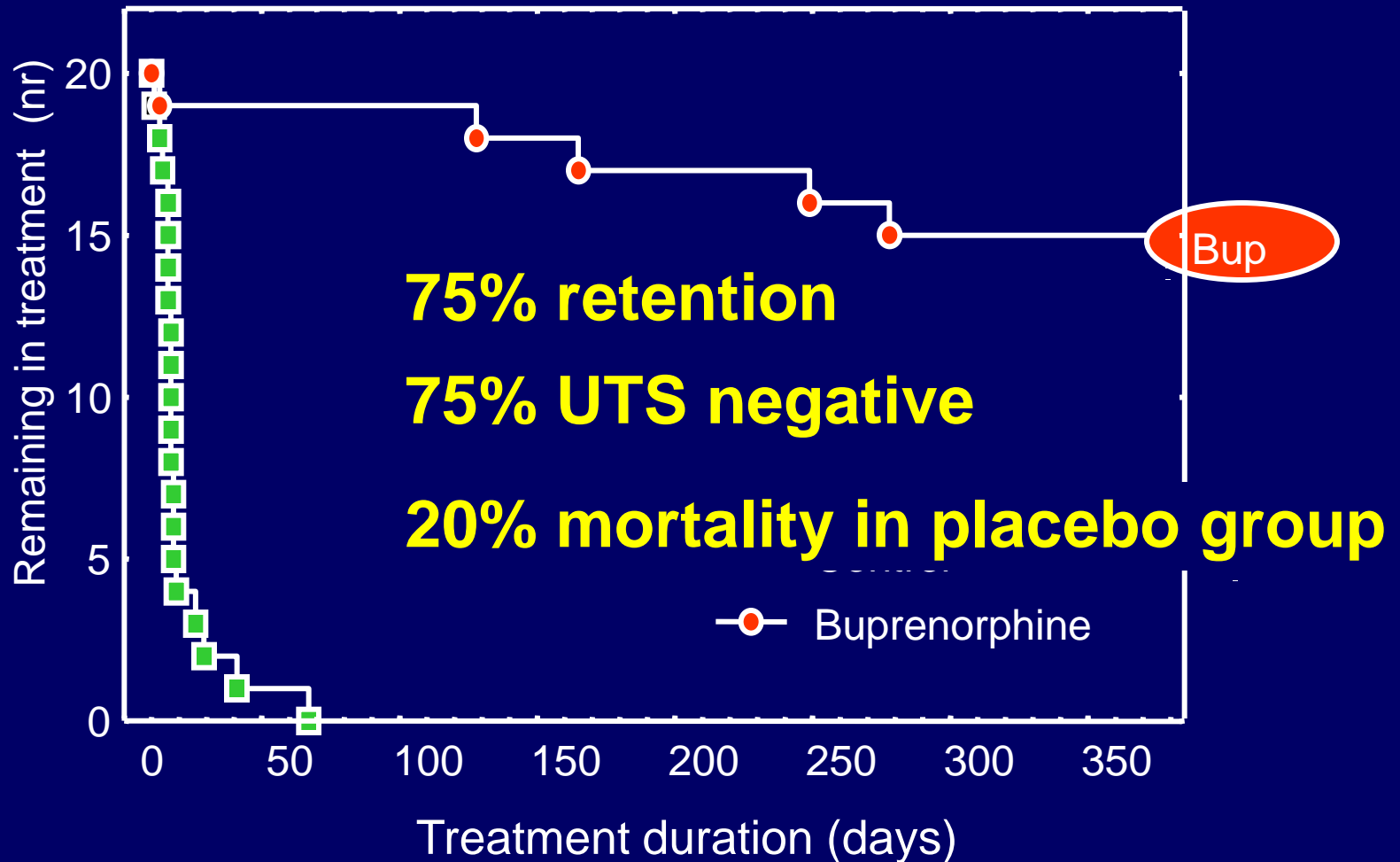
Methadone (Dolophine®)

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Inc.

Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



Treatment Retention and Mortality Bup vs Placebo- all got "1-1 drug counseling"



75% retention

75% UTS negative

20% mortality in placebo group

—●— Buprenorphine

Bup= 16 mg a day double blind with
Placebo

Sedative-Hypnotics

Benzodiazepines

Xanax[®], Valium[®], Halcion[®], Librium[®],
Rohypnol[®], Klonopin[®], Restoril[®], Ativan[®]

Barbiturates

Seconal[®], Nembutal[®], Amytal[®], phenobarbital

Others

Chloral hydrate, GHB, GBL, Placidyl[®], etc.

Benzodiazepines

Very Long Acting

Halazepam (Paxipam[®])

Prazepam (Centrax[®])

Flurazepam (Dalmane[®])

Intermediate Acting

Clonazepam (Klonopin[®])

Chlordiazepoxide (Librium[®])

Diazepam (Valium[®])

Short Acting

Alprazolam (Xanax[®])

Temazepam (Restoril[®])

Oxazepam (Serax[®])

Lorazepam (Ativan[®])

Very Short Acting

Triazolam (Halcion[®])

Effects of Benzodiazepines

Anxiety control (e.g., panic attack)

Relaxation

Drowsiness & sleep

Control seizures

Reduced muscular coordination

Dulled physical sensations

Use with Heroin/Opioids Triples
Lethality

Benzodiazepine Use in the United States

Mark Olfson, MD, MPH^{1,2}; Marissa King, PhD³; Michael Schoenbaum, PhD⁴

Design, Setting, and Participants A retrospective descriptive analysis of benzodiazepine prescriptions was performed with the 2008 LifeLink LRx Longitudinal Prescription database (IMS Health Inc), which includes approximately 60% of all retail pharmacies in the United States. Denominators were adjusted to generalize estimates to the US population.

Results

In 2008, approximately 5.2% adults 18 to 80 years used benzodiazepines.

The percentage increased with age from 2.6% (18-35 years) to 5.4% (36-50 years) to 7.4% (51-64 years) to 8.7% (65-80 years).

Benzodiazepine use was nearly twice as prevalent in women as men.

The proportion of benzodiazepine use that was long term increased with age from 14.7% (18-35 years) to 31.4% (65-80 years).

Effect of Anxiolytic and Hypnotic drug prescriptions on Mortality Hazards: retrospective cohort study.

Weich S1, Pearce HL, Croft P, Singh S, Crome I, Bashford J, Frisher M.

PARTICIPANTS:

34 727 patients aged 16 years and older first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001, and 69 418 patients with no prescriptions for such drugs (controls) matched by age, sex, and practice. Patients were followed-up for a mean of 7.6 years (range 0.1-13.4 years).

RESULTS:

The age adjusted hazard ratio for mortality = 3.46 (95% confidence interval 3.34 to 3.59) and 3.32 (3.19 to 3.45) after adjusting for other potential confounders.

Dose-response associations with mortality found for all three classes of study drugs

(benzodiazepines, Z drugs (zaleplon, zolpidem, and zopiclone), and other drugs).

Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature.

Dodds TJ1,2.

DATA SOURCES:

A PubMed search of English-language publications from database inception until October 11, 2016,

A total of 17 studies were included in this review.

RESULTS:

Benzos ^ Suicide Risk (OR's = 3 to 5 x in most studies)

CONCLUSIONS:

Benzodiazepines appear to cause an overall increase in the risk of attempting or completing suicide.

Possible mechanisms of pro-suicidal effects

Part I - Drug Testing: Detection Period Range

Alcohol BAL/Breath	1/2 – 1 day
Alcohol EtG	1-4 days
Amphetamines	2 – 4 days
Barbiturates (most)	2 – 4 days
phenobarbital	up to 30 days
Benzodiazepines	3-5 days,
Cups <u>don't show-</u> lor, clon, alprazolam	
Cocaine	12 – 72 hours
Codeine	1 – 3 days
Darvon [®]	6 – 48 hours

COMPARISON OF CLONAZEPAM COMPLIANCE BY MEASUREMENT OF URINARY CONCENTRATION BY IMMUNOASSAY AND LC-MS/MS IN PAIN MANAGEMENT POPULATION.

[WEST R](#), [PESCE A](#), [WEST C](#), [CREWS B](#), [MIKEL C](#), [ALMAZAN P](#), [ROSENTHAL M](#), [LATYSHEV S](#).

- Samples from 180 patients taking clonazepam met these medication criteria
- Positivity rates were **21%** (38 samples) by immunoassay (cups) .
- The positivity rate was **70%** (126 samples) if the LC-MS/MS cutoff was set at 200 ng/mL. (chromatography)
- Positivity rate was **87%** (157 samples) if the LC-MS/MS was set at 40 ng/mL.

Part II - Drug Testing: Detection Period Range - Urine Testing

Dilaudid	2 – 4 days
Heroin	2 – 4 days
Marijuana - Single use	1 – 3 days
Casual use - 4 joints/wk	5 – 7 days
Daily use	10 – 15 days
Chronic heavy use	1 – 2 months
Methadone	2 – 5 days
PCP - Casual use	2 – 7 days
Chronic use	up to 30 days

Treatment for Stimulant Addiction

Withdrawal 1-5 days

Sedatives, antipsych.

/sleep nutrition

Initial- Intensive Oupt groups
or Inpt

Longer-term Recovery

1-1, grps, AA, CA, NA, COD?

Meds ??? COD meds?

Hep C/HIV Screen





Medical Treatments for Opioid Addiction

Naloxone (short acting antag: for OD)

Naltrexone (longer acting antag: helps decrease craving and use)

Methadone (full synth opioid decreases use/craving/crime)

Clonidine (Decrease WD Sx)

Buprenorphine (Partial opioid blocks use/OD/craving)



Current Issues in Addiction Treatment

1. Heroin epidemic and OPIOID OD's
2. Health Care Reform ??
3. Expanding use of Medications for treatment
4. Developing New Meds for Addictions
5. Developing more treatment resources
6. Coerced treatment /voluntary treatment ?
7. Abstinence-oriented vs. harm reduction ?
8. Integration into Primary Care
9. And don't forget the Anonymous programs