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Approaches to Detoxification of Patients during the Opioid Epidemic

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DISCLOSURE

I have nothing to disclose.

KernMedical

Objectives

1. Identify the epidemiology and pharmacological characteristics of central nervous system depressants that augment the clinical complexity for the treating physician of patients who present for treatment during the so-called “opioid epidemic”.
2. Outline the neurobiology of neuroadaption to drugs of abuse and relate these to clinical complications associated with their discontinuation.
3. Differentiate between approaches to safe and effective detoxification of patients who present for treatment of opioid use disorder but use other drugs of abuse in addition to opioids.

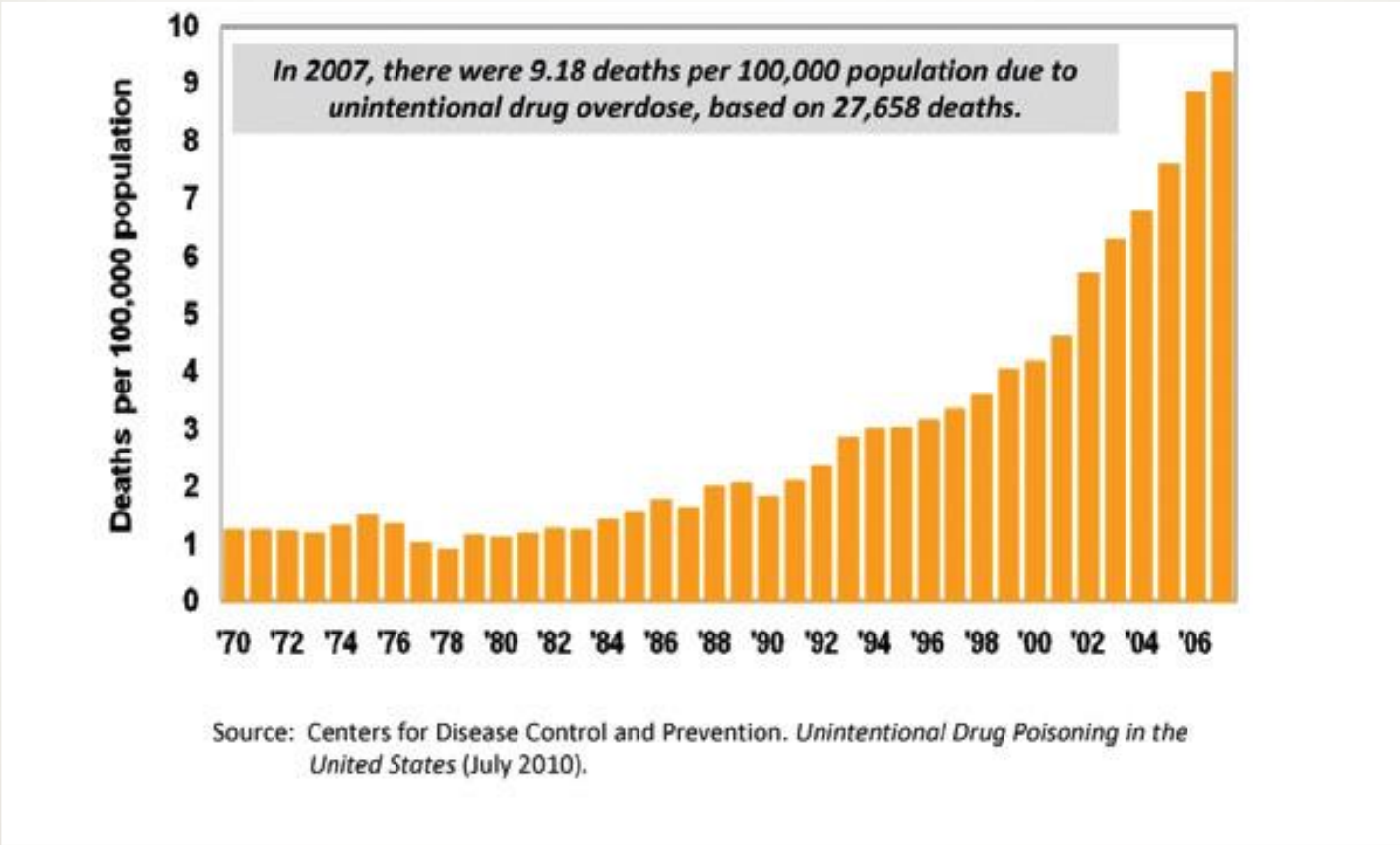
Daily Intelligencer / INTERESTING TIMES

The Opioid Epidemic Is This Generation's AIDS Crisis

By **Andrew Sullivan**

Snow covers a cemetery in Gloucester, Massachusetts. Photo: John Moore/Getty Images

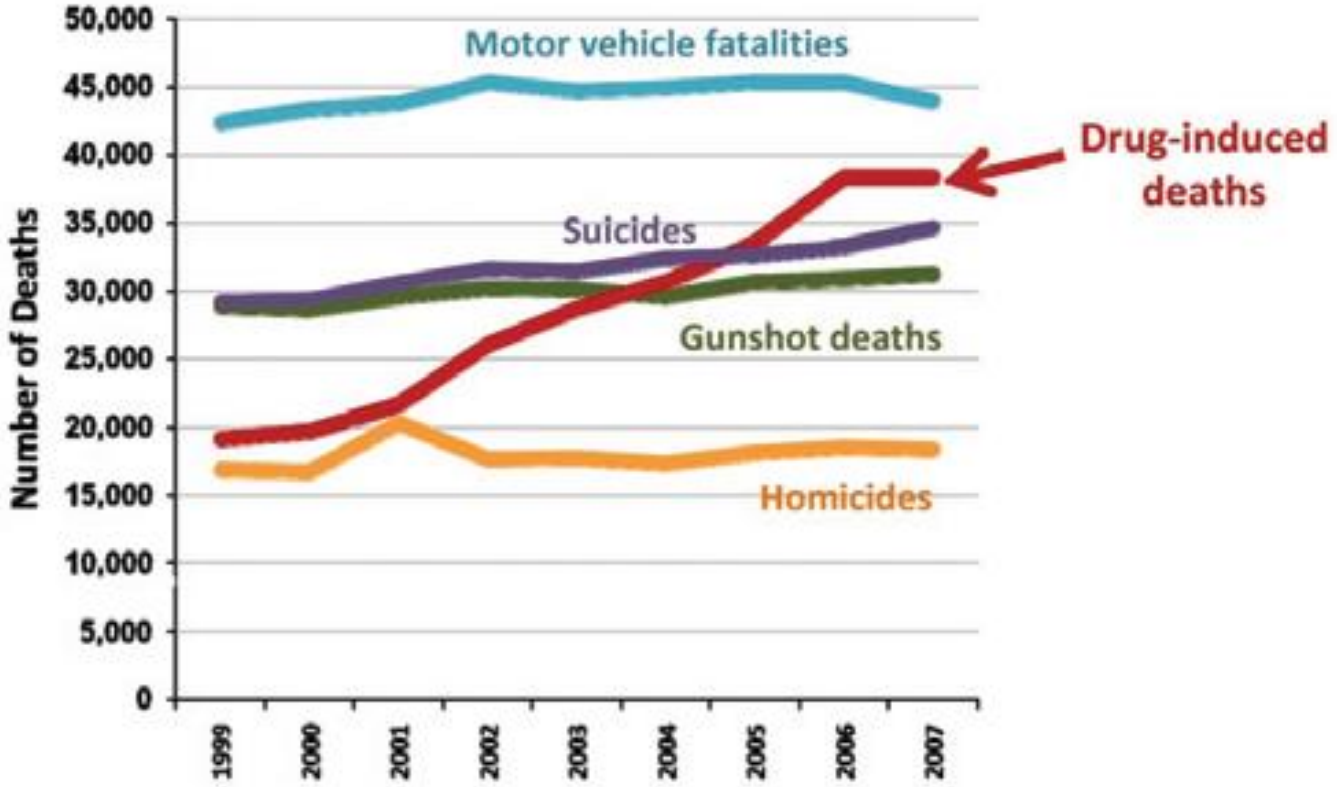
Clarion Call from the CDC Came in 2012: U.S. Drug Overdose Deaths, 1970-2007



Source: Centers for Disease Control and Prevention. *Unintentional Drug Poisoning in the United States* (July 2010).

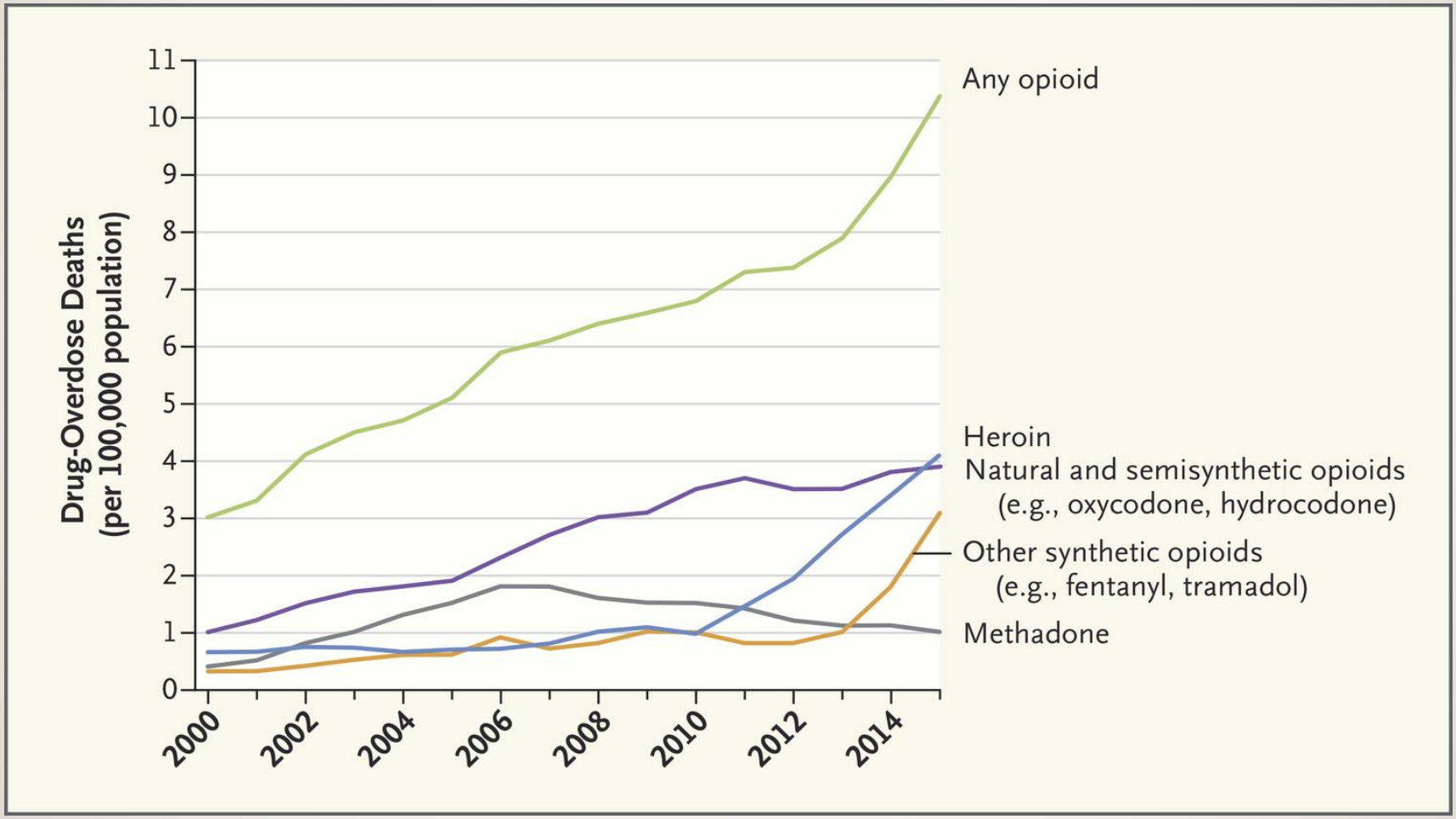
CDC MMWR / January 13, 2012 / Vol. 61 / No. 1

Drug-induced Deaths Second Only to Motor Vehicle Fatalities, 1999-2007



Source: National Center for Health Statistics, Centers for Disease Control and Prevention. National Vital Statistics Reports *Deaths: Final Data* for the years 1999 to 2007 (2001 to 2010).

Opioid Overdose Deaths by Type of Opioid, United States, 2000–2014



Frank RG, Pollack HA. N Engl J Med 2017;376:605-607.

Remember that ***opioids are not the only drugs*** involved in the Opioid Epidemic!

Table 48–1 Prevalence of Substance Use in Last Month (Per 100 Persons Aged 12 Years or Older)

Drug	Prevalence (%)
Alcohol	51.8
• Binge drinker*	23.1
• Heavy drinker**	6.7
Tobacco	27.4
An illicit drug	8.9
• Marijuana	6.9
• Cocaine	0.6
• Methamphetamine	0.1
• Hallucinogens	0.5
• Heroin	0.1
Nonmedical use of psychotherapeutic drugs	2.7
• Pain relievers	2.0
• Tranquillizers	0.9
• Stimulants	0.4
• Sedatives	0.1

*Defined as having five or more drinks on the same occasion on at least 1 day in the 30 days prior to the survey.
**Defined as binge drinking on at least 5 days in the past 30 days.

Martin PR *in* Ebert MH, Leckman JF, Petrakis IL. *Current Diagnosis & Treatment: Psychiatry, 3e;* 2019.

Table 48–2 Prevalence of Substance-Use Disorders During the Previous Year (Per 100 Persons Aged 12 Years or Older)*

Substance-Use Disorder	Prevalence (%)
Any substance-use disorder	8.7
• Alcohol abuse or dependence, no illicit drug-use disorder	5.9
• Illicit drug abuse or dependence, no alcohol use disorder	1.7
• Alcohol and illicit drug abuse or dependence	1.1
—Marijuana abuse or dependence	1.8
—Cocaine abuse or dependence	0.4
—Opioid abuse or dependence	0.8

*Prevalence rates obtained using DSM-IV criteria in which construct substance-use disorder is dichotomized as abuse (mild substance-use disorder) or dependence (moderate/severe substance-use disorder).

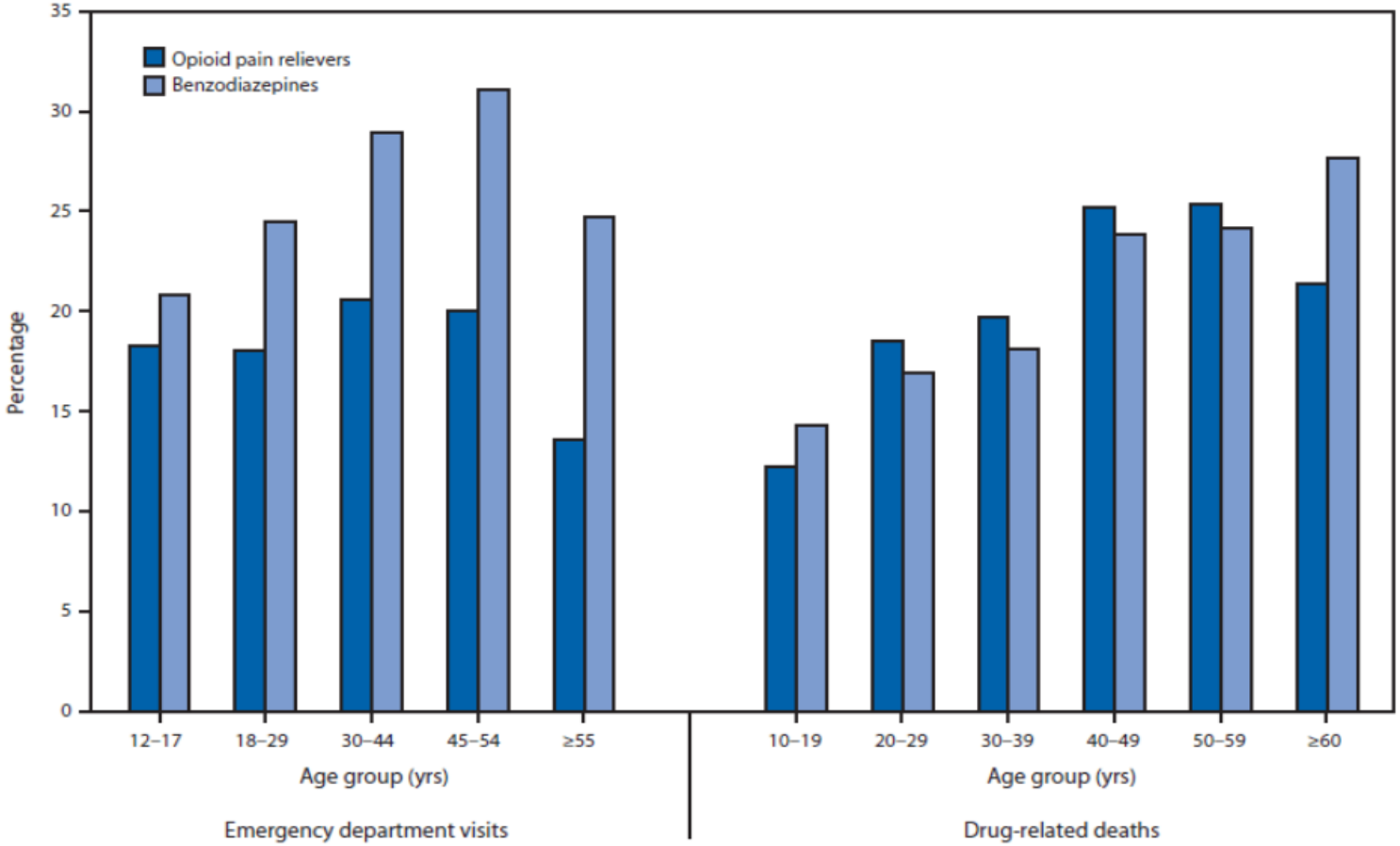
Martin PR *in* Ebert MH, Leckman JF, Petrakis IL. *Current Diagnosis & Treatment: Psychiatry, 3e;* 2019.

Increasing Prevalence of 12-Month Alcohol Use, High-Risk Drinking, and DSM-IV Alcohol Use Disorder (2001-02 to 2012-13)

	Alcohol Use (%)	High Risk Drinking (%)	DSM-IV AUD (%)
2001-2002	65.4	9.7	8.5
2012-2013	72.7	12.6	12.7
Percentage Increase	11.2	29.9	49.4

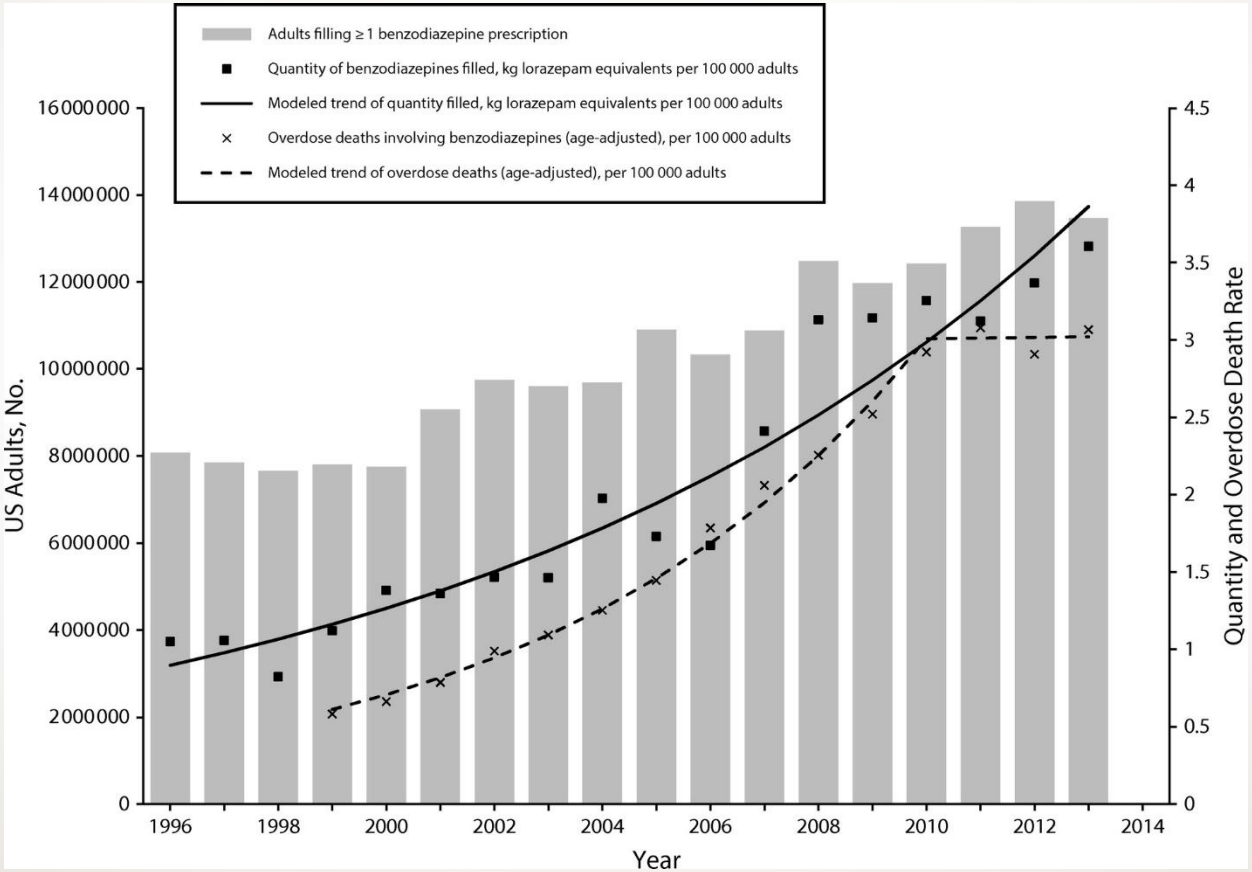
Grant et al, JAMA Psychiatry. 2017;74(9):911-923.

FIGURE. Percentage of opioid pain reliever and benzodiazepine drug abuse–related emergency department visits in the United States and drug-related deaths in 13 states that involved alcohol, by age group — Drug Abuse Warning Network, 2010



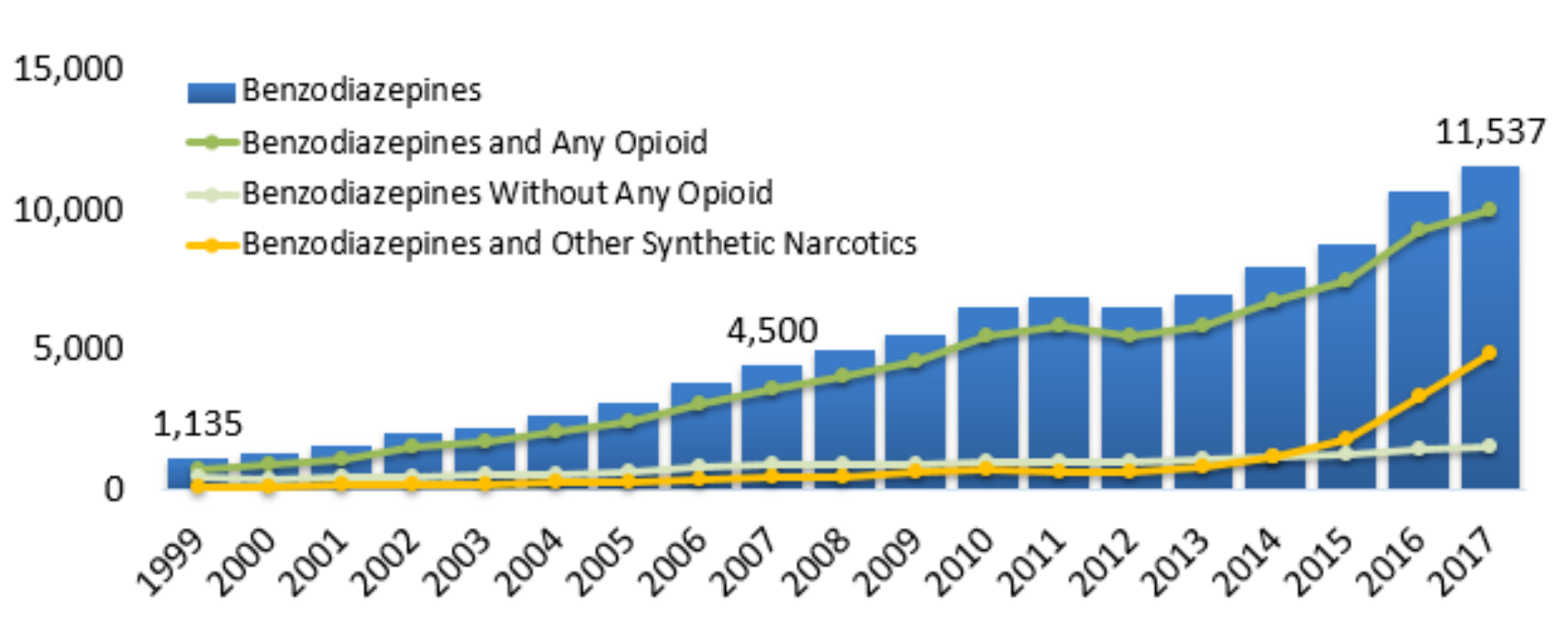
CDC MMWR October 10, 2014 / 63(40);881-885

Benzodiazepine Prescriptions, Quantity, and Associated OD Deaths in US (1996–2013)



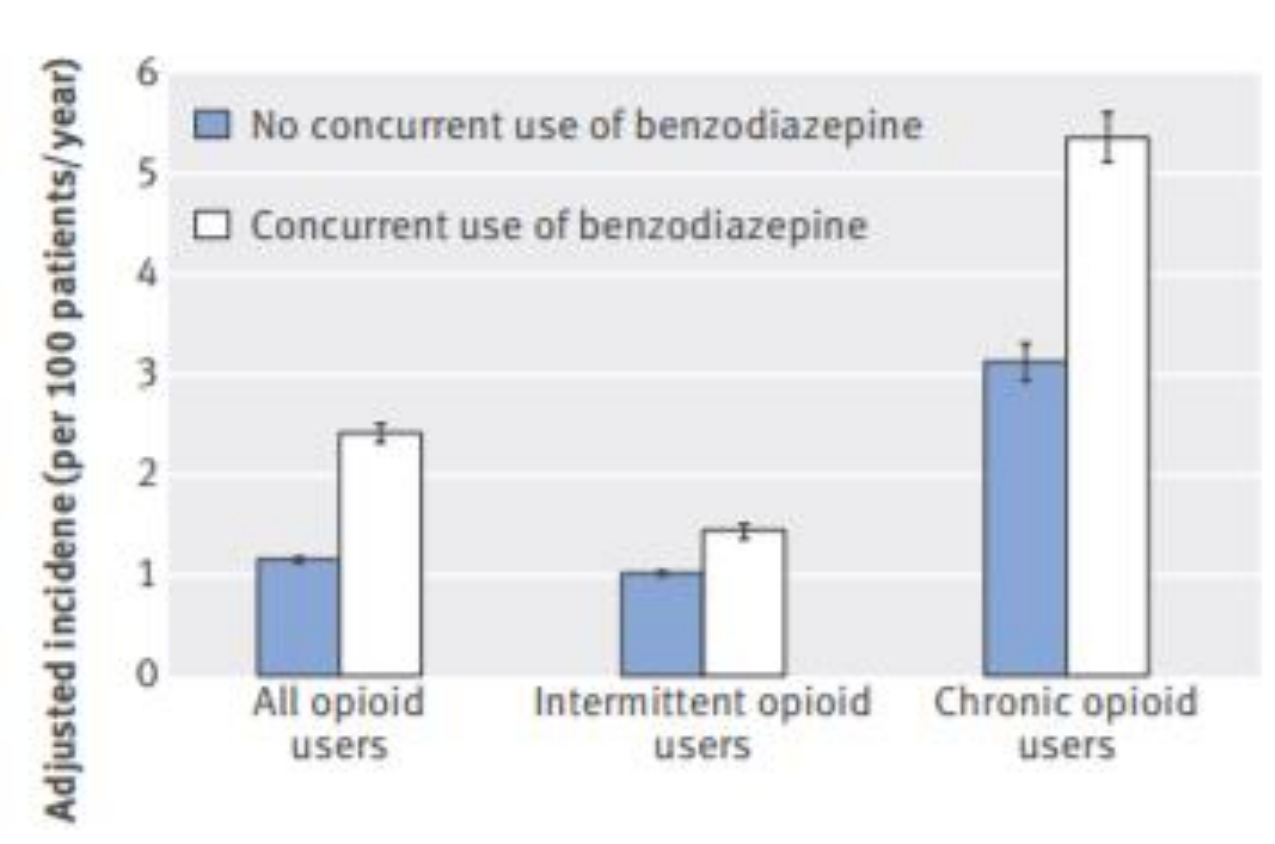
Bachhuber et al. Am. J. Pub. Health 106: 686 (2016)

National Drug Overdose Deaths Involving Benzodiazepines, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Adjusted incidence of “opioid” overdose



Sun et al, BMJ 2017

A Case Example

CS is a 56 year old female who presented for SI, HI, and worsening depression. SI was in the context of functional decline and poor health; HI was directed toward "people selling methamphetamine to my children, destroying their lives." **She denied substance abuse; admitted to occasionally smoking marijuana to help with sleep/pain; had documented prescriptions for benzodiazepines and opioids; and UDS was positive for BZD, opiates, and cannabis.** She asked to continue her home diazepam, Lortab and gabapentin while in hospital. She requested AMA discharge when she started to feel better because she was worried about her children on methamphetamine. She eventually admitted to abusing both benzodiazepines and opioids and agreed to their discontinuation. Detoxification required loading with 1080 mg phenobarbital which made her more comfortable. She felt incapable of staying abstinent from opioids and requested MAT. She was induced on 8/2 mg buprenorphine/naloxone daily and was started on oxcarbazepine 300 mg bid for PTSD and mood instability. **She enrolled in our MAT program on discharge. She attends regularly, has remained euthymic, and UDS monitoring remains negative (except cannabis).**

Sedative/Hypnotic/Anxiolytic: Medications or Drugs of Abuse?

- **Alcohol** identified on 5000-year-old archeological traces; alcoholism mentioned in the Bible, e.g., "Wine is a mocker and beer a brawler: whoever is led astray by them is not wise" (Proverbs 20:1)
- **Bromides**, chloral and paraldehyde date to the 19th century; 21 % of patients admitted to Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital had positive bromide blood levels (Wuth, 1927)
- **Barbiturates** first used in 1903; first published case of barbital abuse in 1904 (Fernandez & Clark)

Sedative/Hypnotic/Anxiolytic: Medications or Drugs of Abuse?

- **Non-barbiturate sedative-hypnotics** first used in mid-1950s; abuse followed shortly: ethinamate (Cahn, 1959), glutethimide (Battegay, 1957), meprobamate (Lemere, 1956), methaqualone (Ewart & Priest, 1967), and methyprylon Jensen, 1960); also, note **carisoprodol** (Soma) is a congener of meprobamate
- **Benzodiazepines** have been the most widely prescribed psychotropics since 1960's; a myriad of publications have documented their abuse (e.g., Marks, 1978)
- **Benzodiazepine agonists** ("Z drugs"-zaleplon, zolpidem, eszopiclone) date to late 1990s; are now recognized to have abuse liability (e.g., Griffiths & Johnson, 2005)

Sedative/Hypnotic/ Anxiolytics: Lessons Learned

- Each new wave of sedative-hypnotics is initially marketed with claims of pharmacologic novelty, particularly a ***lack of dependence liability*** and hence, ***"minimal risk of abuse"***
- Reports of the ***abuse of every sedative-hypnotic*** have appeared within a few years of the introduction of each new drug of this class
- Dependence on each new drug is recognized, as are challenges of safe discontinuation, e.g., ***delirium, seizures***
- Perhaps the only real "advance" has been that neuroadaptation to newer drugs becomes more subtle, and hence, difficult to recognize, complicating differential diagnosis….
- Also, ***many physicians tend to become complacent***, thinking that newer drugs can be used with impunity (earlier ones were the *actual* problem)….
- Hence, much ***potentially treatable psychopathology may be disguised*** for convenience (of both patient and physician) as anxiety is but a symptom…

Why discontinue CNS depressants (even if patient wishes not to)?

- Adverse effects of chronic use of CNS depressants include:
  - Alcohol ± benzodiazepine ± other CNS depressant use disorder
  - Cognitive impairment, confusion, anterograde amnesia
  - Enhanced anxiety (neuroadaptation), progressing to increasing depression, suicidal behavior
  - Psychomotor dysfunction, falls
  - Disrupted sleep architecture, daytime sedation, automobile accidents, etc.
  - Delirium, disinhibition
  - Worse outcomes in diverse psychiatric disorders, esp. PTSD, SUD, including OD morbidity/mortality
- Anxiolytic and hypnotic drugs were associated with an age adjusted hazard ratio for mortality of 3.32 over a mean observation period of 7.6 years (Welch et al., BMJ 2014)
- **Accurate diagnosis and appropriate psychiatric treatment may not be possible** in patients who are actively using CNS depressants

Treatment of SUD begins with Management of Withdrawal

- Careful clinical evaluation with emphasis on medical and psychiatric complications
- ***Identification and appropriate management of the relevant withdrawal syndrome(s)***
- Inpatient, outpatient, residential, aftercare
- Psychotherapies (social or milieu, insight-oriented, behavioral, individual, and group)
- Introduce/encourage participation in 12-step self-support groups, e.g. AA, NA, CA
- Chronic (life-long) illness with expected relapses that should be anticipated and managed in a non-punitive manner

Safe Treatment: Consider Withdrawal Syndrome Severity for Each Abused Drug

1. ***Barbiturates, nonbarbiturate hypnosedatives***
2. ***Alcohol***
3. ***Benzodiazepines***
4. Opioids
5. Cannabinoids

Discontinuation of CNS depressants

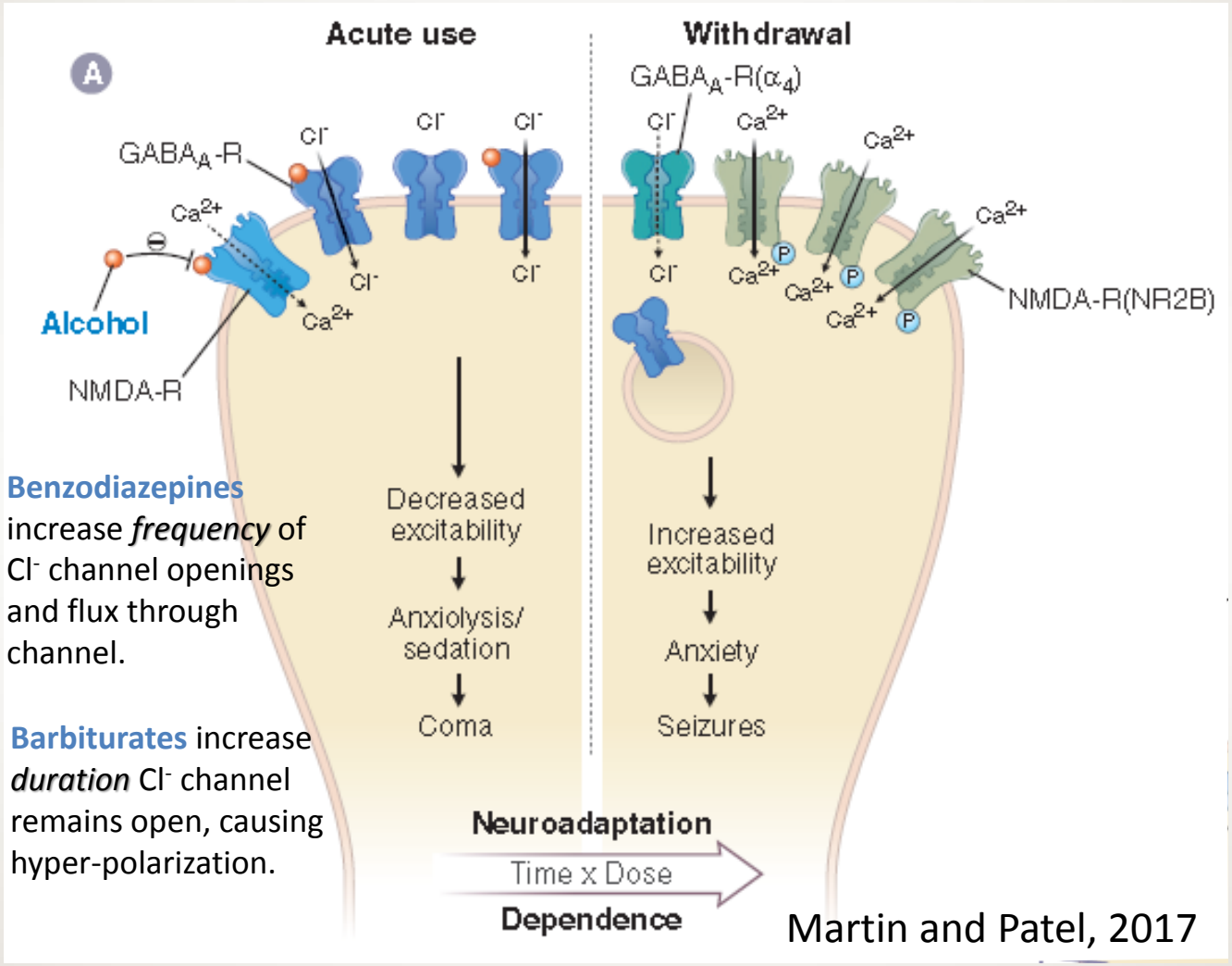
CNS Depressants	Withdrawal Seizures (%)	Withdrawal Delirium (%)	Withdrawal Minor (%)	(N)	Reference
Barbiturates	30	25	25	85	Wulff, 1959*
Barbiturates	66	48	?	100	Whitlock, 1970
"Sedatives", "Tranquilizers"	18	14	?	110	Swanson, 1973
Benzodiazepines, Meprobamate, Methaqualone, Barbiturates	9	35	60	55	Allgulander, 1978
Alcohol	"Delirium tremens occurs in 5%, with mortality in these as high as 15%"				Sellers & Kalant, 1976

*Only study in which patients were observed without treatment—40% of abusers of short-acting barbiturates suffered withdrawal convulsions, delirium or both which were absent during withdrawal from long-acting barbiturates.

Goals of CNS Depressant Discontinuation

- Relief of symptoms
- Prevention or treatment of complications (e.g., seizures, delirium)
- Accurate post-withdrawal ***diagnosis***
- Appropriate ***treatment of drug use disorder and co-occurring disorders***

CNS Depressants: Intoxication

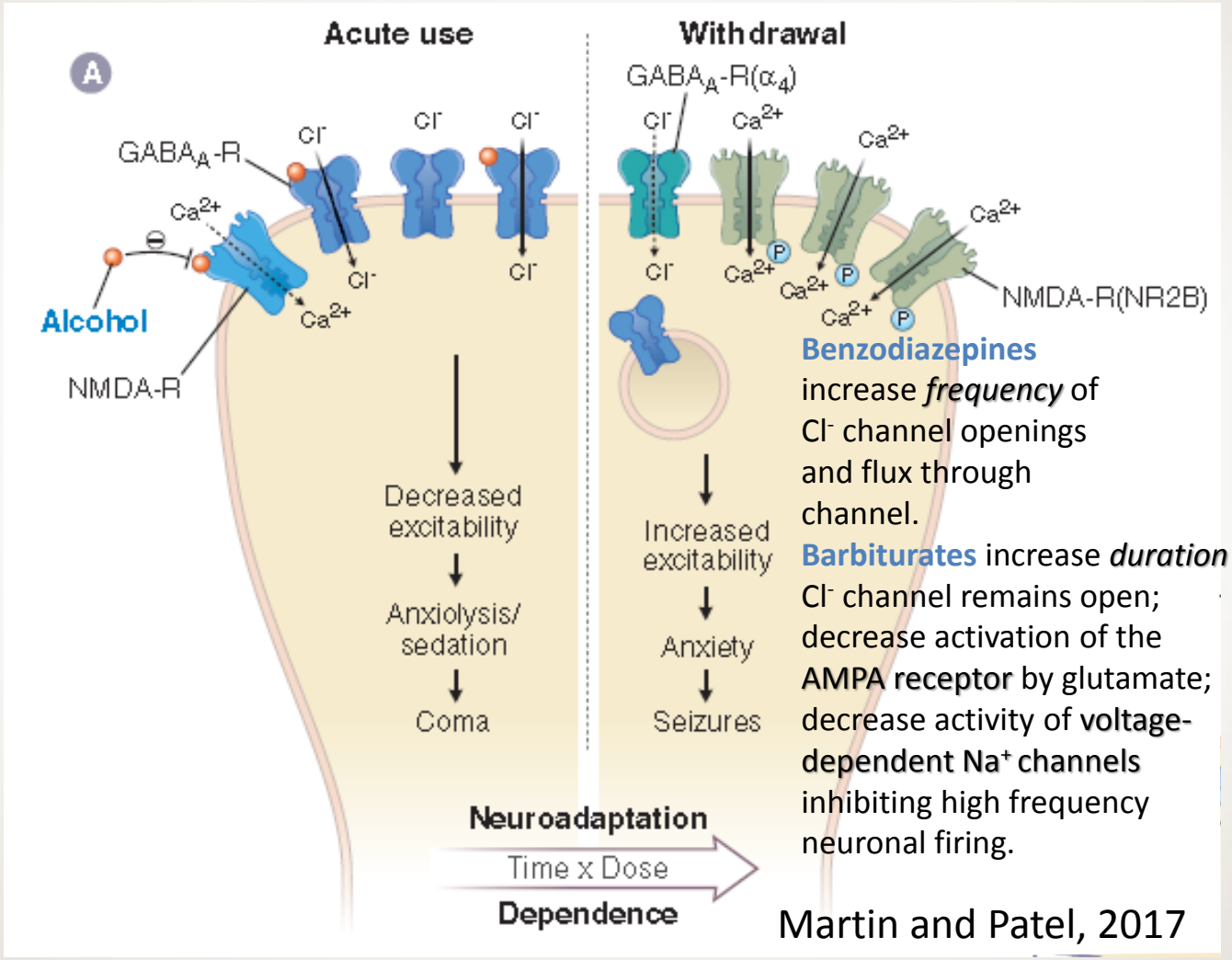


Benzodiazepines increase ***frequency*** of Cl^- channel openings and flux through channel.

Barbiturates increase ***duration*** Cl^- channel remains open, causing hyper-polarization.

Martin and Patel, 2017

CNS Depressants: Withdrawal



Benzodiazepines increase ***frequency*** of Cl^- channel openings and flux through channel.

Barbiturates increase ***duration*** Cl^- channel remains open; decrease activation of the **AMPA receptor** by glutamate; decrease activity of **voltage-dependent Na^+ channels** inhibiting high frequency neuronal firing.

Martin and Patel, 2017

Clinical Determinants of CNS Depressant Withdrawal Severity

- Barbiturates (non-barbiturate hypnosedatives) > alcohol > benzodiazepines > non-BZP GABA agonists
- Short-acting > long-acting (elimination rate; active metabolites)
- Quantity used (more > less)
- Combinations of CNS depressants may have synergistic effects
- History of severe previous withdrawal episodes
- History of seizures (± withdrawal)

Intoxication

- Disinhibition (inappropriate sexual or aggressive behavior, impaired judgment, mood lability)
- Hypotension (note usual BP)
- Somnolence, stupor, or coma
- Impaired attention or memory
- Slurred speech
- Incoordination
- Ataxic gait
- Nystagmus

Withdrawal

- Anxiety or psychomotor agitation
- Tremor, hyperreflexia
- Craving
- Autonomic hyperactivity (pulse, BP, T, sweating, arrhythmia)
- Insomnia
- ***Sensory distortions or transient hallucinations***
- Nausea or vomiting
- ***Seizures***
- ***Delirium***

Intoxication can be enhanced by GABA agonists and reversed with benzodiazepine antagonists, e.g. flumazenil.

How to discontinue CNS depressants

- Abrupt withdrawal of CNS depressants in a physically dependent person is challenging due to distressing symptoms and potentially life-threatening consequences. Historically, the following approaches to discontinuation of CNS depressants have been employed:
  - A small doses of a short-acting drug with cross-tolerance/dependence to the drug of abuse (e.g., pentobarbital) was administered until intoxication is attained; thereafter, this stabilizing dose was gradually tapered (days to weeks) (Ewing & Bakewell, 1967)
  - Substitution of a long-acting cross-tolerant/dependent agent (e.g., phenobarbital) followed by slow tapering (days) (Smith & Wesson 1970)
  - A **symptom-triggered (objective) loading dose technique (e.g. phenobarbital) without need to taper doses** which offers significant advantages, including promoting focus on recovery rather than drug-seeking and enhancing the physician-patient alliance (Martin et al, 1979)
- The symptom-triggered loading dose strategy has found wide application worldwide for detoxification from other drugs of abuse, especially in the treatment of alcohol withdrawal (Sellers et al, 1983)
- Trials of other agents (e.g. sympatholytic, other anticonvulsant) not compelling

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Symptom-triggered intravenous administration

INTRAVENOUS PHENOBARBITAL THERAPY IN BARBITURATE AND OTHER HYPNOSEDATIVE WITHDRAWAL REACTIONS: A KINETIC APPROACH

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St. Louis

Vol. 26, No. 2, pp. 256-264, August, 1979

Intravenous phenobarbital therapy in barbiturate and other hypnosedative withdrawal reactions: A kinetic approach

Phenobarbital (0.03 to 0.04 mg/kg/min) was infused intravenously in 7 patients with clinical hypnosedative withdrawal reactions until patients slept but were arousable. The infusion time to reach this clinical end point was 7.8 ± 1.1 hr (mean ± SEM), the total dose was 992 ± 144 mg, and the peak serum phenobarbital concentration was 26.1 ± 5.1 μg/ml. A user of minimal hypnosedatives required 54% less phenobarbital and 65% lower concentration than any of the abusers to reach an equivalent state of intoxication. The mean serum half-life (t½) was 57.5 ± 4.9 hr for hypnosedative abusers and 86 ± 3 hr for 8 normal volunteers ($p < 0.001$). Only the patient with the shortest t½ (36.4 hr) required oral phenobarbital supplements to prevent withdrawal symptoms. Dosage supplements required can be calculated from the postinfusion rate of fall of serum phenobarbital. Slow infusion of large amounts of phenobarbital provides a safe, efficacious single-dose treatment.

Peter R. Martin, M.D., C.M., Bhushan M. Kapur, Ph.D., Edwin A. Whiteside, M.D., and Edward M. Sellers, M.D., Ph.D. *Toronto, Ontario, Canada*
Division of Clinical Pharmacology, Clinical Institute, Addiction Research Foundation and Toronto Western Hospital, Departments of Medicine and Pharmacology, University of Toronto

Oral administration

Barbiturate and hypnosedative withdrawal by a multiple oral phenobarbital loading dose technique

Although intravenous phenobarbital loading is effective in barbiturate withdrawal, controlled infusions of drug are inconvenient. To develop a practical and more widely applicable method, oral loading doses of phenobarbital were given to 21 barbiturate addicts, whose estimated mean daily intake of barbiturates was 1 gm (range 0.5 to 4 gm). Twelve had a past or present history of barbiturate withdrawal seizures. Phenobarbital was given orally at a rate of 120 mg/hr until a predetermined clinical end point of phenobarbital effect was achieved. This end point was the presence of at least three of the following: nystagmus, drowsiness, ataxia, dysarthria, or emotional lability. The total phenobarbital loading dose ($\bar{x} \pm SD$) was 23.4 ± 7.1 mg/kg, median phenobarbital concentration after loading was 35.9 mg/l (range 13.2 to 71.6 mg/l), and median half-life ($t_{1/2}$) of phenobarbital was 90 hr (range 38 to 240 hr). One patient with $t_{1/2}$ = 38 hr was given supplemental doses of phenobarbital. None developed seizures or other evidence of barbiturate withdrawal.

Geoffrey M. Robinson, M.B., Ch.B., Edward M. Sellers, M.D., Ph.D., and Eva Janecek, B.Sc.Phm. *Toronto, Ontario*
Clinical Institute, Addiction Research Foundation, and Departments of Pharmacology and Medicine, University of Toronto

CNS Depressant Protocol

WITHDRAWAL SIGNS - MILD		- MODERATE TO SEVERE
Blood pressure elevation	+1	Diastolic rise >20mmHg in 2 hours or less
Increased pulse	+1	Tachycardia increased 20bpm in 2 hours or less
Agitated, irritable	+1	Marked agitation, irritability
Restless, anxious	+1	Marked increase in anxiety, restless
Lightheaded, dizzy	+1	Progressive confusion, disorientation
Paresthesia, tingling	+1	Twitching or fasciculation
Mild tremor	+1	Severe tremor
Nausea, anorexia	+1	Vomiting or dry heaves
Mild diaphoresis	+1	Increasing diaphoresis
Insomnia	+1	Pre-seizure aura, bright lights Visual or tactile hallucinations
TOTAL # MILD SIGNS	**PLUS**	**AT LEAST 2 MODERATE TO SEVERE SIGNS**

Discontinue (120 mg phenobarbital/hr): 2+ signs of intoxication (Drowsy, ataxia, nystagmus)

Mistakes to Avoid

- ***Insufficient phenobarbital dosing*** might result in recurrence of withdrawal symptoms/seizures
  - Patient is not yet in withdrawal when load initiated
  - Cross-tolerant medications are continued while loading, esp. neuroleptics (lower seizure threshold), anxiolytics, less effective anticonvulsant with shorter half-life
  - Premature discontinuation of load (e.g., “low” BP, disinhibition)
  - Load can always be reinitiated (e.g., if load started prior to withdrawal signs due to significant seizure history)
- Use in **pregnancy** due to teratogenicity
- Monitor **drug interactions** (e.g., warfarin)

Pharmacokinetic Advantages of Phenobarbital

- Acid dissociation pH, **slow CNS permeation**, low side effect profile, including less reinforcing properties than benzodiazepines
- High doses can be administered over 10-15 hours as a single procedure providing a body “depot” of phenobarbital that serves to maintain brain levels
- Because elimination half-life is 90-120 hours, brain phenobarbital levels decrease very slowly, providing a “pharmacological umbrella” for >10 days, that allows coverage while the brain re-equilibrates, preventing withdrawal complications

Pharmacodynamic Advantages of Phenobarbital

- Enhances efficacy of GABA by increasing time Cl^- channel remains open (greater influx of Cl^- ions for each activated $GABA_A$ channel)
- **Broad spectrum CNS depressant** also decreases activation of AMPA glutamate receptor, voltage-dependent Na^+ channels inhibiting high frequency firing
- Therefore, **effective for treating all CNS depressant withdrawal syndromes** (benzodiazepines are only effective for alcohol/benzodiazepines):
  - **Barbiturates, non-barbiturate sedative-hypnotics, muscle relaxants**
  - **Alcohol**
  - **Benzodiazepines, GABA agonists**

Load *vs* Taper

- Less **TIME** and greater **EFFICIENCY**—vital in an era of shortened LOS
- Provides objective evidence for **tolerance** *ergo* **severity of dependence** and need for addiction treatment *per se*
- May provide insights about underlying **DIAGNOSIS**, e.g.
  - Disinhibition (hyperthymic disorder)
  - Comfortable calming (MDD, PTSD)
  - Confusion (neurocognitive disorder)
- Requires long-term monitoring, may fog actual other psychiatric diagnosis, delay appropriate treatment
- Focus for the physician-patient relationship becomes **whether** to reduce the drug dosage
- Emerging anxiety causes **fear of withdrawal** (patient and physician)
- Patients may be continued on benzodiazepine for weeks to months or never be detoxified

What *can* go wrong (but rarely does)

- Robinson et al (1981) first implemented oral STPLP; total phenobarbital loading dose: 23.4 ± 7.1 mg/kg (**1640 mg in average person**); median peak blood concentration 35.9 mg/L (range 13.2 to 71.6 mg/L); and median $t_{1/2}$ 90 hours (range 38 to 240 hr); complications that can occur:
  - Hypotension (usually orthostatic, sedated patients lie down)
  - Falls (requires fall precautions)
  - Allergic reaction (unpredictable but rare)
  - Disinhibition (can require staff time, but might be informative with respect to diagnosis)
  - Respiratory depression is not a significant concern **(unless combined with opioids?)**
  - **It is *almost* impossible to over-dose patient with symptom-triggered administration protocol is followed UNLESS PATIENT IS ALSO ADMINISTERED OPIOIDS**

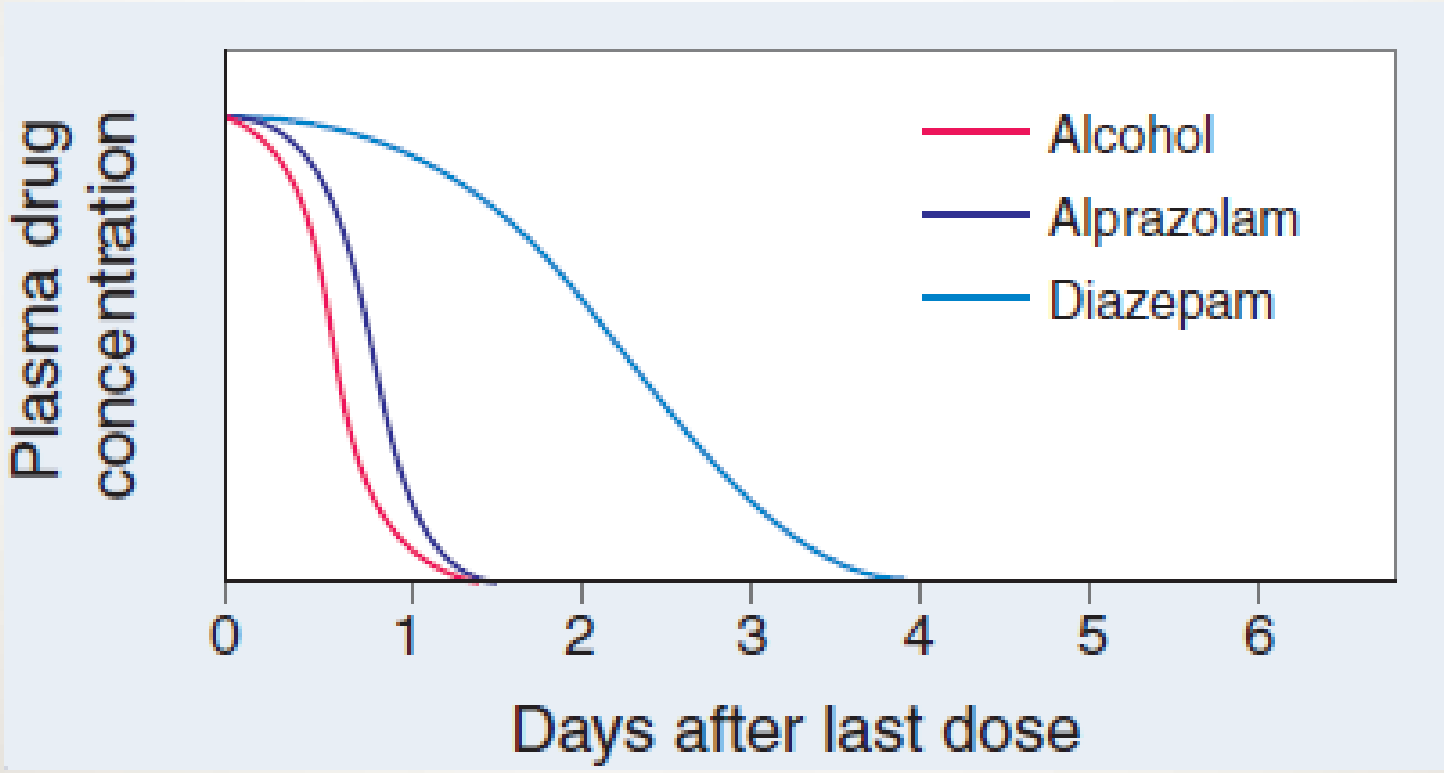
What *can* go wrong (but rarely does)

- The safety of the approach has received more recent support from others, e.g., Kawasaki et al (2012) who reviewed 20 years of experience detoxifying patients from benzodiazepines at Hopkins using a similar protocol for administering phenobarbital and reported the following rates of complications:
  - **Seizures 0%**
  - **Delirium 1.0%**
  - Falls 0%
  - Sedation 27.1%
  - Left AMA 17.1%
  - ED visits within 30 days 7.1%
  - Readmission with 30 days 6.1%

Treatment Goals of CIWA *vs* CNSDP

- *Symptom-triggered* treatment (Clinical Institute Withdrawal Assessment, CIWA-A) with **diazepam** is designed to **suppress alcohol withdrawal syndrome** during a short period of risk (12-48 hr) only
- *Symptom-triggered* treatment (Central Nervous System Depressant Protocol, CNSDP) with **phenobarbital** is to designed provide coverage for **all other CNS depressant** withdrawal syndromes (period of risk, 6-100 hr) using **intoxication as a biological endpoint**

Elimination of alcohol and benzodiazepines from plasma



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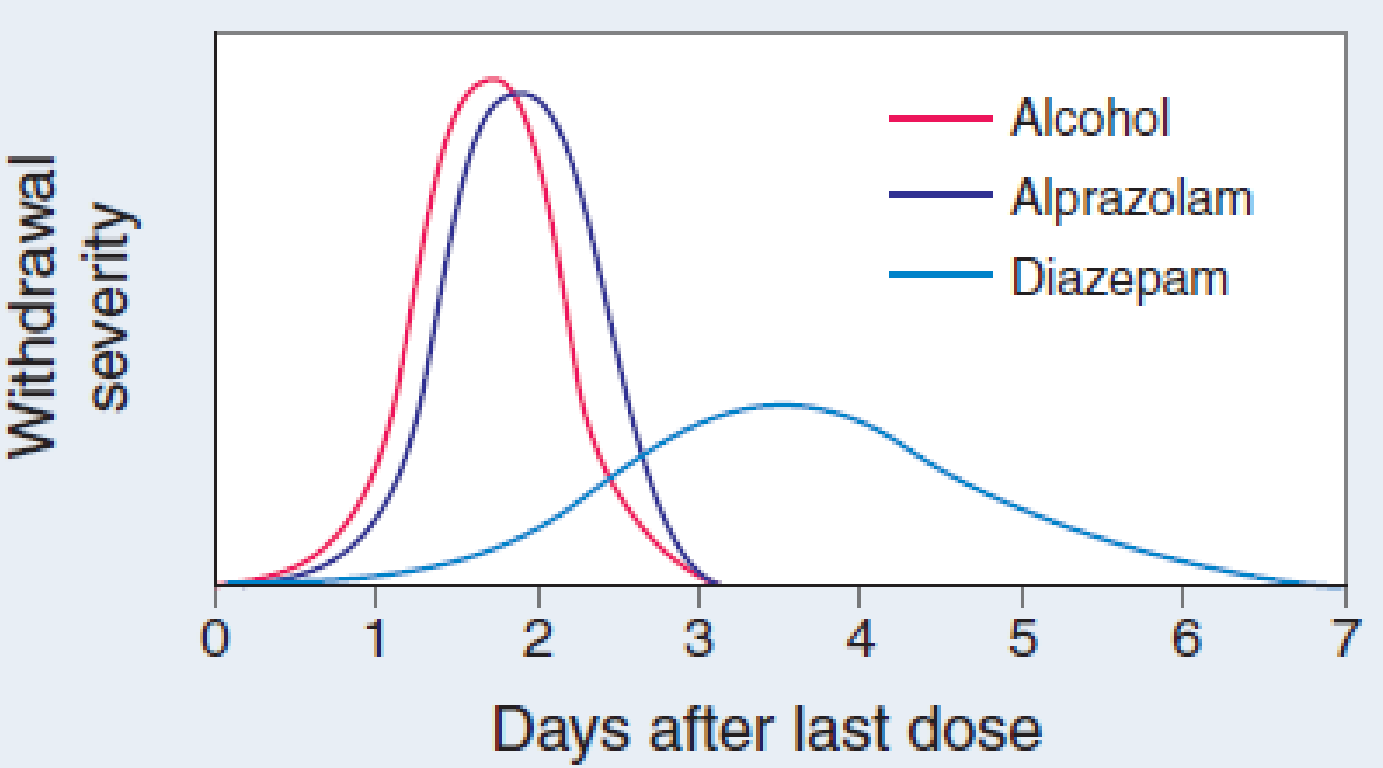
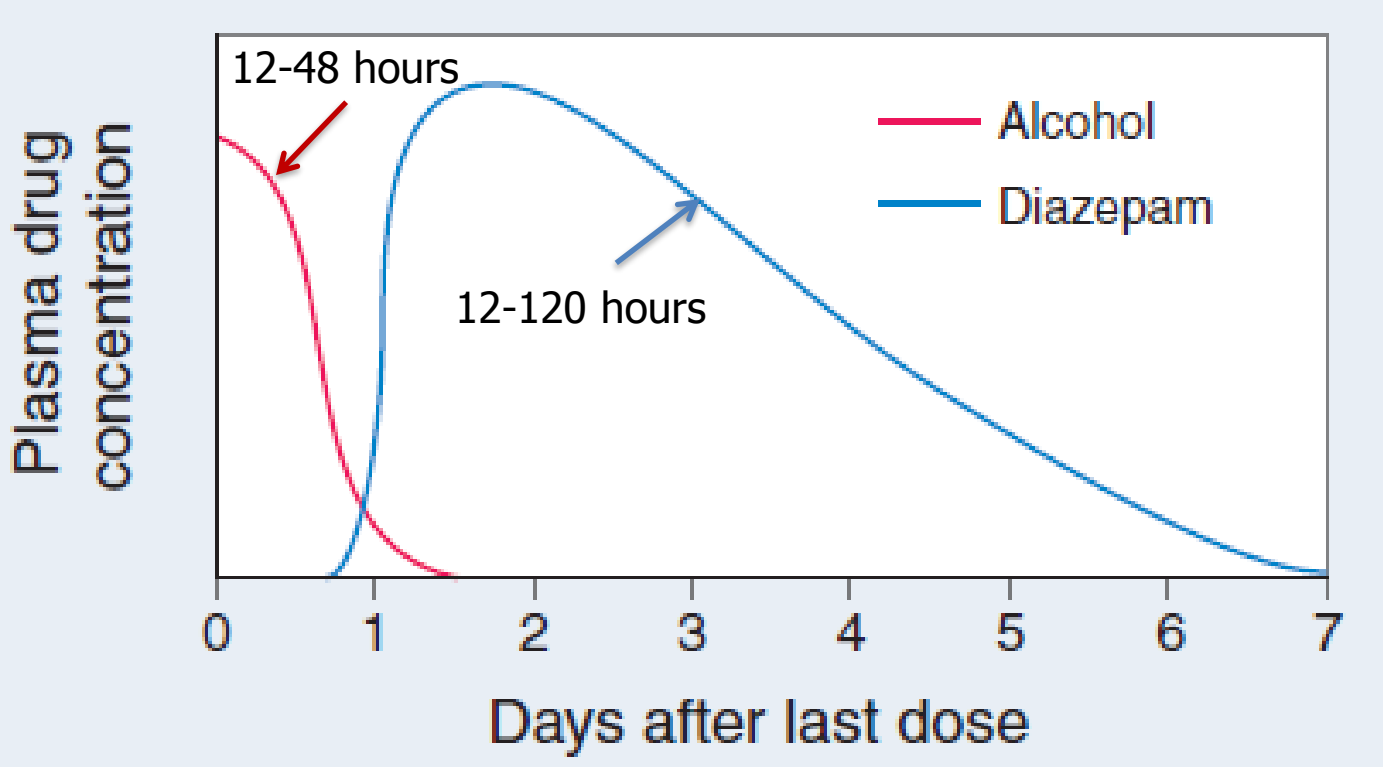
Onset, severity and duration of CNS-depressant withdrawal syndrome



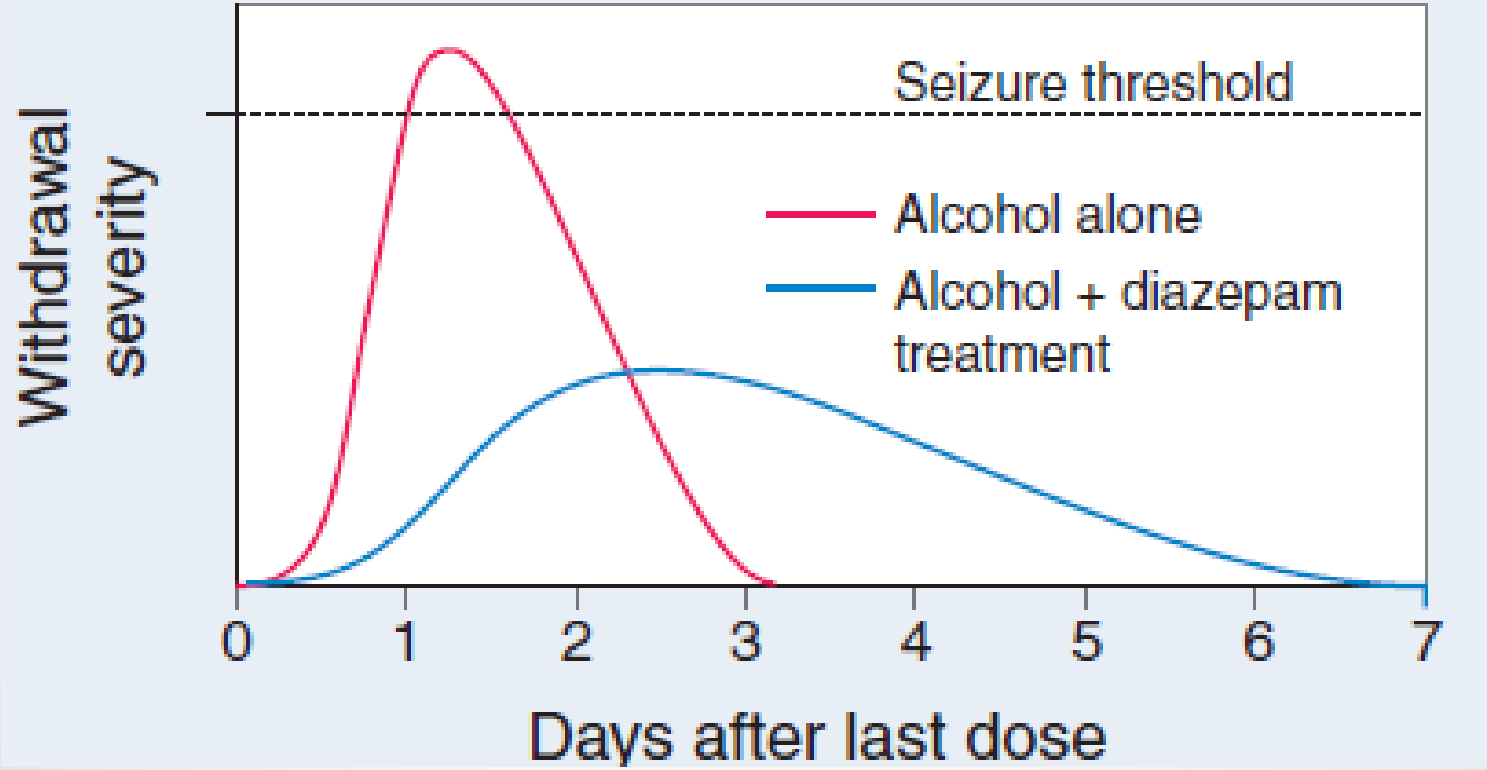
Martin and Patel, 2017

Time required until system re-equilibrates and to maintain $GABA_A$-receptor occupancy



Martin and Patel, 2017

Gradual reduction in receptor occupancy reduces withdrawal severity/complications



Martin and Patel, 2017

Recommendations

- CNSDP and CIWA protocols are both very safe and effective when used appropriately but are **NOT** interchangeable (diazepam is not a “safer” version of phenobarbital)
- Combining diazepam and phenobarbital can result in enhanced toxicity:
  - **Choose the correct protocol at the front end**
  - If unsure about which protocol is indicated, start the phenobarbital load and continue until completion;
  - only start diazepam when certain that only alcohol detoxification is required;
  - do not switch from diazepam to phenobarbital or *vice versa* as this may result in neuropsychiatric toxicity

Withdrawal from Multiple Substances: Manage in Sequence

1. **CNS depressants**
   - Stabilizing phenobarbital/diazepam dose objectively determined (symptom based)
   - Auto-tapered due to slow elimination/active metabolites
   - Benzodiazepines/Barbiturates ***MUST NOT*** be co-prescribed with an opioid agonist due to significant risk of respiratory compromise/ death
2. **Opioids**
   - Alleviate withdrawal signs and symptoms (COWS protocol) and provide estimate of maintenance dose if MAT requested
   - MAT comprises maintenance with opioid partial/full agonist under comprehensive treatment program and monitoring

Opioid Intoxication and Withdrawal

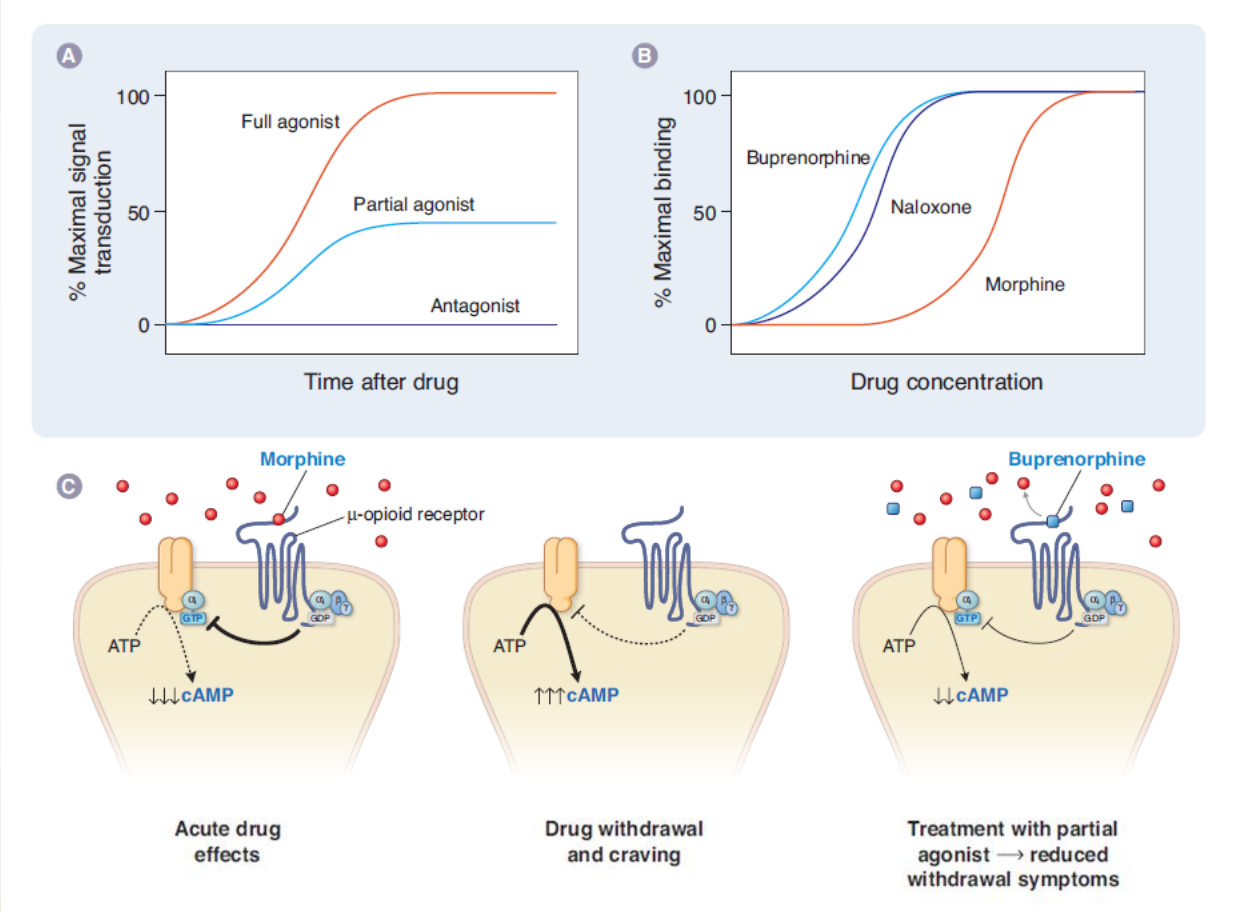
Intoxication

- Activation/"rush" (early/low doses) and sedation /apathy/ "nod" (late/high doses)
- Euphoria or dysphoria
- Feelings of warmth, facial flushing, or itching
- Impaired judgment, attention, or memory
- Analgesia
- Constipation
- Pupillary constriction
- Drowsiness
- Respiratory depression, areflexia, hypotension, tachycardia
- Apnea, cyanosis, coma

Withdrawal

- Depressed mood, anxiety, dysphoria
- Craving
- ***Piloerection ("goose flesh"), lacrimation, rhinorrhea***
- ***Hyperalgesia, joint/muscle aches***
- ***Diarrhea and gastrointestinal cramping***, nausea, or vomiting
- Pupillary dilation and ***photophobia***
- Insomnia
- Autonomic hyperactivity (P, BP, T , sweating), hyperreflexia
- ***Yawning***

Treatment of opioid withdrawal *vs*. medication-assisted treatment



Martin and Patel, 2017

Summary

- Manage CNS depressant withdrawal first due to associated morbidity/mortality
- Do not co-administer opioids with CNS depressants (risk of respiratory depression)
- Start Clinical Opioid Withdrawal Scale (COWS)-triggered opioid detoxification only upon completion of CIWA/CNSDP
- Consider whether goal is detoxification or opioid agonist maintenance (MAT)