VANDERBILT UNIVERSITY
MEDICAL CENTER

Detoxification of Patients from Central Nervous System Depressants: Which Protocol to Use and Why?

Why discontinue CNS depressants?

- Adverse effects of chronic use of CNS depressants (other than use disorder) include:
  - Cognitive impairment, confusion, anterograde amnesia
  - Enhanced anxiety, depression, increased suicidal behavior
  - Psychomotor dysfunction, falls
  - Disrupted sleep architecture, daytime sedation, automobile accidents, etc.
  - Delirium, disinhibition
  - Documented worsened outcomes in diverse psychiatric disorders, esp. PTSD, SUD
- 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 treatment** may not be possible in patients who are actively using if CNS depressants are not discontinued

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 case of barbital abuse (Fernandez & Clark, 1904)

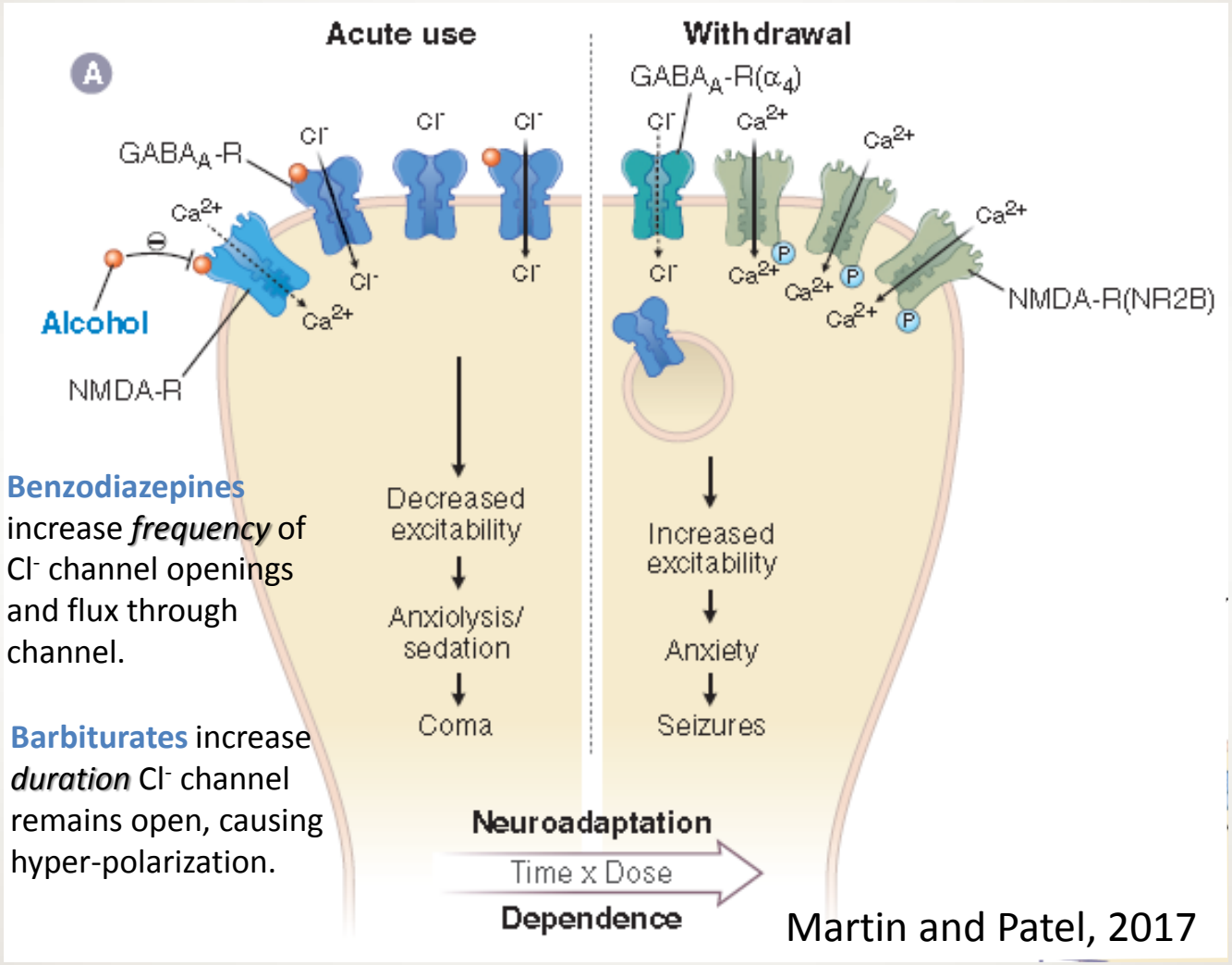
Sedative/Hypnotic/Anxiolytic: Medications or Drugs of Abuse?

- **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 modification 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 discontinuation without complications, 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 problem)….
- Hence, much potentially treatable psychopathology may be disguised for convenience (of both patient and physician) as anxiety is but a symptom…

CNS Depressants: Intoxication



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

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

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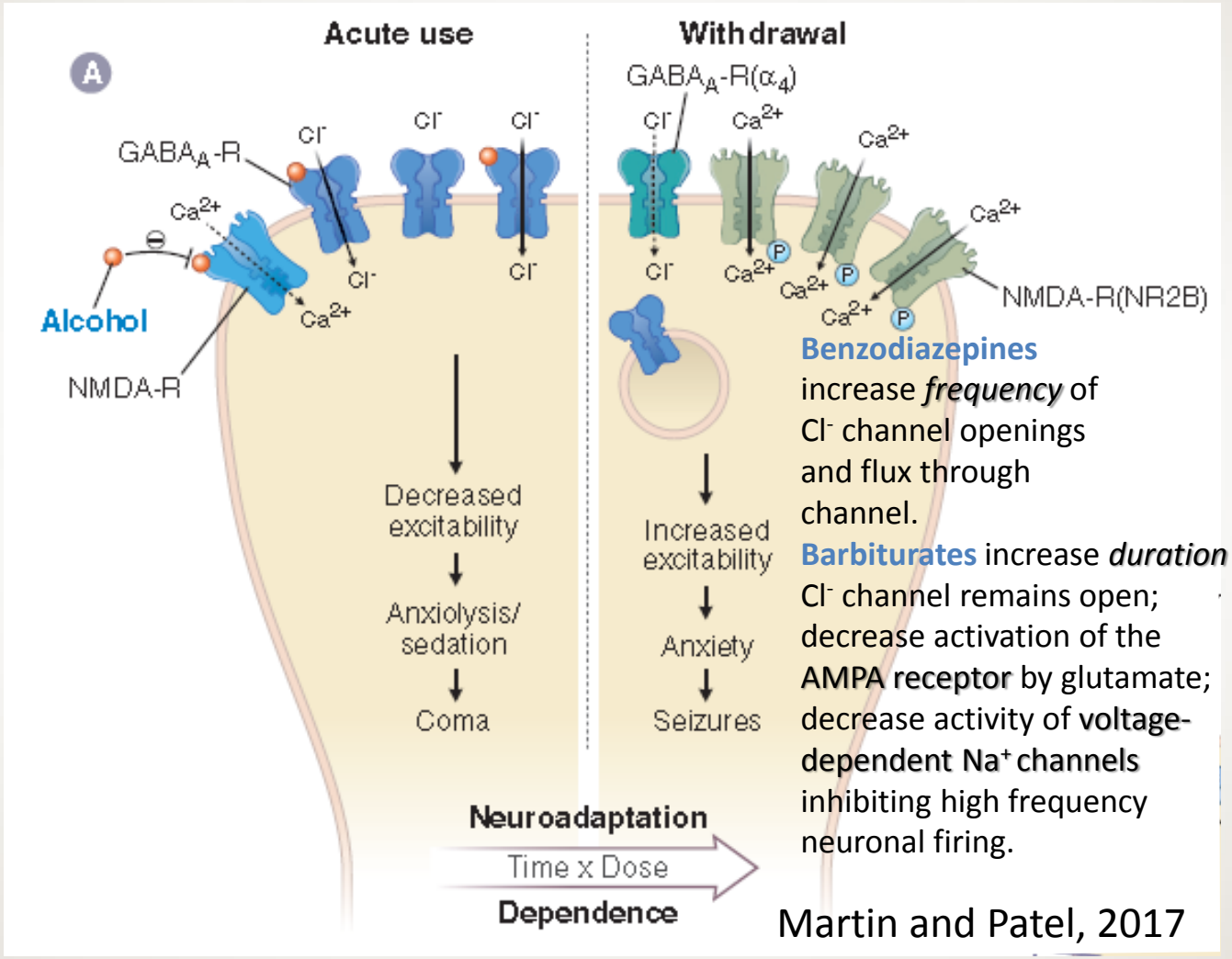
CNS Depressants: Withdrawal



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.

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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.

Determinants of Severity of CNS Depressant Withdrawal

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

Minor benzodiazepine withdrawal symptoms (or recurrence of anxiety?)

Psychological symptoms	
Anxiety, possible terror and panic attacks	Agitation and restlessness
Mood swings	Paranoia
Impaired concentration	Impaired memory
Indecision	Dysphoria
Nightmares	Insomnia
Bodily symptoms	
Perspiration	Increased urinary frequency
Hot and cold flushes	Headache
Muscular spasms, twitches cramps	Stiffness
Aches and pains	Fatigue and weakness
Numbness and tingling	Electric shock sensations
Blurred vision	Dizziness
Loss of appetite and weight loss	Nausea and vomiting
Tachycardia	Postural hypotension
Dry mouth	Chest pain
Flu like symptoms	Gastrointestinal problems
Perceptual symptoms	
Increased sensitivity to touch	Increased sensitivity to sound (hyperacusis)
Tinnitus	Objects moving
Metallic taste in mouth	Taste and smell disturbances
Increased sensitivity to light	Photophobia
Derealization (feelings of unreality)	Depersonalization

Lader, Addiction, 2011

Major benzodiazepine withdrawal symptoms

Delirium tremens	Delusions
Convulsions, status epilepticus	
which may end in death	
Catatonia, which may result in death	
Depression (often severe) [276]	
possible suicidal ideation	
Self-harm	Suicide
Suicidal ideation	Attempted suicide
Homicidal thoughts	Violence
Organic brain syndrome	Psychosis
Confusion	Mania

Lader, Addiction, 2011

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 without need for taper** with 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)

Load *vs* Taper

- Both can be effective
- 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**
- Requires long-term monitoring, may fog actual diagnosis, and 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

Goals of CNS Depressant Discontinuation

- Relief of symptoms
- Prevention or treatment of complications (e.g., seizures, delirium)
- Accurate post-withdrawal ***diagnosis***
- Appropriate ***treatment***

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)

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**

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
  - **It is *almost* impossible to over-dose patient with symptom-triggered administration protocol is followed**

What *can* go wrong (but rarely does)

- The safety of our 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%

What *can* go wrong (but now does at VPH)

- During about 30 years of use at Vanderbilt detoxifying patients from various combinations of CNS depressants, the symptom-triggered phenobarbital loading dose protocol has proved remarkably free of complications
- In the last year, **increased falls** have been documented on all VPH units
- Additionally, **increased sedation and dysphoria**
- Despite no known changes in the protocol and **relatively lower doses of phenobarbital**

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)

Why the recent the problems?

- **Insufficient phenobarbital dosing** might result in recurrence of withdrawal symptoms/seizures

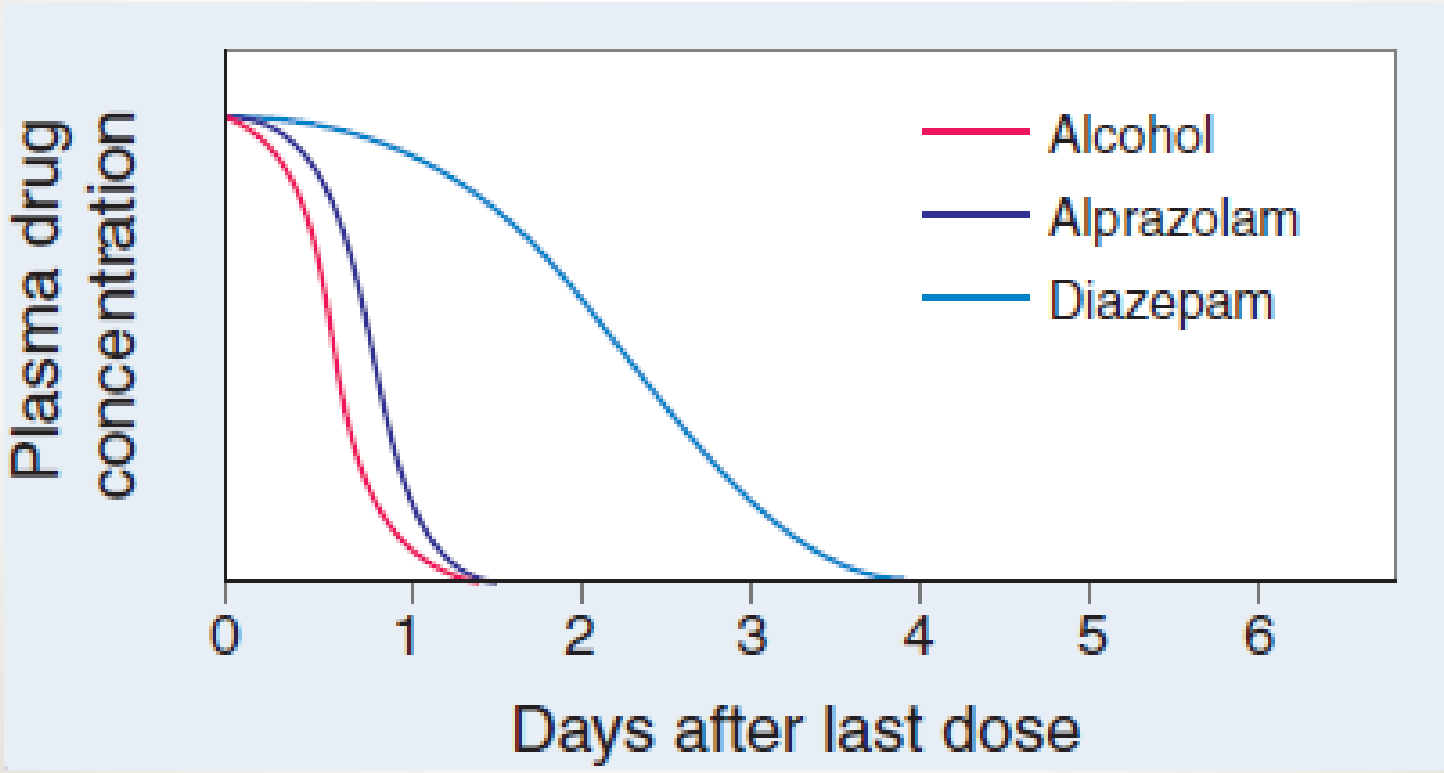
The patient is not yet in withdrawal at the point the phenobarbital load (CNSDP) is initiated because of previous "therapeutic" administration of benzodiazepines

  - 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)

Treatment Goals of Protocols

- 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 hrs) only
- Symptom-triggered treatment (Central Nervous System Depressant Protocol, CNSDP) with **phenobarbital** is to designed provide coverage for **all other CNS depressant** withdrawal syndromes (including alcohol, 6-100 hrs) using intoxication as a biological endpoint

Elimination of alcohol and benzodiazepines from plasma



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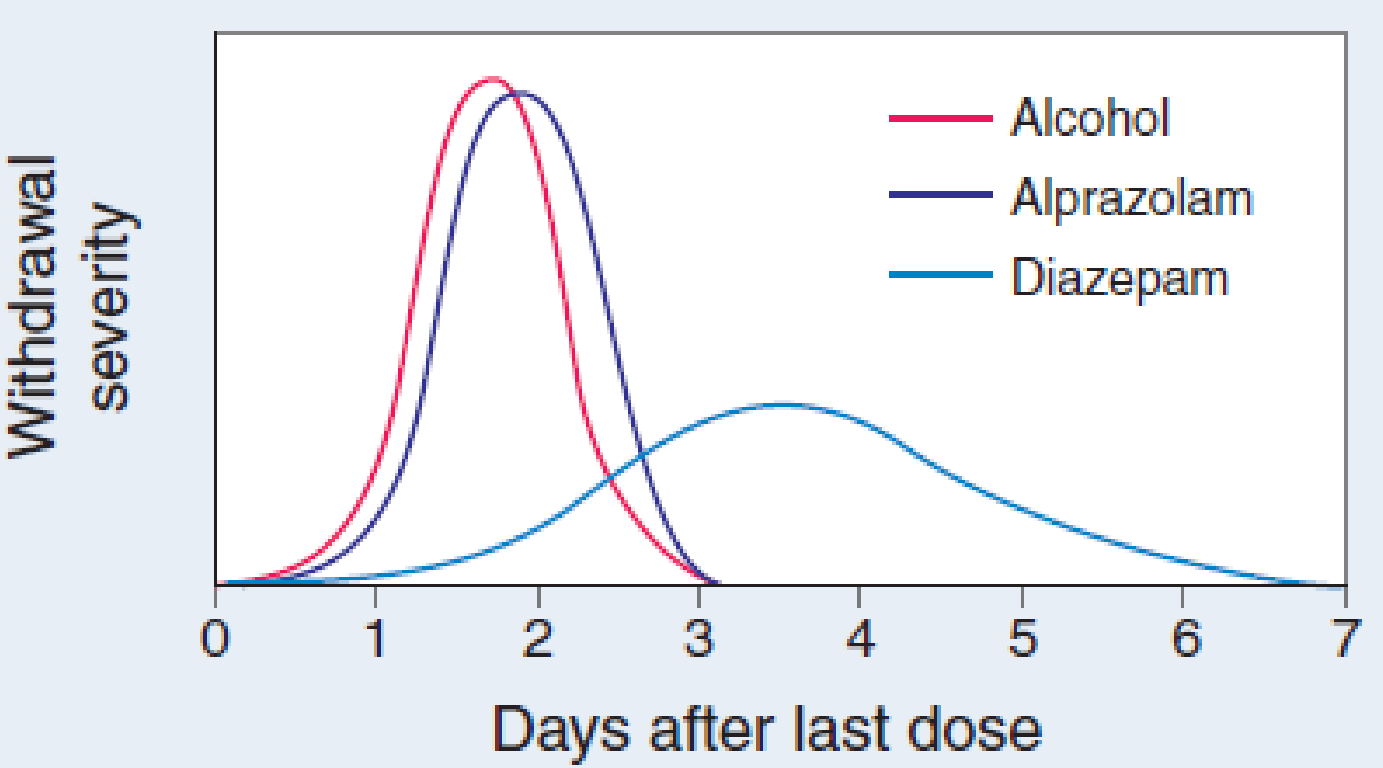
Onset, severity and duration of CNS-depressant withdrawal syndrome



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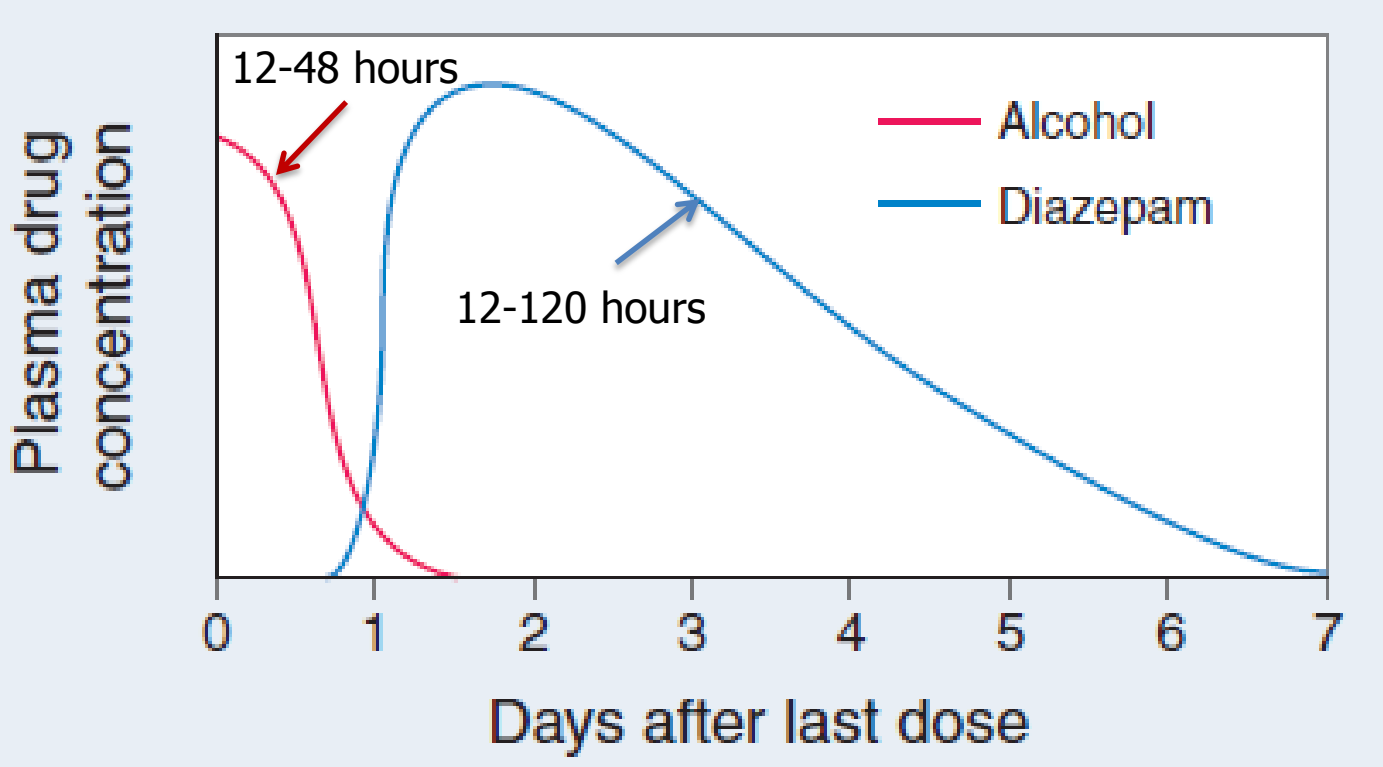
Time required until system re-equilibrates and to maintain $GABA_A$-receptor occupancy



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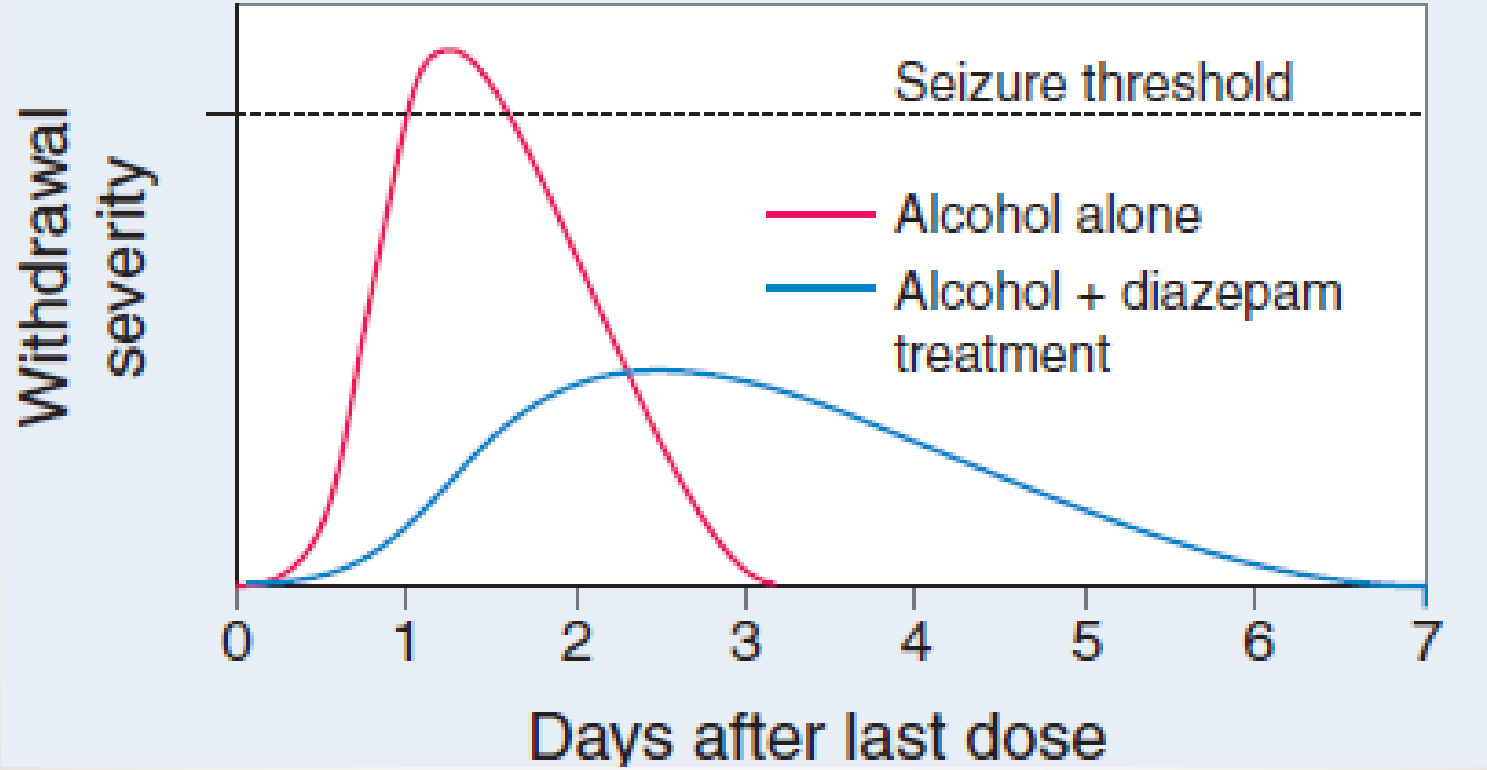
Gradual reduction in receptor occupancy reduces withdrawal severity/complications



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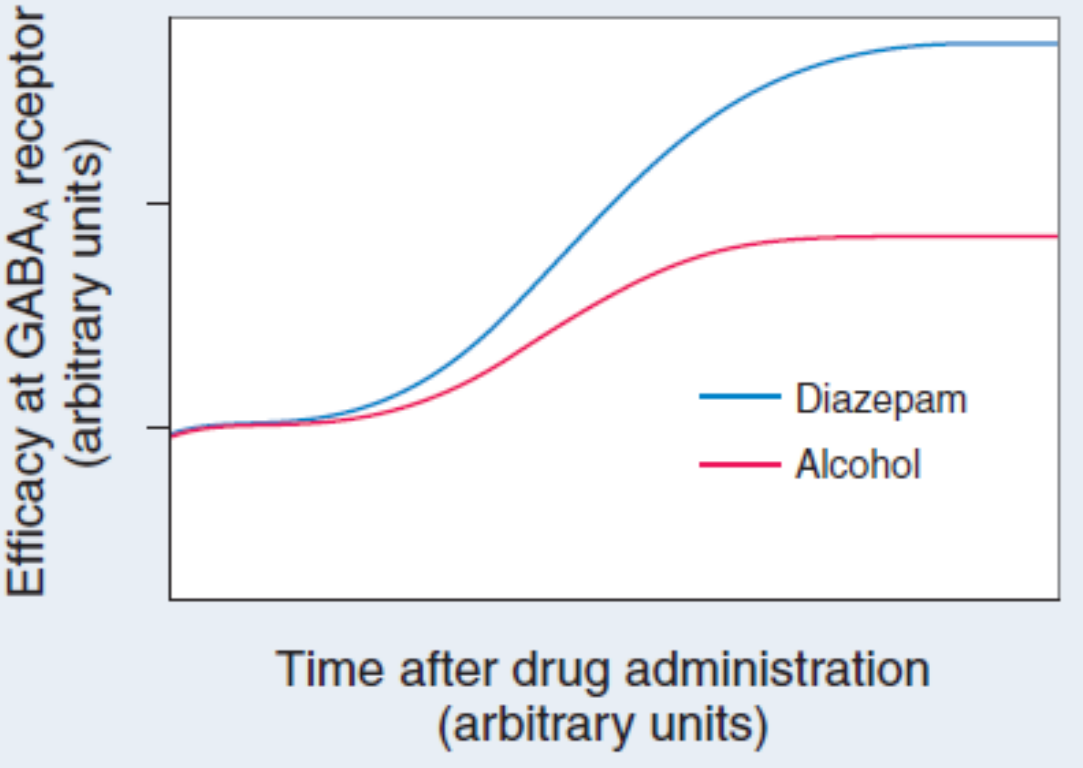
Diazepam has higher efficacy at $GABA_A$ receptors than alcohol



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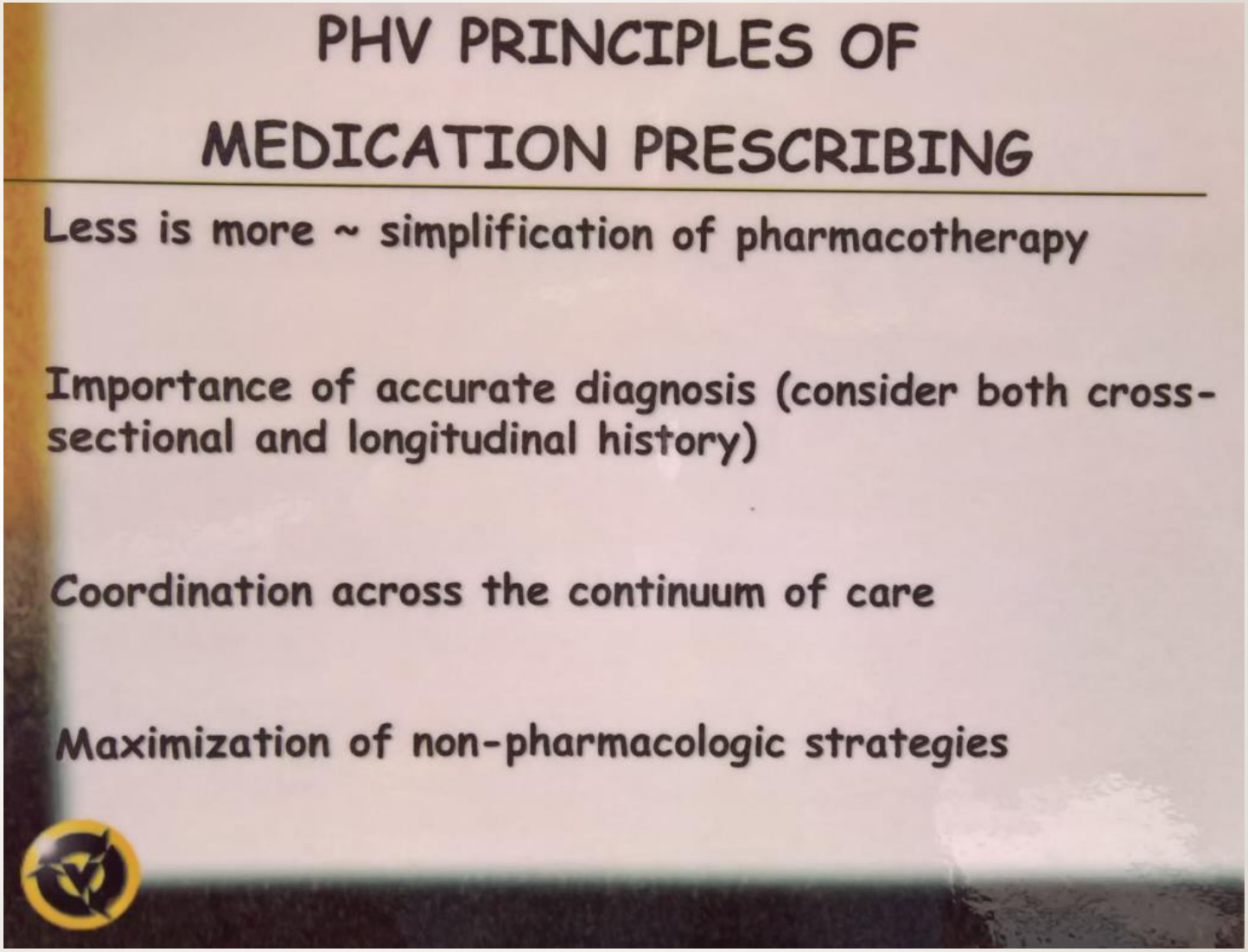
Recommendations

- These 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 nothing other than alcohol detoxification is involved;
  - do not switch from diazepam to phenobarbital or *vice versa*


PHV PRINCIPLES OF
MEDICATION PRESCRIBING
Less is more ~ simplification of pharmacotherapy
Importance of accurate diagnosis (consider both cross-sectional and longitudinal history)
Coordination across the continuum of care
Maximization of non-pharmacologic strategies