

Benzodiazepine Withdrawal Workshop

VASAM

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Goals and Objectives

Goals: Identify signs and symptoms of Benzodiazepine dependence.

Provide safe and effective agonist withdrawal treatment.

Objectives: Working knowledge of addiction phenomena as related to Benzodiazepine dependence, disease and treatment:

Tolerance, Dependence, Sensitization, Opponent Process, Allostatic state and Allostatic load.

Group interaction

Introduce yourselves to your neighbors.

Share experiences and beliefs about benzodiazepine use.

What do you expect to learn from this workshop?

Report to the whole group

Tolerance, Dependence, Sensitization

- The neurobiological phenomena which constitute the essence of addiction. Everyone who works in addiction treatment needs to be fully conversant with these phenomena and pass this info on to their patients and their families.

Tolerance

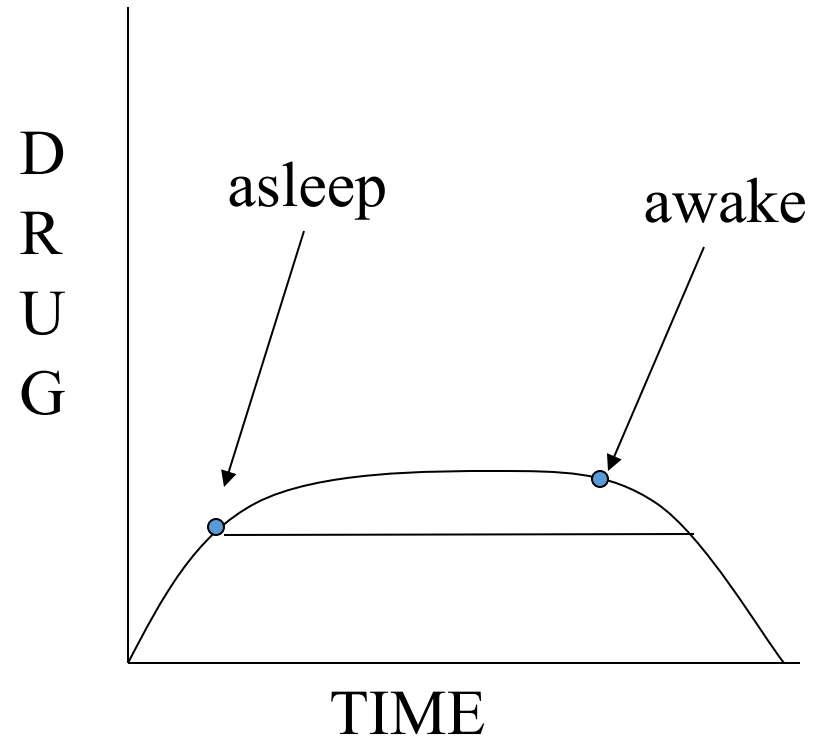
A state in which an organism no longer responds to a drug

- a higher dose is required to achieve the same effect

Benzodiazepine Tolerance

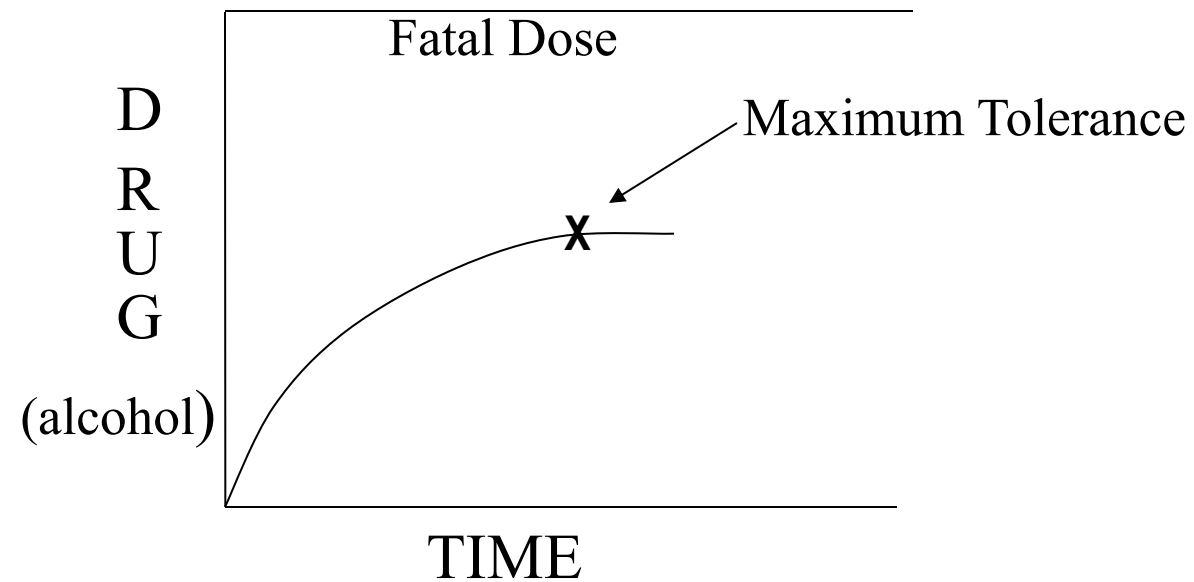
- Tolerance characteristics
 - Acute tolerance
 - Chronic change in tolerance
 - Cross tolerance
 - Maximum tolerance
 - Tolerance remembered

Diagram of AcuteTolerance



Single dose barbiturate, injection to naïve subject

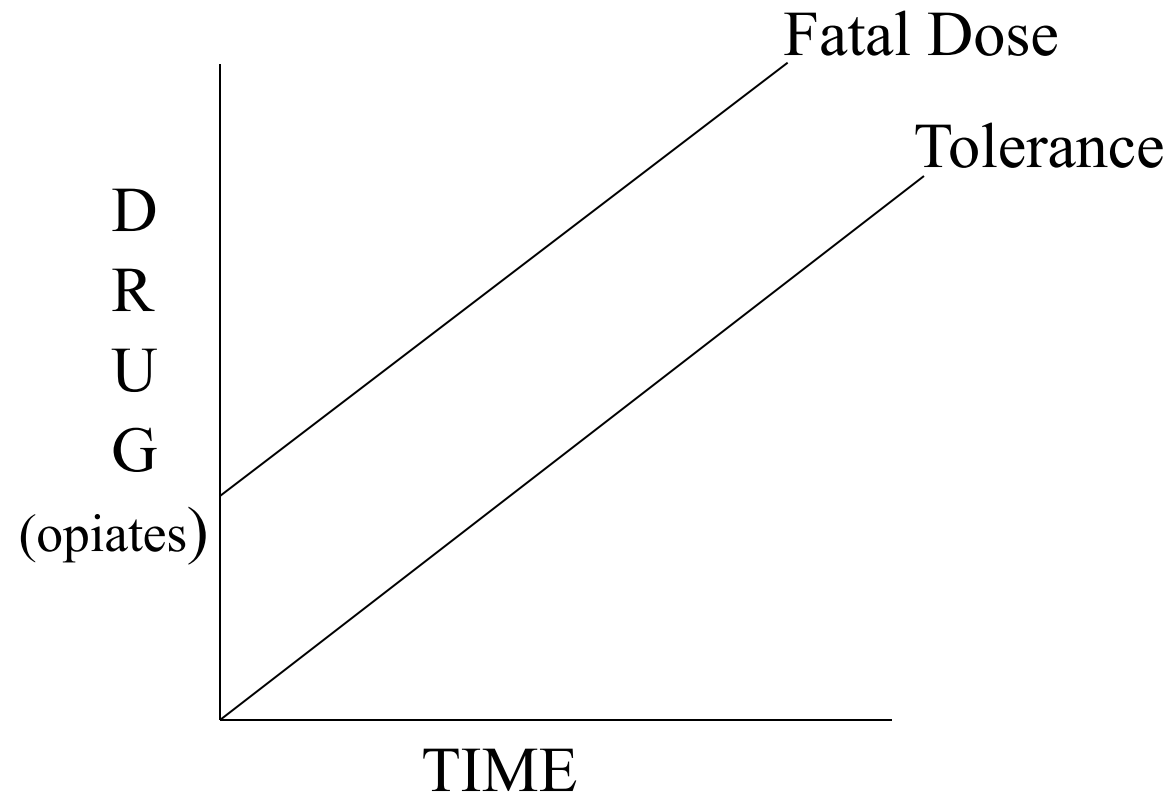
Diagram of Chronic Change in Tolerance



Chronic Change in Tolerance to
Alcohol and Other Sedative Type Drugs

Diagram of

Chronic Change in Tolerance



Chronic Change in Tolerance to Opiates

Cross Tolerance

- Alcohol/Benzodiazepines/Barbituates share the same tolerance in the depressant category.
- Cocaine/Amphetamines share tolerance in the stimulant category.
- All Opioids share cross tolerance.

Remembering Tolerance

- The tolerance set point is remembered following discontinuation of chronic use.
- Relearning tolerance after a period of abstinence is faster. It will not take as long to reach the previous set point in future relapses, days or weeks, not months or years.
- Immediate return to the old point might result in fatality if it was a very high dose. The concept of “Remembering” does not mean one can immediately return to the old set point it means the time to get there is shorter in future go-rounds.

Dependence

A state in which an organism functions normally only in the presence of a drug

- manifested as a physical disturbance when the drug is removed (withdrawal)

Benzodiazepine dependence

- Dependence characteristics:

- Acute dependence

- Chronic dependence (Opponent Process Theory and Allostatisis)

- Cross dependence

ACUTE DEPENDENCE

Examples:

A hangover after first drug use

Kicking in bed at night after midazolam (Versed) for colonoscopy earlier in the day

Primary and Secondary Effects of Addicting Drugs Depressants

Primary effect Depressant = D

Secondary effect Stimulation = S

Stimulants

Primary effect Stimulant = S

Secondary effect Depression = D

Opiates

Primary effect Pain killer = PK

Secondary effect Pain = P

In the beginning...

D	S	Pk
—	—	—
s	d	p

Following larger and more
extensive use....

d	s	p
—	—	—
S	D	P

These changes are progressive, the secondary effect grows over time with continued or episodic drug use.

Now here's the paradox (a truth contained in the opposite)

Therefore over time all addicting drugs cause the symptoms they are designed to relieve.

Xanax causes anxiety

Amphetamines cause depression

Caffeine causes headaches

Oxycontin causes pain.

All manifestations of the secondary drug effect.



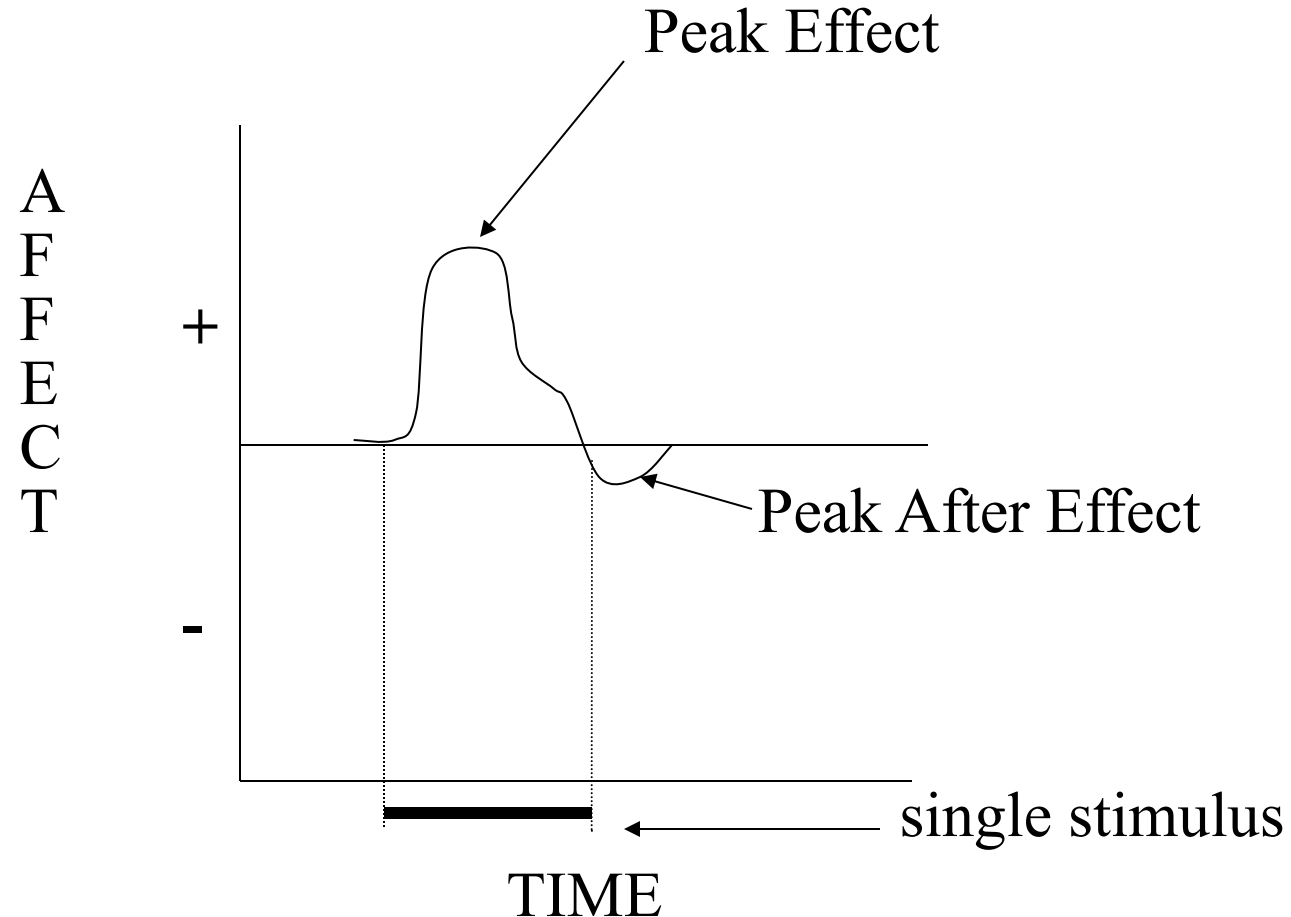
**Benzo withdrawal a return of anxiety?
I'm afraid I disagree with you doctor.**

Another look at the same phenomena measuring affective response: Opponent Process Theory in which emotional reactions to a stimulus are followed by opposite emotional reactions with progressive changes over time with increased stimulus.

Reference: Solomon

Diagram of the Tolerance and Dependence Phenomena

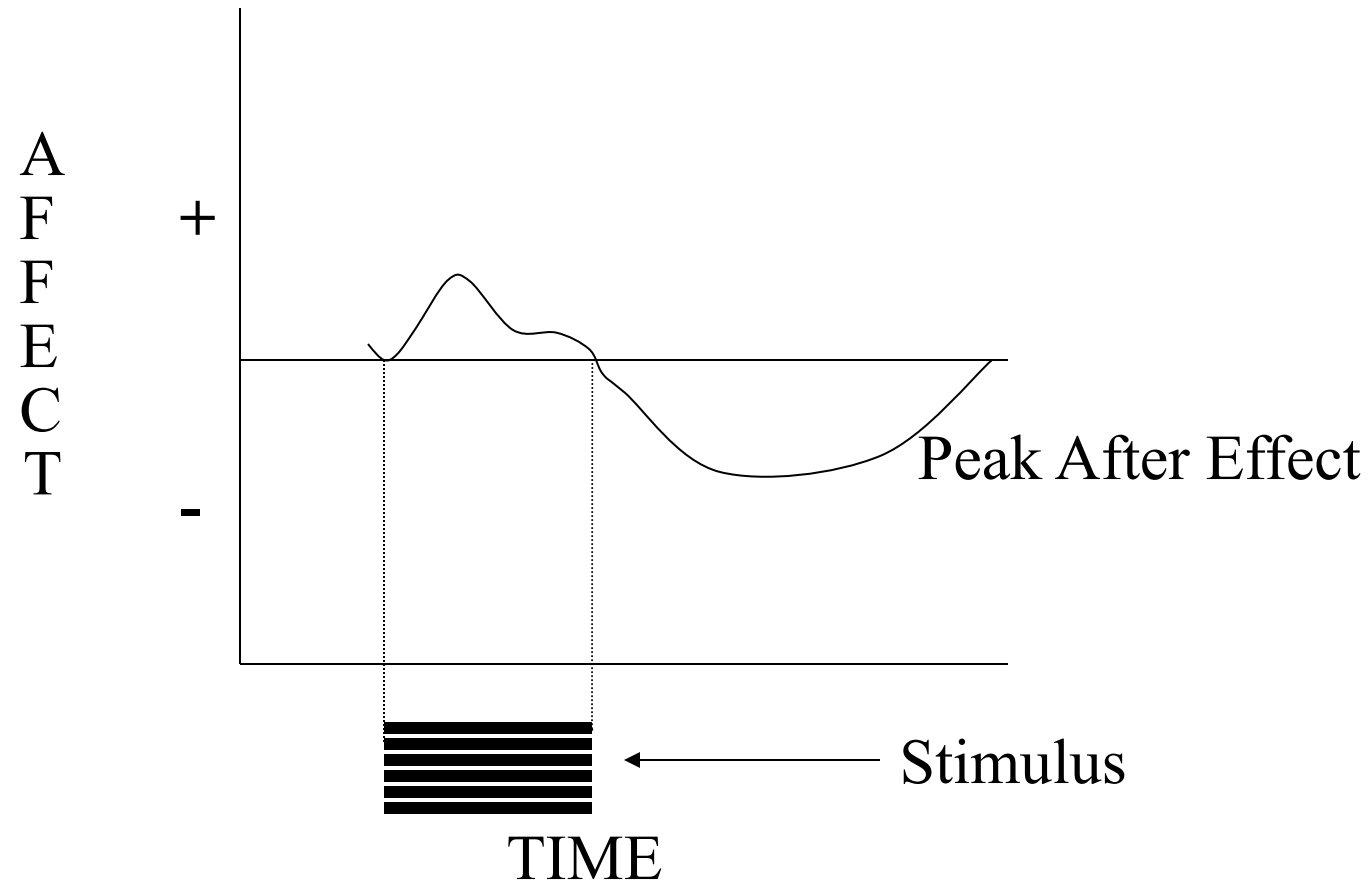
Opponent process theory - Part I



Affective Change with a Single or Few Stimulus(i)
To an Opiate Naïve Subject

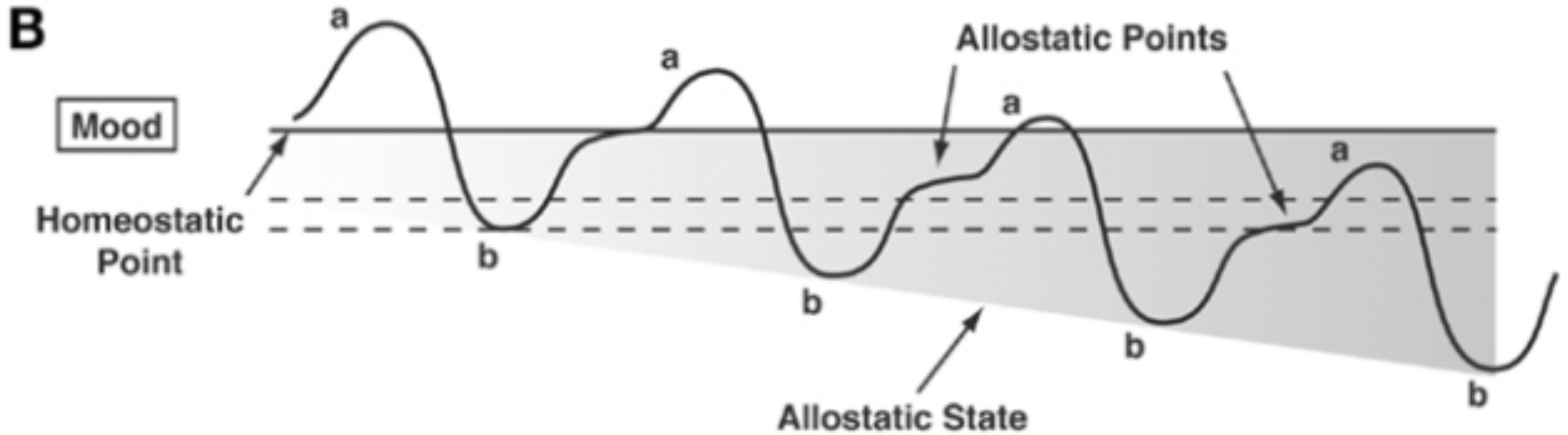
Diagram of the Tolerance and Dependence Phenomena

Opponent process theory - Part 2



Affective Change After Repeated Stimulation Over Time

Allostasis. A= reward system B= anti reward



Allostasis=Homeostasis with Consequences

- Allostasis is the process of the brain seeking stability when faced with a chronically administered noxious stimulus. A function of tolerance and dependence when the stimulus is an addicting drug.
- The “Allostatic state” is the deviation of from the normal (Homeostatic) operating level
- The “Allostatic load” is the cost to the individual from the deviation accumulating over time with constant or increasing exposure to the addicting drug.
- With discontinuation of the benzodiazepine the deviation will correct over a very long period of time but not without profound discomfort unless intervened upon with agonist therapy involving tapering doses of the agonist over a long period of time. Spontaneous recovery from the Allostatic state with abstinence appears to be quicker with alcohol and opiates.
- Allostasis was coined by stress physiologists in 1988 and the concept adopted to apply to addiction by Koob.

- Reference : Koob

Cross Dependence

- An example is using benzodiazepines to treat alcohol withdrawal. Long acting benzodiazepines are the best choice for this, because, Lorazepam even in high doses may not succeed in riding serious withdrawal because of short half life.

Sensitization, (Refers to Craving)

Of tolerance, dependence and sensitization, sensitization is the most powerful force in bringing about relapse (more powerful than withdrawal according to Robinson). Sensitization describes the phenomenon in which small amounts of the drug and the environment in which it is used become salient, that is gain undo power in sustaining continued use and “triggering” relapse.

A saying often heard among AA/NA members is, “ One is too many and a thousand not enough”. “ One is too many..” refers to sensitization and “...a thousand not enough” refers to tolerance.

The benzo patient who has no access to Benzodiazepine may crave alcohol.

Benzodiazepine receptors

Benzodiazepines act at the GABA_A receptor and are labeled positive allosteric modulators. They do not replace GABA but enhance GABA inhibitory actions at the receptor. They do not fit directly into the GABA_A receptor, like opiates fit directly into the opiate receptor. For this reason they are not agonists but act like agonists. There are three major groupings, Alpha with six subunits, Beta with three sub units and Gamma with three subunits.

Alpha 2 is more related to anti-anxiety and amnesia.

Alpha 1 is more related to sedation.

Alpha 5 anti convulsion.

Some benzos act more at one sub unit like Clonazepam at Alpha 5 but all benzos act at all the receptors.

Benzodiazepine Withdrawal-- Dr Ashton



Profiles of Benzo dependent patients

Two groups:

1. Taking benzos as prescribed without abuse and without other indication of addiction. This group can set boundaries. These are the patients Dr. Ashton is referring to.
2. Poly drug use and/or history of addiction, very likely not able to set boundaries.

Group one is not referred to NA. Group two is referred to traditional addiction treatment including NA. Residential programs and half way houses usually will not take patients on benzo agonist therapy or will want to taper them off quickly.

Signs and symptoms of Benzo withdrawal

- Anxiety and constitutional symptoms: panic attacks, tremor, agitation, insomnia, palpitations, muscle spasms, anorexia, visual disturbances, sweating, dysphoria, tendency to isolate, fear of driving and abdominal pain.
- Hypersensitivity to stimuli can affect some senses causing tinnitus, metallic taste, numbness, tingling, and strong odors.
- Perceptual distortions: floor undulating, walls tilting, walking on cotton wool.
- Seizures, depersonalization, hallucinations, muscle twitches, body distortions, depression and suicidal ideation.

reference: Ashton

Ashton Withdrawal Treatment approach

- Match tolerance of the offending benzodiazepines with diazepam and taper slowly according to the Ashton tables.
- Phenobarbital may be substituted. 30mg or 32.4mg equals 10 mg of diazepam.
- Dr. Ashton suggests blending the short acting offending drug with diazepam and tapering the short acting while increasing the long acting, ending up with diazepam alone. I use only diazepam. The only disadvantage it takes about five days to get the full effect when starting it alone.

Group interaction

All participants will be provided with selected sections of the Ashton Manual relating to withdrawal symptoms and the principles of agonist therapy using diazepam for review in small groups.

Principle learning:

Unique withdrawal symptoms/ protracted withdrawal/influence of ½ life on withdrawal symptoms and choice for agonist therapy.

Case studies will be distributed for analysis and treatment recommendations and report back to the whole group.

Flumazenil - Benzodiazepine antagonist

A benzodiazepine antagonist used to reverse an overdose in the emergency setting and now used to treat withdrawal in some clinics i.v. or subcutaneous over several days. Research is underway on an implant.

There is a seizure risk. Does Flumazenil take away the long term withdrawal symptoms?

References

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