

CLINICAL PRACTICE GUIDE LINES FOR MANAGEMENT OF BARBITURATES AND BENZODIAZEPINE DEPENDENCE

Dr. Shiv Gautam¹, Dr. Sanjaya Jain², Dr. Lalit Batra³, Dr. Preeti Lodha⁴

INTRODUCTION :

Over the time (Benzodiazepines introduced in 1960) it was recognised that Benzodiazepines could produce severe physiological dependence (*American psychiatric Association task force on Benzodiazepines dependence 1990*) and could be a drug of abuse. Nonetheless, their medical utility in treatment of disabling anxiety, episodic sleep disturbances and seizure has made them indispensable to medical practice. The sedative-hypnotics include a chemically diverse group of medications include prescribing sleeping medications, and most medications used for treatment of anxiety and insomnia.

1. Pharmacologically alcohol is appropriately included among sedative hypnotics however it is generally considered separately as it is in DSM- IV- TR (*American Psychiatric Association - 2000*).
2. Although Buspirone is marketed for the treatment of anxiety its pharmacological profile is sufficiently different that it is not included among sedative- hypnotics.
3. Antidepressants may also have anti-anxiety properties and their sedative properties are often of clinical utility in sleep induction. They too are usually excluded from sedative- hypnotics classification. **Benzodiazepines abuse and dependence** Benzodiazepines are not common primary drugs of abuse; most people do not find the effects of Benzodiazepines reinforcing or pleasurable (*Chutuape and de wit 1994; de wit et al 1984*) sedative- hypnotics' abusers prefer pentobarbital to diazepam, even at high doses (*Griffiths et al 1980*). Benzodiazepines are commonly misused and abused among patients receiving methadone maintenance (*Barnas et al 1992; Iguchi et al 1993*).

1-Sr. Professor, 2-Associate Professor, 3-Asstt. Professor, 4-Resident Doctor
Psychiatric Centre, SMS Medical College, Jaipur

Table 1 : Medications usually included in the category of Sedative hypnotics

Generic Name	Common therapeutic use	Therapeutic dose (mg/dl)	Dose equal to 30 mg. of Phenobarbital for withdrawal (mg.)	Phenotarb Conversion Constant
A. BARBITURATES				
Amobarbital	Sedative	50-150	100	0.33
Buta parkital	Sedative	45-120	100	0.33
Butal bital	Sedative/ Analgesic	100-300	100	0.33
Phenobarbitone	Hypnotic	50-100	100	0.33
Secobarbital	Hypnotic	50-100	100	0.33
B. BENZODIAZEPINES				
1. Alprazolam	Antianxiety	0.75 - 6	1	30
2. Chloridazepoxide	Antianxiety	15-100	25	1.2
3. Clonazepam	Anticonvulsant	0.5 - 4	3	15
4. Chlorazepate	Antianxiety	15-60	7.5	4
5. Diazepam	Antianxiety	5-40	10	3
6. Estazolam	Hypnotic	1-2	1	30
7. Flunitrazepam	Hypnotic	1-2	-	-
8. Flurazepam	Hypnotic	15-30	15	2
9. Holazepam	Antianxiety	60-160	40	0.75
10. Lorezepam	Antianxiety	1-16	2	15
11. Midazolam	Anaesthesia	-	-	-
13. Nitrazepam	Hypnotic	5-10	5	6
12. Oxazepam	Antianxiety	10-120	.0	3
14. Prazepam	antianxiety	20-60	10	3
15. Quazepam	Hypnotic	15	.5	2
16. Temazepam	Hypnotic	7.5 - 30	15	2
17. Triazolam	Hypnotic	0.125-0.5	0.25	120
C. OTHERS				
1. Chloral hydrate	Hypnotic	250-1000	.500 mg	0.06
2. Gluethemide	Hypnotic	250-500	.500 mg.	0.06
3. Meprobamate	Antianxiety	1200-1600	1200	0.025
4. Methyprylon	Hypnotic	200-400	200	0.15
5. Zaleplon	Hypnotic	5-20	10	3
6. Zolpidom	Hypnotic	5-10	5	6

Patient's who become physically dependent on Benzodiazepines can be classified into one of the three groups:

1. Street drug abusers who self-administer Benzodiazepines as one of many in a pattern of poly-drug abuse.
2. Alcoholic individuals & prescription drug abusers who are prescribed Benzodiazepines for treatment of chronic anxiety & insomnia.
3. Non-drug abusing patients with depression or panic disorders who are prescribed high doses of Benzodiazepines for long periods. Benzodiazepines are rarely their primary drug of abuse even if their use of Benzodiazepines does not meet DSM-IV-TR criteria for abuse (APA, 1994) most people would call the use of Benzodiazepines by street drug abusers "ABUSE" because it falls out of the context of medical treatment & is part of a poly-drug abuse pattern. **Is Benzodiazepines dependence genetic?** Alcohol & prescription drug abusers who are receiving treatment for chronic anxiety or insomnia are at significant risk for Benzodiazepines dependency. They may receive Benzodiazepines for a long time & they may be biologically predisposed to develop Benzodiazepines dependency. In a study Alprazolam (1mg.) in alcoholic men found that alprazolam produced positive mood effects in alcoholic men not reported by nonalcoholics (Ciraulo et al 1988). The difference in subjective response may be genetic. Similar mood elevating effects of alprazolam were found to be greater in daughters of alcoholic parents (Ciraulo et al 1996). Similar results have been found in sons of alcoholic parents (Cowley et al 1992, 1994). Flunitrazepam is among the Benzodiazepines with the highest abuse potential (Farre et al 1996, Bond et al 1994) and considerable appeal among heroin addicts (Thiron et al 2002; Salvaggio et al 2000). Few cases of Zolpidem abuse/dependence have been reported. It appears that at a very high dosage levels Zolpidem produce tolerance and a withdrawal syndrome similar to that of other sedative hypnotics (Cavallaro et al 1993) but pre-clinical data relating to the issue of zolpidem tolerance are contradictory. The Benzodiazepine antagonist Flumazenil precipitated withdrawal in the midazolam treated animals but not in those treated with zolpidem (Perrault et al 1992) but animal studies suggested that zolpidem is reinforcing and that it produced tolerance & physical dependence (Griffiths et al 1992).

Like Zolpidem, Zaleplon is chemically unrelated to Benzodiazepines and binds to the omega-1-receptor (a sub unit of GABA Benzodiazepine receptor). Animal studies (Ator et. al. 2000) and healthy volunteers with a history of drug abuse (Rush et al, 1999) suggest abuse potential similar to Triazolam.

DIAGNOSTIC CRITERION

Acute Intoxication (Table-2)

ICD-10 RESEARCH CRITERIA	DSM-IV TR
A. General criterion of acute intoxication must be met.	Recent use of sedative hypnotic, Anxiolytic
B. There is dysfunctional behavior as evidence by at least one of the following :- 1. Euphoria and disinhibition: 2. Apathy and sedation 3. Abusiveness of aggression 4. Lability of mood 5. Impaired attention 6. Anterograde amnesia 7. Impaired psychomotor performance 8. Interference with personal functioning.	Clinically significant maladaptive behavioral or psychological changes (e.g. inappropriate sexual or aggressive behavior, mood lability, impaired judgment, impaired social or occupational functioning) that developed during or shortly after sedative & hypnotic or anxiolytic use.
C. At least one of the following signs must be present- 1. Unsteady gait 2. Difficulty in standing 3. Slurred speech 4. Nystagmus 5. Decreased level of consciousness 6. Erythematous skin lesions or blisters.	One (or more) of the following sign, developing during or shortly after sedative, hypnotic or anxiolytic use ; 1. Slurred speech 2. In coordination 3. Unsteady gait 4. Nystagmus 5. Impairment in attention or memory 6. Stupor or coma
D.	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

DIAGNOSTIC CRITERION

Sedative/hypnotic withdrawal state (Table-3)

ICD-10 RESEARCH CRITERIA	DSM-IV TR
A. The general criteria for withdrawal must be met.	Cessation of (or reduction in) sedative - hypnotic or anxiolytic use that has been heavy and prolonged.
<p>B. Any three of the following signs must be present :</p> <ol style="list-style-type: none"> 1. Tremors of the tongue, eyelids or outstretched hands 2. Nausea or vomiting. 3. Tachycardia 4. Postural hypotension 5. Psychomotor agitation 6. Headache 7. Insomnia 8. Malaise or weakness 9. Transient visual, tactile or auditory hallucination or illusions. 10. Paranoid ideation 11. Grand mal convulsions <p>Comment : If delirium is present, the diagnosis should be sedative or hypnotic withdrawal state with delirium.</p>	<p>Two (or more) of the following developing within several hours to a few days after criterion A :</p> <ol style="list-style-type: none"> 1. Autonomic hyperactivity (eg. sweating or a pulse rate greater than 100 beats/min. 2. Increased hand tremors 3. Insomnia 4. Nausea or vomitings 5. Transient visual, tactile or auditory hallucinations or illusions 6. Psychomotor agitation 7. Anxiety 8. Grand mal seizures
C.	The symptoms in criteria B cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D.	The symptoms are not due to general medical condition and are not better accounted by another mental illness. Specify if : Any perceptual disturbances

CLINICAL PRESENTATION :

Table : 4 Characteristics of syndromes related to benzodiazepine withdrawal

Syndrome	Signs and symptoms	Time course	Response to reinstatement of benzodiazepine
High-dose withdrawal	Anxiety, insomnia, nightmares, major motor seizures, psychosis, hyperpyrexia, death	Begins 1-2 days after a shortacting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Symptom rebound	Same symptoms that were present before treatment	Begins 1-2 days after a short acting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped; last 7-17 days	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Protracted, low dose withdrawal	Anxiety, agitation, tachycardia, palpitations, anorexia, blurred vision, muscle spasms, psychosis, increased sensitivity to sounds and light, paresthesia	Signs and symptoms emerge 1-7 days after a benzodiazepine is reduced to below the usual therapeutic dose	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Symptom reemergence	Recurrence of the same symptoms that were present before taking a benzodiazepine (e.g., anxiety, insomnia)	Symptoms emerge when benzodiazepine is stopped and continue unabated with time	Signs and symptoms reverse 2-6 hours after usual therapeutic dose of a benzodiazepine

Adopted from; David E Smith, Donald R Wesson: Benzodiazepines and other sedative-hypnotics: Textbook of treatment of substance use disorders: American Psychiatric Press 1999.

The long term use of Benzodiazepines or other sedative hypnotics at dosage above the therapeutic dose range produces physical -dependence and all drugs have similar withdrawal symptoms that may be severe and life threatening. Therapeutic doses of benzodiazepines taken daily for months to years may also produce physiological dependence.

I. High dose withdrawal syndrome

Human studies have established that large doses of chlordiazepoxide (*Hollister et al 1961*) and diazepam (*Hollister et al 1963*) taken for 1 month or more, produce a sedative hypnotic withdrawal syndrome. The syndrome is quantitatively similar for all sedative hypnotics however the time, course and intensity of signs and symptoms may vary depending on the drug.

A) With short acting sedative hypnotics (*eg. Pentobarbital, secobarbital, meprobamate and methaqualone*) and short acting benzodiazepines (*Oxazepam, alprazolam, Traizolam*) withdrawal symptoms begins 12-24 hrs. after last dose and peak intensity reaches between 24-72 hours.

B) With long acting drugs (*Phenobarbital, Diazepam & Chlordiazepoxide*) withdrawal symptoms peak on the 5th - 8th day.

II. Low dose BDZ's withdrawal -

Variously referred as therapeutic dose withdrawal, normal dose withdrawal or BDZ discontinuation syndrome.

Table : 5 Signs and Symptomts of the Benzodiazepine Discontinuation Syndrome

The following signs and symptoms may be seen when benzodiazepine therapy is discontinued; they reflect the return of the original anxiety symptoms (recurrence), worsening of the original anxiety symptoms (rebound), or emergence of new symptoms (true withdrawal):

Disturbances of mood and cognition

Anxiety, apprehension, dyphoria, pessimism, irritability, obsessive rumination, and paranoid ideation

Disturbances of sleep

Insomnia, altered sleep-wake cycle, and daytime drowsiness

Physical signs and symptoms

Tachycardia, elevated blood pressure, hyperreflexia, muscle tension, agitation/motor restlessness, tremor, myoclonus, muscle and joint pain, nausea, coryza, diaphoresis, ataxia tinnitus, and grand mal seizures

Perceptual disturbances

Hyperacusis, depersonalization, Blurred vision, illusions, and hallucinations

adoped from : *Domenic A. Ciraulo and Ofra Sarid-Segal: Sedative- Hypnotic or Anxiolytic-related disorders, P-1310; Comprehensive Textbook of Psychiatry; kaplan and Sadock; Lippincott Williams and Wilkins - 2005.*

Factors influencing the development of BDZ discontinuation syndrome

- a) Dosage of benzodiazepines
 - b) Duration of benzodiazepines Treatment
 - c) Rate of drug taper
 - d) Psychopathology (Personality traits)
1. Mild withdrawal symptoms may occur with abrupt discontinuation of therapeutic doses after 4 weeks of benzodiazepines treatment. There is risk of rebound insomnia after few days to 1 wk of treatment with sedative-hypnotic drugs with short elimination $T_{1/2}$. benzodiazepines with long $T_{1/2}$ are less likely to induce rebound insomnia on abrupt discontinuation.
 2. The likelihood of serious withdrawal syndrome increases as treatment continues, many authorities sees 4 months of treatment at therapeutic doses as a critical point in the development of clinically significant physiological dependence.
 3. If benzodiazepine are abruptly discontinued, the withdrawal symptoms related to short half life agents appears earlier and may be more intense than that with longer half-life drugs (*Rickels et al 1990b*)
 4. Most studies monitor withdrawal symptoms for 2 wks, which may be the time of peak symptoms with some drugs with long $T_{1/2}$.
 5. Some studies in animals indicate that periodic administration of the BDZ's antagonist Flumazenil during the chronic administration of Lorazepam, Diazepam, Triazolam or Clobazam may attenuate withdrawal syndrome.
 6. Personality traits: Withdrawal severity is greater in patients with higher scores on the dependence scale of the MMPI-2 (Minnesota Multiphasic personality inventory), high pre-withdrawal levels of anxiety and depression, lower education level and passive dependent personality disorder.

III. Overdose

The BDZ's in contrast to the barbiturates and the barbiturate like substances have a large margin of safety when taken in overdoses .The ratio of lethal to effective doses is approximately 200 to 1 or higher. Even when grossly excessive amount (>2 gms) are taken in suicide attempts the symptoms include only drowsiness, lethargy, ataxia, some confusion & mild depression of user's vital signs. Barbiturates, & other sedative hypnotic drugs like Meprobamate, Chloral hydrate, Methaqualone, hydroxybutyrate are hardly the drugs of abuse in Indian context that is why they are not given significant stress.

Pharmacological Management

A. High dose BDZ withdrawalGeneral strategy :

1. to use decreasing dosages of the agent of dependence(30% dose reduction on day 2 and 3.
2. To substitute Phenobarbital or some other long acting barbiturates for the addicting agent & gradually withdraw the substituted medication (*Smith & Wessen 1970, 1971, 1983*).
3. Used for patients dependent on alcohol and benzodiazepines both: substitute chlordiazepoxide & taper it over 1-2 wks
4. Valproate/Carbamazepine may be prescribed.Phenobarbital substitution

It can be used to withdraw patients who have lost control of their BDZ use or are dependent on multiple sedative - hypnotics, including alcohol. I. Pharmacological rationale:

- a. Phenobarbital is long acting hence little change in blood levels between doses.
- b. Lethal doses are many times higher than toxic doses
- c. Signs of toxicity (sustained nystagmus, slurred speech & ataxia) are easy to observe.
- d. Low abuse potential (*Griffith and Roache 1985*)
- e. Intoxication usually does not produce disinhibition
- f. Excreted primarily through kidneys, is non toxic to liver, and can be used in the presence of significant liver disease.

II. Stabilization phase:

A. calculation of dosage B. Titration of dosage

A. Calculation:

The patient's average daily sedative-hypnotic dose is converted to Phenobarbital withdrawal equivalents (The conversion equivalent is in tabulated form in table-1) Although many addicted patients exaggerate the number of pills they are taking, patient's history is best guide to initiate pharmacotherapy. Patients who have overstated the amount of drug they are taking will become intoxicated during the first day or two of treatment which can be easily managed by omitting one or more doses of Phenobarbital & recalculating the daily doses. Method of Dosage: Computed daily dosage in 3 divided doses 3 times a day (if the patient is using significant amount of other sedative-hypnotics including alcohol the amount of all the drugs are converted to Phenobarbital equivalents and added together i.e. 30 cc of 100 proof alcohol is equated to 30 mg of phenobarbital for withdrawal purpose. (Max. Starting dosage: 500 mg/d).

B. Titration of dosage:

Before receiving each dose the patient is checked for signs of phenobarbital toxicity: **Sustained Nystagmus (most reliable sign)**, Ataxia, Slurred speech.

- If nystagmus present - scheduled dose is withheld.- If all 3 signs present Next 2 doses are withheld & daily dosage for the following day is halved.
 - If patient is in acute withdrawal/ has had or is in danger of having withdrawal seizures — Initial doses of Phenobarbital by I.M. injection and if Nystagmus & other signs of intoxication develop 1-2 hr after the 1M dosage the patient is in no danger from barbiturate withdrawal. Patients are maintained on the initial dose of Phenobarbital for 2 days.
Note: If the patient has signs of neither withdrawal nor Phenobarbital toxicity, then the patient enters in withdrawal phase of treatment.
- III. Withdrawal Phase: Phenobarbital is decreased by 30 mg/day.
- If signs of toxicity develop during withdrawal, the daily doses of Phenobarbital is decreased by 50% and the 30 mg/d withdrawal is continued from the reduced dosage.
 - If signs of sedative-hypnotic withdrawal, the daily dosage is increased by 50% & the patient is re-stabilised before continuing the withdrawal.

B. Low Dose benzodiazepines Withdrawal

No special treatment is needed. Most patients experience only mild to moderate symptom rebound that disappears after few days to weeks. During early abstinence, patients need support & reassurance that rebound symptoms are common & that with continued abstinence the symptoms will subside. Some patients experience severe symptoms that may be quite unlike pre-existing symptoms. The Phenobarbital regimen described earlier will not suppress symptoms to tolerable levels, but increasing the Phenobarbital dose to 200 mg/d & then tapering the Phenobarbital over several months can be an effective protocol for treating low dose withdrawal. Gradual reduction of the Benzodiazepine
It is used primarily for treatment of physiological dependence on long acting benzodiazepines arising from treatment of an underlying condition. The patient must be cooperative and able to adhere to dosing regimens and must not be abusing alcohol or other drugs.

Valproate & carbamazepines

Medications used in treatment of seizure disorders have found clinical utility in treatment of mood and anxiety disorders (*Kech et al 1992*) and in patients with co-morbid anxiety and alcohol dependence (*Brady et al 1994*). The medications most studied are Valproates & Carbamazepines. Both of these do not produce subjective effects that sedative- hypnotics abusers find desirable. Valproate has received some clinical attention. Some clinical attention for treatment of alcohol withdrawal (*Hammer and Brady 1996, Hillborn et al 1989*) and has been proposed for Benzodiazepine withdrawal (*Roy Byrne et. al 1989*) Clinical case reports of its use in BDZ withdrawal have appeared (*Apelt and Emrich 1990; McElroy et. al 1991*). When used for low dose Benzodiazepine withdrawal a dosage of 500-1500 mg/d can be used. Carbamazepine is used widely in Europe for treatment of alcohol withdrawal. Case reports & controlled studies suggest its utility in treating BDZ's withdrawal (*Klein et al 1986, Lawlor 1987, Neppe and Sindorf 1991; Rickels et al 1990a; Ries et al 1989; Roy Barne et al 1993; Schweizer et al 1991*) withdrawal protocols use Carbamazepine in a dosage of 200-800 mg/ day.

Out-patient Treatment of withdrawal

Although withdrawal from high dosages of barbiturates and other sedative hypnotics should generally be done in a hospital, but as a matter of fact many patients have to be treated in part, if not exclusively, as outpatients. With patients who are withdrawing from therapeutic dose of benzodiazepines a slow out patient taper is a reasonable strategy and should be continued as long as the patient can tolerate withdrawal symptoms. Hydroxyzine: H-1 receptor antagonist indicated for the use in anxiety & tension due to psychological factors. It has been tried with some success for benzodiazepines withdrawal however evidence based is inconsistent. (*Charles B. Nemeroff and Jared S. Tutnam: Antihistamines; p- 2774; The Comprehensive Textbook Of Psychiatry; Kaplan and Saddock's; 8th Edi; Lippincott Williams and Wilkins-2005.*)

Guidelines for treatment of Benzodiazepine Discontinuance Syndrome

Evaluate and treat concomitant medical and psychiatric conditions. Obtain drug history and urine and blood samples for drug and ethanol assay.

Determine required dose of benzodiazepine or barbiturate for stabilization, guided by history, clinical presentation, drug -ethanol assay, and (in some cases) challenge dose.

Detoxification from supratherapeutic dosages :

Hospitalize if there are medical or psychiatric dosages:

Social supports, or polysubstance dependence or if the patient is unreliable.

Some clinicians recommend switching to a longer-acting benzodiazepine for withdrawal (e.g., diazepam [Valium], clonazepam [Klonopin]); **other** recommend stabilizing on the drug that the patient was taking or on phenobarbital.

After stabilization, reduce dosage by 30% on the second or third day and evaluate the response, keeping in mind that symptoms that occur after decreases in benzodiazepines with short elimination half-lives (e.g., lorazepam [Ativan]) appear sooner than with those with longer elimination half-lives (e.g., Diazepam).

Reduce dosage further by 10-25% percent every few days, if tolerated.

Use adjunctive medications if necessary-carbamazepine, gabapentin, B. adrenergic receptor antagonists, divalproex, clonidine, and sedative antidepressants have been used, but their efficacy in the treatment of the benzodiazepine abstinence syndrome has not been established.

Detoxification from therapeutic dosages:

Initiate 10-25% percent dose reduction and evaluate response. Dose, duration of therapy, and severity of anxiety influence the rate of taper and the need for adjunctive medications.

Most patients taking therapeutic doses have uncomplicated discontinuation. Psychological interventions may assist patients in detoxification from benzodiazepines and in the long-term management of anxiety.

PROPOSED GUIDELINES For MANAGEMENT OF SEDATIVES-HYPNOTICS' DEPENDENCE

Primary Goals :

- Avoid dangers of withdrawal from sedatives; seizures and delirium tremors.
- Successfully withdraw the patient from sedative use without substantial discomfort.
- Arrange for adequate follow up care to avoid relapse.

1. OVERDOSE

- Not common primary drugs of abuse; most people do not find the effects of sedative-hypnotics reinforcing or pleasurable.
- The Benzodiazepine in contrast to the barbiturates and the barbiturate like substances have a large margin of safety when taken in overdoses
- The ratio of lethal to effective doses is approximately 200 to 1 or higher.
- Even when grossly excessive amount (>2 gms) are taken in suicide attempts the symptoms include only drowsiness, lethargy, ataxia, some confusion & mild depression of user's vital signs.
- Flumazenil used as antagonist.

2. IN PATIENT DETOX PROTOCOL

• **Lowdose Benzodiazepine Withdrawal**

- Various referred as therapeutic dose withdrawal, normal dose withdrawal or BDZ discontinuation syndrome
- **Evaluate** and treat concomitant medical and psychiatric conditions. Obtain drug history and urine and blood samples for drug and ethanol assay.
- **Determine** required dose of benzodiazepine or barbiturate for stabilization.
- **Initiate** 10-25% percent dose reduction and evaluate response.
- Dose, duration of therapy, and severity of anxiety influence the rate of taper and the need for adjunctive medications.
- **Most patients** taking therapeutic doses have uncomplicated discontinuation.
- Psychological interventions may assist patients in detoxification from benzodiazepines and in the long-term management of anxiety.

(B) Detoxification from supratherapeutic dosages.

- **Evaluate** and treat concomitant medical and psychiatric conditions. Obtain drug history and urine and blood samples for drug and ethanol assay.
- **Determine** required dose of benzodiazepine or barbiturate for stabilization.
- Guided by history, clinical presentation, and (in some cases) challenge dose
- **Hospitalize** if there are medical or psychiatric causes.
- **Social supports**, or polysubstance dependence or if the patient is unreliable.
- **Some** clinicians recommend switching to a longer-acting benzodiazepine for withdrawal (e.g., diazepam, clonazepam; other recommend stabilizing on the drug that the patient was taking or on phenobarbital.
- Reduce dosage by 30% on the second or Third day and evaluate the response.
- Keep in mind that symptoms that occur after decreases in benzodiazepines with short elimination half-lives (e.g., lorazepam) appear sooner than with those with longer elimination half-lives (e.g., Diazepam).
- **Reduce** dosage further by 10-25% percent every few days, if tolerated.
- **Use adjunctive medications** if necessary-carbamazepine, gabapentin, B. adrenergic receptor antagonists, divalproex, clonidine, and sedative antidepressants have been used.

General strategy for Detoxification from Supratherapeutic Dosages:

- To use decreasing dosages of the agent of dependence(30% dose reduction on day 2 and 3.
- To substitute Phenobarbital or some other long acting barbiturates for the addicting agent & gradually withdraw the substituted medication. (*Elaborated below*)
- Used for patients dependent on alcohol and benzodiazepines both: substitute chlordiazepoxide & taper it over 1-2 wks
- Valproate/Carbamazepine may be prescribed.

Phenobarbital substitution

I. Pharmacological rationale:

- Phenobarbital is long acting hence little change in blood levels between doses.
- Lethal doses are many times higher than toxic doses.
- Signs of toxicity (sustained nystagmus, slurred speech & ataxia) are easy to observe.
- Low abuse potential.
- Intoxication usually does not produce disinhibition.
- Excreted primarily through kidneys, is non toxic to liver, and can be used in the presence of significant liver disease.

METHOD:

Day -1

- Phenobarbital equivalents of the abused drug
- If multiple sedative hypnotics than the amount of all the drugs are converted to Phenobarbital equivalent and added together.
- If patient is alcoholic too than 30 cc of 100 proof alcohol is equivalent to 30 mg of Phenobarbital

Day -2

- 30 mg/day reduction
- If no sign of toxicity of continue tapering in similar manner.
- If signs of toxicity (all the 3 signs i.e. Sustained Nystagmus (most reliable sign), ataxia, slurring speech 50% dose reduction)

Day -3

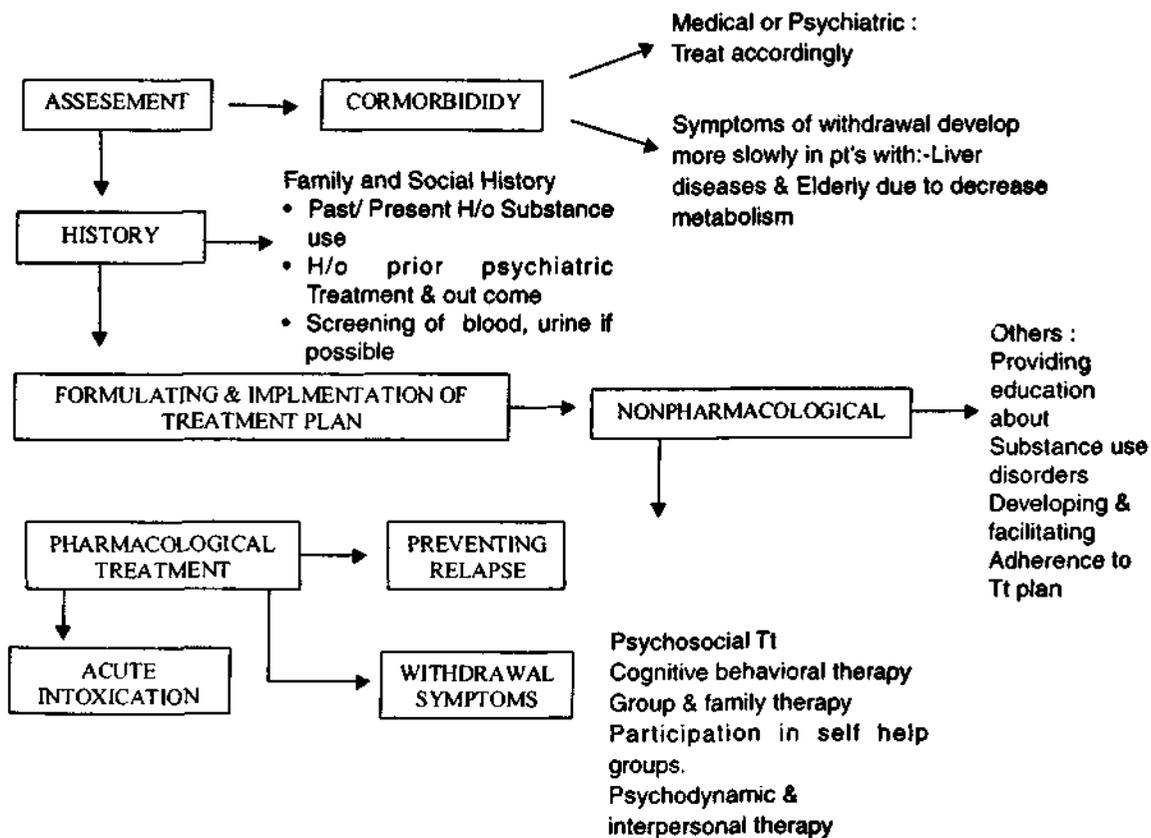
- 30 mg/d reduction
- If signs of sedative hypnotic withdrawal than 50% increment in Phenobarbital dosage, re stabilize and than tapering as above.

3. OUT PATIENT DETOX PROTOCOL

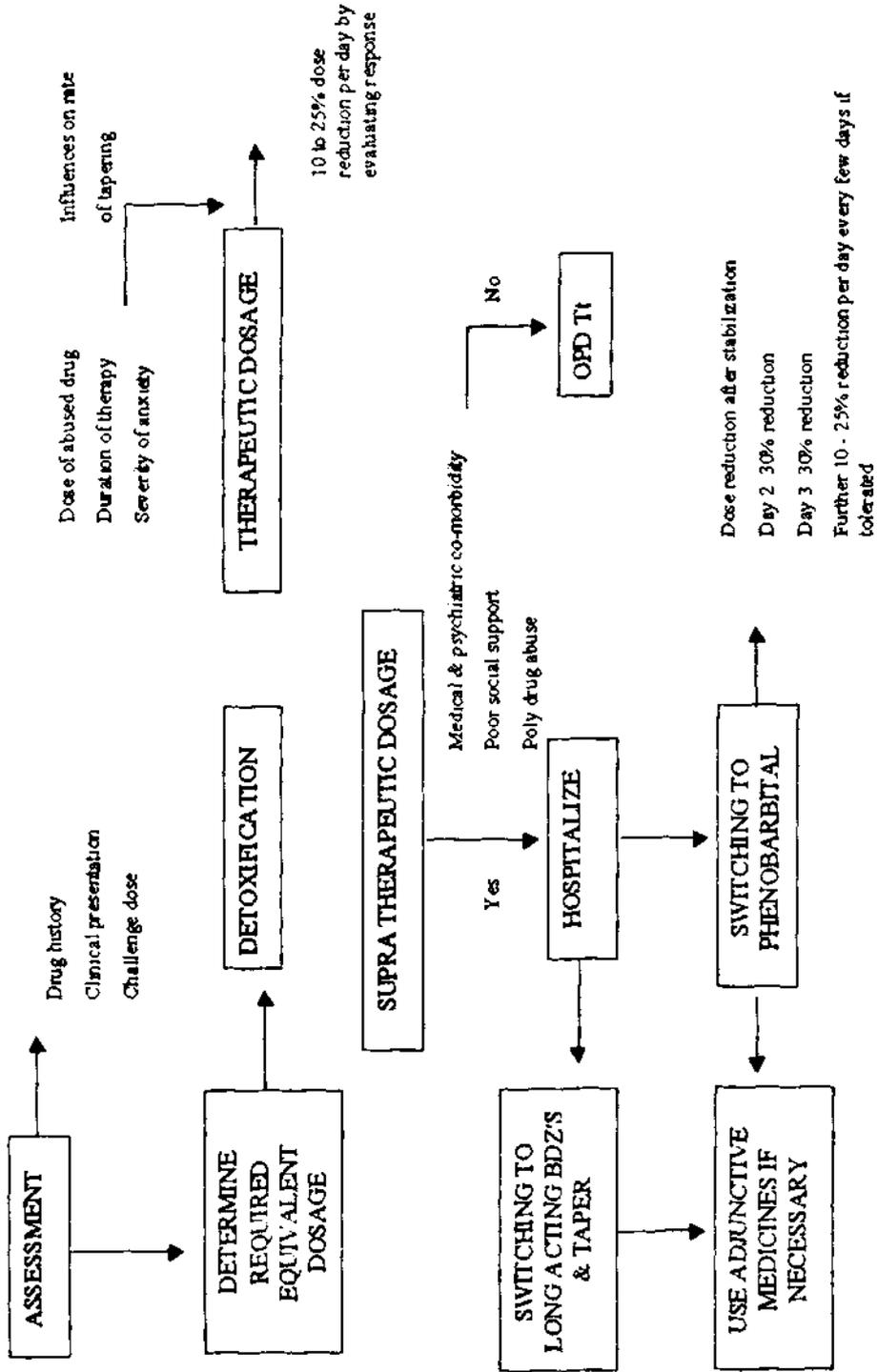
- Create a rapport with the patient. Discuss with the patient the plan to discontinue the abused sedative - hypnotic drug.
- Ask the patient to maintain chart of their abused drug.
- Review the chart with the patient. Determine the maximum dose taken each day as well as the average dose taken each day. Ask the patient to continue the charting while taking the average daily dose as a fixed daily dose. Ask the patient to maintain a log of symptoms that are observed on days when patient feels like having a higher dose.
- After long-term benzodiazepines use, of a minimum of 6 months duration for completion of the taper is recommended. Treat the symptoms, which the patient observed either pharmacologically or via other modalities.
- Ensure that the patient is taking the daily dose in divided doses. Three times a day dosing schedule is a reasonable starting point , this will result in diminished withdrawal symptoms at any time of day during the course of the taper.

- Educate the patient.
- Taper of medication
- If patient has taking 1 mg of sedatives 3 times a day.
- Taper as follows.
- 1 Month 0.75 mg., 1 mg, 1 mg
- II Month decrease the patient's dose by another quarter milligram, removing the amount at the time for which the patient reports the least symptoms but also make sure that the 3 doses are roughly equivalent to each other.
- Even at very low doses close to the end of the taper, the patient will probably describe marked relief following ingestion of their doses.
- (Adapted from: Stuart Gitlow (2001)).

OVER VIEW OF THE ORGANISATION & SCOPE OF RECOMMENDATION IN THIS PROPOSED GUIDE LINES



OVERVIEW OF PHARMACOLOGICAL TREATMENT OF SEDATIVE-HYPNOTICS DEPENDENCE



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