

Benzodiazepines: Therapeutic vs Abuse Potential

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Abstract : Ever since their introduction in 1961, benzodiazepines quickly displaced most of the barbiturates and became one of the most frequently prescribed classes of drugs. Their wide variety of physiological effects, high therapeutic ratio and favourable side effect profile makes them useful in the treatment of a number of medical and psychiatric disorders. Recently, new indications of their use have appeared (ego OCD), which further enhances their therapeutic potential. However, with long-term use, tolerance, dependence and withdrawal effects become major disadvantages. This leads to their continuing use without accepted medical indications and is more appropriately labeled benzodiazepine abuse. In most cases, this can be treated with gradual dose reduction along with psychological support. Rational prescribing practices limiting their role to short periods in management of acute conditions will help to bring down incidence of benzodiazepine abuse. New understanding about GABA- BZD receptor and introduction of partial benzodiazepine agonist (ego Abecarnil) further expands their therapeutic utility. In this paper, after a brief Introduction, neuropharmacology of benzodiazepine is discussed under the headings of chemical structure, pharmacokinetics and pharmacodynamics. An account of GABA-BZD receptor and molecular basis of action is included to facilitate understanding of benzodiazepine's action, side effects and abuse potential. The use of benzodiazepines in insomnia and anxiety - their major indications, in medical practice is discussed. In addition, indications in other psychiatric disorders - some of them recent, are examined. The abuse of benzodiazepine is much talked about and less understood topic. An attempt is made to elucidate benzodiazepine discontinuation syndromes, sift through confusing terminology of abuse and critically examine the extent and physical and psychological basis of abuse. The need to treat benzodiazepine abuse and the various options available are discussed. Finally a few guidelines are presented to minimize abuse of benzodiazepine therapeutic practice. This is followed by summary and conclusion.

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INTRODUCTION

After introduction into medical practice by Randall et al in 1960¹, benzodiazepine quickly displaced barbiturates and other sedative hypnotics in most

indications of their use. Their high therapeutic ratios compared to barbiturates, widespread efficacy, favorable side effect profile and lack of induction of liver enzymes made them one of the

most widely prescribed drugs in 1970's and 1980's. The high margin of safety in overdose in particular, resulted in liberal prescribing attitude. This led to concerns in medical community and public in general about overmedication with benzodiazepines. Reports in media further strengthened the perception that abuse and dependence might account for substantial portion of benzodiazepine use.

A number of studies in 1970's showed that discontinuation of benzodiazepines led to characteristic withdrawal syndrome.² Other concluded that there is virtually no recreational or inappropriate use of benzodiazepine.³ Even after more than 4 decades of use, there are contrasting views about abuse, addiction, tolerance and dependence of these drugs.

In last 15 year's efforts to search for anxiolytic agent not active at benzodiazepine receptor has yielded only few worthwhile agents viz, buspirone, pregabalin etc. There is growing recognition that benzodiazepine are unlikely to be displaced in near future by other agents to treat insomnia and anxiety disorders which are frequently chronic, recurrent and associated with high disability.² In addition, new indications of some benzodiazepine e.g. clonazepam in obsessive-compulsive disorder have appeared. Thus, it is of clinical importance to realize the therapeutic potential of this class of drugs, their abuse liability, ways limit the same and realize maximum benefit from their use. In this review we would discuss the pharmacokinetics, pharmacodynamics, molecular basis of action, therapeutic indications, adverse effects, abuse, dependence, discontinuation syndromes, treatment of dependence and prevention of dependence of benzodiazepines.

Neuropharmacology Structure

The structure of benzodiazepine is composed of a benzene ring (A) fused to a 7 membered diazepine ring (B) along with 5 aryl substituent ring

(C). Various modifications in ring systems have yielded compounds with similar activities. Addition of a triazolo or an imidazolo ring at position 1 & 2 yields high potency triazolo benzodiazepines (e.g. alprazolam) and imidazo benzodiazepine (e.g. zolpidem).

Pharmacokinetics

Benzodiazepines are generally well absorbed from gastrointestinal tract. Intramuscular absorption of diazepam is erratic whereas of lorazepam and midazolam is rapid and complete. The onset of pharmacological action (anxiolytic, skeletal muscle relaxant, anti convulsant and hypontic) is within 15-45 min whereas after intravenous injection administration it is in 1-5 minutes. Plasma concentration of benzodiazepines and their metabolites which in general are active, exhibits considerable inter-patient variation and therapeutic concentrations are difficult to define. Benzodiazepines are widely distributed in body tissues. They have high lipid solubility, which correlates with extent of plasma binding. The more lipid soluble agents have rapid uptake in brain followed by redistribution into less well-perfused tissues (adipose, muscle).⁴ Thus, there is need for multiple dosing inspite of apparently long half life.

Benzodiazepines are metabolized in liver and conjugated metabolites are excreted principally in urine, the elimination half life exhibit wide inter-patient variation. As the active metabolites are biotransformed more slowly than parent compound: the duration of action (biological half life) is more than elimination half-life of parent compound. Based on elimination half life benzodiazepines can be divided into 4 categories: ultra short acting (e.g. Midazolam), short acting (half life < 6 hours, e.g. Triazolam), intermediate acting (half life 6-24 hours, e.g. temazepam, Estazolam) and long acting (half life > 25 hours, e.g. -Flurazepam), as shown in table-1.

Table-1: Equivalent potency, dose and half life of various benzodiazepines⁵

Benzodiazepine	Potency Equivalent Dose	Half life (< 6hrs. Short; Intermediate 6-24 hrs; Long >24 hrs)
Lorazepam	2	Intermediate
Alprazolam	1	Intermediate
Clonazepam	0.5-1.0	Long
Diazepam	10	Long
Oxazepam	30	Intermediate
Chlordiazepoxide	25	Intermediate
Flurazepam	30	Long
Triazolam	0.25	Short
Zolpidem	10	Short

Pharmacodynamics

The GABA - Benzodiazepine receptor

Benzodiazepines bind to the GABA receptor, which exists as multi subunit ligand gated chloride channel. Numerous varieties of subunits make up the GABA receptor expressed in different neurons. Till date $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6, \alpha_7, \alpha_8$ and $\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7, \beta_8$ isoforms subunits have been discovered.^{6,7} The functional properties of the receptor including agonist affinity, conductance, rate of desensitization and benzodiazepine sensitivity are determined by the different subunits constituting the receptor. The benzodiazepine binding site is conferred by the gamma subunit and its affinity to the drug is determined by the alpha subunit present (α_1 and α_2).⁷ Based on constituent subunits, three benzodiazepine receptor subtypes have been described, two of which are called central benzodiazepine receptors and one is called a peripheral benzodiazepine receptor.⁸

Type I receptors abundant in cerebellum and also found in neocortex, amygdala, and cingulate cortex. These receptor mediate the anxiolytic, sedative and anticonvulsant effects of benzodiazepine agonists. Type II receptors are found in neocortex, striatum, hippocampus, spinal cord and pyramidal neurons. These areas are related to cognitive psychomotor and muscle

relaxant functions. Type III receptors are found in peripheral tissues and may regulate synthesis of neuroactive steroids.⁸

The multiplicity of subunits with different drug affinities constituting the GABA receptor and the diverse location of the receptor subtypes in the CNS provides the molecular basis of pharmacological diversity of benzodiazepine actions.

Based on pharmacological effect on receptors the benzodiazepine can be divided into Full agonist, partial agonist, inverse agonist and antagonists⁶. The full agonist produces maximum pharmacological effects at therapeutic concentration (e.g. Diazepam). The partial agonists produce sub-maximal pharmacological effects at therapeutic concentration (e.g. abecarnil). The inverse agonist produce pharmacological action opposite to that of agonist (e.g. Diazepam - binding inhibitor) and the antagonist blocks the effect of both agonist and inverse agonist (e.g. flumazenil).

Molecular basis of action

GABA is the most abundant inhibitory neurotransmitter in the brain.⁶ Benzodiazepines modulate GABA neurotransmission by potentiating GABA's action of increasing chloride conductance, which in turn results in membrane hyperpolarization which is responsible for neuronal inhibition.⁷ The potentiation of inhibitory circuits at various levels of neuraxis is thought to produce diverse pharmacological actions of benzodiazepines.⁶ The remarkable safety of benzodiazepine lies in the fact that they required endogenous release of GABA to produce their effects, as benzodiazepines only act as facilitators.⁷ Unlike barbiturates they do not have any direct action on GABA receptor and hence have no effects in absence of GABA.⁶

Benzodiazepines: Therapeutic Indications

All benzodiazepines have similar actions and

there is no evidence to suggest that anyone benzodiazepine is more effective than other if adequate dosage is given.⁹ However, differences in their pharmacokinetic properties have led to varying patterns of therapeutic application. There is reason to believe that a number of distinct mechanism of action contribute in varying degrees to sedative hypnotic, muscle relaxant, anxiolytic and anti-convulsant effect of benzodiazepines. While benzodiazepines affect activity at all levels of neuraxis some structures are affected to much greater extent than are others. Benzodiazepines have a varied efficacy with rapid onset of action and have minimal side effects. For this reason, they have replaced their predecessor for multiple indications. Some of the common psychiatric indications of benzodiazepines include insomnia, anxiety disorders, depression, mania, schizophrenia, obsessive compulsive disorders, agitation, akathisia, catatonia, alcohol withdrawal, opioids withdrawal etc. In addition to the psychiatric conditions benzodiazepines are also used in several medical conditions like seizures (clonazepam, diazepam and clobazam), muscle relaxation (diazepam), pre-anaesthesia (diazepam, lorazepam) and anaesthesia (midazolam).

Insomnia is the most common indication for the use of benzodiazepines, especially in primary practice. However it is important to remember that besides using benzodiazepines for insomnia the underlying identifiable medical and psychiatric causes of insomnia should be addressed. In recent times drugs like zopiclone and zolpidem are preferred to other drugs because of their established efficacy and relative safety. However, when benzodiazepines are used, the choice of particular benzodiazepine must be individualized according to patient response and tolerance, age, pharmacokinetic and pharmacodynamic characteristics of drug and the underlying sleep disorder. Drug with short half life may have decreased effectiveness during end of night (early

morning insomnia) and also may result in rebound insomnia after several nights use. Benzodiazepines with long half life on the other hand are likely to result in residual day time sedative effects with consequence of impaired intellectual and psychomotor function. These may however be useful in patients who have day time anxiety and in whom some sedation is acceptable. For transient and short term insomnia (upto 3 weeks) benzodiazepines should be used in low doses and those with short half life should be given for several nights. Reevaluation is recommended if continued use exceeds 2-3 weeks. Management of long -term insomnia is more complex. Identification of underlying cause and non pharmacological approaches (sleep hygiene, adequate exercise, relaxation training and behaviour modification like sleep restriction and stimulus control) are more important than pharmacotherapy. If drug therapy is employed, intermittent therapy (e.g. every 3rd day with a benzodiazepine having relatively long half life) has been suggested.⁸

Being potent anxiolytic agents benzodiazepines are used in generalized anxiety disorder (prevalence 4.1-6.6%), adjustment disorder with anxiety but not anxiety associated with life events. Benzodiazepines are most effective in controlling somatic symptoms whereas psychological symptoms respond more to buspirones and tricyclic antidepressants.¹⁰ Benzodiazepines require some underlying tone to exert anxiolytic effect which is directly proportional to the severity of anxiety.¹¹ Most patients should be treated for predetermined specific and relatively brief periods with benzodiazepines. For short term benzodiazepine can be prescribed for 2-4 weeks. In anxiety with intermittent exacerbation, benzodiazepine can be prescribed for a short duration of 4-6 weeks in addition to regular treatment with buspirone or tricyclic antidepressants.¹⁰ Efficacy for long term use (>4 months) is controversial and the need for

continued therapy should be periodically reassessed. Some patients with generalized anxiety disorder may warrant maintenance treatment with benzodiazepines.³

High potency benzodiazepines like alprazolam and clonazepam are useful in treatment of panic disorder. For both generalized anxiety disorder and panic disorder SSRI are effective agents that lack abuse potential. They also reduce hyper arousal in post traumatic stress disorder. Optimum duration of treatment of anxiety with benzodiazepine is still under debate. The main advantages of benzodiazepines are rapidity of onset, consistent efficacy and wide treatment e.g. preoperatively is often managed margin of safety when used for brief periods by benzodiazepines.

However, long term effectiveness of benzodiazepines in treatment of anxiety and insomnia has been poorly supported by experimental evidence.² There is rapid development of tolerance⁴ to a range of their effects along with undesirable personal consequences like lack of control, emotional numbing and memory problems.² It discourages patients from developing and making use of their personal resources in coping with life's vicissitudes. It also impairs learning of behavioral strategies to cope with a stress.

In depression benzodiazepines can be added to antidepressant therapy in the first few weeks to provide symptomatic relief of anxiety and insomnia. This is more so with selective serotonin reuptake inhibitors, which commonly have side effects of stimulation and sleep impairment.¹² Moreover, some studies have demonstrated antidepressant effects of high potency benzodiazepines like alprazolam comparable to imipramine in mild to moderate depression.¹³

Clonazepam and lorazepam are often used in adjunctive treatment of mania. They control insomnia, agitation, aggression and dysphoria. In schizophrenia benzodiazepines have been

used to control acute exacerbation of schizophrenia not controlled by conventional antipsychotics. Clonazepam which is suggested to have serotonergic properties is useful in treating anxiety component of obsessive compulsive disorders. Among other indications of benzodiazepine, parenteral lorazepam is used to manage psychiatric agitation in emergency situations. Besides the above, benzodiazepines are also used to manage akathisia and lorazepam is used in transient resolution of catatonia.

Adverse effects

Data regarding adverse effects attributable to benzodiazepines alone is quite limited. Moreover, effects might be subtle and difficult to differentiate from original symptoms.¹⁴ All benzodiazepines cause some degree of sedation in beginning of treatment. They can also cause memory problem especially in new learning of which patient might not be aware of. This is more pronounced in use of high potency benzodiazepines. Psychomotor effects including ataxia, dysarthria, incoordination, diplopia, vertigo and dizziness are common and related to dose and individual susceptibility. However, tolerance to these effects including sedation develops in 4-7 days of regular daily dosing. In the elderly there may be impairment of psychomotor function especially with long half life benzodiazepines and consequently increased risk of falling and hip fractures.¹³ High potency, short half life benzodiazepines like alprazolam appear to have cognitive effects like confusion, amnesia, behaviour agitation and hallucinations. Benzodiazepines may also contribute to suicide potential both in their use and withdrawal state.¹⁴

Discontinuation Syndromes

To understand the complex and controversial area of benzodiazepines abuse, it is necessary to first understand the various constellations of symptoms triggered by discontinuation of benzodiazepines after therapeutic use. These

have been classified into 3 categories, viz., rebound, relapse and withdrawal depending on the time course and clinical picture of syndrome.^{2,14} It should be noted that these categories are not mutually exclusive.

Rebound is characterized by return of original symptoms with a greater intensity for which the benzodiazepine was initially started. It starts within 1-4 days of discontinuation depending on half life of drug.¹⁵ It is reported after as little as 4 weeks of therapy and has a prevalence of 15-30%.² Predisposing factors are use of benzodiazepines with short half life, in higher dose and when they are tapered off rapidly or stopped abruptly. Rebound is considered to be an early manifestation of the receptor changes that are hypothesized to underlie benzodiazepine dependence and withdrawal. It is a self limiting condition with the symptoms returning to pretreatment base line in 1-3 weeks. Relapse may follow rebound discontinuation of treatment or may ever arise during treatment. It is characterized by the return of original symptoms upon drug discontinuation with the same intensity. It denotes the continuation of the underlying disease process and the symptoms continue unabated like the natural course of illness. Benzodiazepine withdrawal affects about a one third of patients taking benzodiazepine for 6 months or more. It is characterized by a constellation of signs and symptoms (as shown in table-2), many if which were not the part of original presentation. Some of the new symptoms are clearly distinguishable from previous anxiety e.g., perceptual symptoms of hyperacusis, phonophobia and photophobia. This syndrome gradually resolves over a 3-6 weeks period or merges into recurrence of anxiety. Severe withdrawal symptoms e.g., seizures and psychosis rarely occur unless patient undergoes abrupt discontinuation of > 40 mg equivalent of diazepam.

Report of persistent withdrawal syndrome¹⁶ lasting

months to years is not validated. Data from animal studies is ambiguous and clinically in many cases it is difficult to differentiate prolonged withdrawal from recurrence of anxiety. Hence symptom continuing for long time after stopping benzodiazepine should not be labeled as withdrawal.¹⁵

Symptoms of Benzodiazepine Withdrawal

Restlessness	Dizziness
Agitation	Tinnitus
Increase in anxiety	Depersonalization
Loss of appetite	Decreased concentration
Diaphoresis	Decreased memory
Hyperacusis	Irritability
Nausea	Depressed mood
Fatigue	Diarrhoea
Insomnia	Headache
Tremors	Palpitation
Paraesthesia	Weakness
Psychosis	Bodyache/stiffness
	Seizures

Various explanations have been put forward for benzodiazepine withdrawal. These include physical changes in the GABA-benzodiazepine receptor number, affinity and sensitivity,^{4,16} personality traits of neuroticism and dependency and reemergence of anxiety after successful treatment with benzodiazepine appear to be more distressing when in fact it is equal in severity to anxiety present before treatment. Besides the above other factors which can predictor withdrawal severity and inability to discontinue benzodiazepine can be divided into drug related factors and clinical variables.^{14,16} The drug related factors include use of higher doses, use of benzodiazepines for longer duration (maximum effect between use of month - 1 year), use of agents with short half life (chance of precipitating a withdrawal/rebound on missing a dose), rapid taper and high potency benzodiazepines (severe with drugs with high receptor binding affinity like alprazolam, and lorazepam, moderate

clonazepam and mixed with diazepam and chlordiazepoxide).¹⁷ The clinical variable which can predict withdrawal include high anxiety and depression at beginning of taper, personality pathology (neuroticism, dependency traits), panic disorder, female gender, elderly and those with past/family history of drug abuse.

Abuse, Dependence and Addiction

The term benzodiazepine abuse encompasses several patterns of abuse, misuse and addiction.¹⁸ The numerous and confusing definition of these terms renders the discussion of benzodiazepine abuse difficult.

In the recent times, 2 types of abuse have been described in the literature, viz., the unintentional abuse and deliberate abuse. In the unintentional abuse, initially the patient begins to use benzodiazepine for an anxiety disorder, but end up using them inappropriately in higher doses than prescribed or keeps on taking for duration longer than needed for remission of their anxiety disorder. Whereas the deliberate abusers are those subjects, who use benzodiazepine for its euphoriant effect. The deliberate abusers usually use other substances of abuse in addition to benzodiazepines. The deliberate abusers in addition to procuring the benzodiazepines from legitimate sources also acquire them various other illegitimate and illegal sources.¹⁹ However, it is important to remember that both types of abusers can become dependent on benzodiazepines.

With regard to dependence to benzodiazepines, two terms are commonly used: pharmacological dependence and addiction. Pharmacological dependence also known as physiological dependence is development of tolerance to the effect of the drug and precipitation of a withdrawal state on discontinuation. The pharmacological dependence develops as a result of natural physiological adaptation in response to the continued use of many substances that affect the nervous system.

Drug addiction is often used interchangeably with drug dependence. However, in relation to benzodiazepine, subjects with addiction, in addition to physical dependence, have compulsive pattern of drug use, which frequently leads to escalation of doses and a preoccupation with acquisition of drug. This result in physical, psychological or social harm to the user and drug use is continued despite that harm.^{3,19} This type of dependence is equivalent to the drug dependence as defined by nosological systems.

Drug abuse implies harm to user secondary to drug use without advancement to compulsive pattern.¹⁴ WHO defines drug abuse as "persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice". In above context, we can envisage benzodiazepine abuse to be occurring in situations like inability to discontinue medically prescribed benzodiazepines;¹⁴ benzodiazepine use without medical prescription,³ e.g. in students, general population; and primary benzodiazepine addiction and benzodiazepine abuse as a part of polydrug abuse.^{3, 14, 20}

Extent of use

As explained previously, differences in criteria used to define abuse, misuse and addiction makes it difficult to define exact prevalence. In West, prescription of benzodiazepine peaked to 103 million in 1975 and declined to 67 million 1981. There is again a gradual increase in last several years largely due to alprazolam which is the 5th most commonly prescribed drug. NIMH survey (1979) revealed that 15% of benzodiazepine users take it for greater than one year and about 0.6% take it for 4 month -1 year. Prevalence in general population in 1981 varied from 7.4-17%¹² and 9.6-16%.²¹ Indian studies show that the use to benzodiazepine in general population ranges from (3.5-53.5%) and use in student population range from 3.5 - 61%.²²

These data show that in absolute terms. a large

number of people are chronic users of benzodiazepine and by definition are benzodiazepine abusers.²³

Population characteristic and pattern of use

Based on dose of benzodiazepine used 2 patterns, of benzodiazepine abuse emerge, i.e., low dose abusers and high dose abusers. Low dose abusers use 15 mg equivalent of diazepam on long term basis without showing signs of dose escalation of drug seeking behaviour.^{3,12} A significant proportion of these have been prescribed benzodiazepine medically and 30-40% of these long-term prescribed users have difficulty in withdrawing. This may be an under estimate as approximate 50% of users decline to enter withdrawal programme.²⁴ In their psychological make up, these long term uses occur high on neuroticism, are sensitive to punishment, have prominent anxiety traits and have poor coping behaviour with stress. American Psychiatric Association task force on benzodiazepine dependence defined following as long term users of benzodiazepine: patients with medical illness especially elderly³, persons with chronic anxiety, persons suffering from panic disorder / agoraphobia, subjects suffering from schizophrenia, persons with chronic insomnia and persons with current or past history of drug dependence.³ High dose abusers are in minority in comparison to low dose abusers and use benzodiazepine in doses 40mg or more mainly in context of poly drug use.³ Co-abuse of benzodiazepine is common with rates of 20-40% in alcoholics and 25%-50% in heroin and methadone users. In India, intravenous diazepam is very commonly co-abused by intravenous buprenorphine abusers. A study conducted in our department had rate as high as 78%.²⁵ The reasons for co-abuse are many. An addict may experiment with several drugs including benzodiazepines and become dependent on them. Alcohol and benzodiazepines show cross tolerance in their neuro-pharmacological effect

and benzodiazepines suppress symptoms caused by alcohol withdrawal. Opioid abusers use benzodiazepines to enhance their sedative effects.²⁰ Intravenous buprenorphine abusers use a cocktail with diazepam to enhance the kick, prolong the duration of effect and suppress side effect like nausea.²⁵

The basis of benzodiazepines dependence

As already discussed, vast majority of abusers take normal dose of benzodiazepines for extended period of time. Two models have been given to explain such behaviours. These include physical and cognitive model. According to physical model, the development of physical dependence apparently account for continuing benzodiazepines use due to negative reinforcement of withdrawal.¹⁴ Thus the motivation of use of benzodiazepines for anxiolysis gradually merges with the need to avoid withdrawal. However, the physical model cannot fully explain all features of benzodiazepines abuse and there are suggestion that physical dependence of benzodiazepines is different form that of other drugs. The various arguments against this model include facts like benzodiazepines abuse does not fit into clinical picture of classical addiction drugs, many of the withdrawal symptoms are impossible to differentiate from anxiety, only a third of long term users suffer from withdrawal,¹⁶ absence of tendency to escalate dose to show reinforcing behaviour,³ evidence from animal studies show that benzodiazepines do not readily maintain self administrating behaviour³ and lack of euphorient action on normal subjects. Cognitive model proposes that there is a disturbance of higher order cognitive process such as beliefs, attitudes and expectations in benzodiazepines abusers. This influences the subjective experience of withdrawal making it appear more intense and prolonged in absence of drug. Expectation and knowledge of withdrawal creates apprehension which may itself be associated with some

symptoms. This is supported by studies which have found more favorable discontinuation rates in non-psychiatric populations.^{2,3,16} Also the long term users have poor coping strategies and require drugs for psychological comfort and as a means to deal with stress. This psychological need for continued benzodiazepine use is demonstrated by a finding that 22% of patients on active medicine had a pseudo-withdrawal thinking they are on a placebo.¹⁶ Moreover about 50% of long-term users dropped out even before starting detoxification. Thus we see that cognitive beliefs combine to intensify withdrawal symptoms and these aspects need to be addressed for successful management of benzodiazepines dependence.

Treatment of benzodiazepines dependence

Long-term benzodiazepines abusers should be encouraged to stop its use because of doubts on continued efficacy, risk of adverse effect like dependence and neuropsychological impairment and socioeconomic costs.²⁴ A full medical, psychiatry, social and drug history should be taken and patient motivation should be assessed.²⁶ Patients should be educated about the nature of anxiety, physiological symptoms, mechanism of drug action and withdrawal in a simplified way. Most of the patients can be managed on outpatient level.²⁴ A few, abusing high dose may require in-patient treatment.²⁶ Four different methods have been suggested for stoppage of benzodiazepines. These are gradual dose reduction, substitution with long acting benzodiazepine, use of adjuvant medications and non-pharmacological modalities.

Gradual dose reduction is probably the best method.^{4,14} After normal therapeutic use a short acting benzodiazepines like alprazolam can be tapered in 7-10 days whereas a long acting benzodiazepines can be withdrawn in 10-14 days. The usual starting dose is 50% of the total dose. This is followed by 25% reduction in 3-7 days.

For long term dependence there is lack of agreement on optional rate of reduction. It ranges from 4-16 weeks with the taper being slowed towards the end. The rate of taper is individually tailored taking into account the life style, personality, environmental stress or support available. The size of dose reduction depends on current dose, with patient on higher dose can tolerate larger dose decrements,²⁴ however the maximum dose reduction at one time should not exceed 25%.¹⁹ Subjects those who are taking short acting benzodiazepine for long duration can be managed by substitution with an equivalent dose of a long acting benzodiazepine (e.g. Chlordiazepoxide).¹⁴ This may be due to fact that stable plasma levels reduce likelihood of withdrawal between doses. Other advantage is that wider dose ranges are available (e.g. diazepam) for titration. Adjuvant drugs may be needed in some patients. Out of numerous drugs tried, propranolol, clonidine, abecarnil and flumazenil have shown equivocal results, whereas carbamazepine, valproate, buspirone, tricyclics and trazodone have shown some promise in decreasing severity of withdrawal.^{2,14,19,27} Adjuvant medication if used should be given for 4 to 6 weeks before taper for maximum therapeutic effect. Medication should be tapered gradually after benzodiazepine withdrawal is complete.¹⁴ All patients require a degree of psychological support which varies individually from encouragement to formal cognitive behaviour or other therapies. Alternative efficacious coping strategies which suit individual patients are implemented like relaxation training, breathing exercise and biofeedback. Cognitive approaches like distraction, manipulation and thought substitution are used to address distortion and catastrophization.¹⁶ With individualized tapering schedules, developing alternative coping skills and cognitive behaviour approach can lead to success rate of 30-70%. Long-term outcome is less clear.²³ Patients need to be followed up

regularly for extended period of time as they remain vulnerable to stress and some symptom persist with a waxing and waning course. There are few contraindications to long time benzodiazepine use in patients who wish to use i.e. forcing unwilling patients to withdraw is usually unsuccessful and causes unnecessary distress.

Preventing Dependence

Measure to limit long term use begins at the start of pharmacological treatment. The United Kingdom committee on Safety of Medicine and the Royal College of Psychiatrists advise reserving benzodiazepine for short term relief of cases that are severe, disabling or subjecting patients to extreme distress.^{14, 16, 28} Good prescribing guidelines should follow six D's viz., diagnosis, dosage, duration, discontinuation, dependence & documentation. For acute problems treatment can begin on tentative basis but for a chronic problem a firm diagnosis should be made. Appropriate treatment plan is outlined and duration discussed with patient, the goal being neither to under or over medicate. Periodic assessment of case should be done and need for continuing benzodiazepine therapy evaluated. Patients should be encouraged to learn alternative coping behaviour for dealing with stress.¹⁴ For chronic insomnia non-pharmacological methods should be used first. Intermittent use (of zolpidem, zopiclone) should be explained giving the patient more control over his medication.²⁹ Physicians should have a high index of suspicion for development to dependence as seen by emergence of withdrawal symptoms following dose reduction, development of tolerance and request for repeat prescriptions.

Summary and Conclusion

The main action of benzodiazepine (hypnotic, anxiolytic, anticonvulsant, myorelaxant and amnesic) confer a therapeutic value in a wide range of conditions. Their rational use requires consideration of the large differences in potency

and elimination rates between different benzodiazepines.

Benzodiazepines are effective anxiolytics and hypnotics but use is commonly complicated by development of tolerance and dependence in long term use. Syndromal withdrawal occurs in one-third of patients discontinuing benzodiazepines. The most wide spread abuse of benzodiazepines is low dose dependence (15 mg equivalent diazepam) without progression to addiction as evidenced by lack of escalation of dose, reinforcing behaviour, impairment of social or occupation functioning. The long-term users of benzodiazepines are a self selected population with high anxiety traits or states.

Most of these patients can be successfully withdrawn from benzodiazepine by combination of gradual dose reduction and psychological support. Development of dependence can be effectively prevented by following rational prescribing practice. As hypnotics benzodiazepines should be used for transient or short term insomnia, courses not exceeding 2 weeks. As anxiolytics benzodiazepines should be used in conjunction with other measure like psychological treatment. Indications include stress reaction, episodic anxiety and as an initial treatment for severe panic and agoraphobia. The duration of treatment should be limited to short (up to 4 weeks) term and only rarely for longer term. The elucidation of receptor subtype and their location offers the ability to tailor drugs for specific therapeutic actions and minimize adverse effects.

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