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# Toxic Reactions to Chronic Use of Benzodiazepines: An Overview

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**Abstract:** Benzodiazepines (BZDs) are the most commonly prescribed hypnotic-anexiolytic-sedative drugs in the world. Their effectiveness and safe usage have made them extremely popular among patients. To date more than 30 different brands of BZDs have been introduced to drug market, which vary enormously in side effects, potency and indications. Thus, due to global consumption and diversity of BZDs, lack of a information indicating the BZDs' side effects sorted by induced signs and symptoms, this study would ease the consultation and follow-up of the patients who have undergone BZD treatment. The review first gives a brief introduction about side effects encountered by BZDs and then classifies the signs and symptoms based on the organ involved and mentions which BZDs are responsible for them. The organs and functions which are influenced are classified under: cardiovascular system, CNS, cognitive function, mood changes, endocrine/metabolic, gastrointestinal tract, blood and bone marrow, liver, eyes, respiratory system, skin, genitourinary tract, musculoskeletal system, ears and miscellaneous. Each of these items is also sub-grouped into several categories.

**Key words:** Benzodiazepines, chronic use, toxicity, adverse effects

## INTRODUCTION

BZDs, introduced into clinical practice in the early 1960s, were hailed as a breakthrough because of their fewer drawbacks comparing with prior anxiolytics and sedative-hypnotics. Their effectiveness in a wide range of disorders, their generally mild side effects along with their safe overdose and combination with other drugs have made BZDs one of the most commonly prescribed drugs, worldwide. BZDs variations in chemical structure and pharmacokinetics lead to major differences in potency, onset and duration of clinical activity, type and frequency of adverse effects both after single and multiple doses and withdrawal phenomena. These differences execute a delicate task to choose the right BZD for every patient[1-3].

**Interaction of bzds with other drugs:** The most important clinical drug interactions encountered with BZDs are associated with their additive effects when combined with other sedative or hypnotic drugs. BZDs are relatively safe drugs and even large overdoses are infrequently fatal unless taken in combination with other drugs. Flumazenil is a benzodiazepine receptor antagonist which specifically reverses the sedative effects of BZDs; however, it does not reverse hypoventilation or respiratory suppression caused by BZDs[4,5].

**Discontinuance syndrome:** Meaningful BZD discontinuance symptoms usually only occur when BZD treatment is abruptly terminated. This syndrome is first manifested by rebound symptoms that resemble the symptoms for which the BZD had been prescribed, except that rebound symptoms are more severe and emerge soon after discontinuation. Rebound anxiety and insomnia are clearly established as possible consequences to the discontinuation of BZDs, particularly those having a short half-life. Symptoms usually disappear rapidly (from a day or two, to 1 or 2 weeks). To avoid these distressing effects, users often restart the medication, leading to long-term BZD use and dependence[3-7].

**Withdrawal phenomena:** Continuous use of a BZD, even at therapeutic doses, will result in withdrawal symptoms in some patients. The longer a BZD is taken, even in therapeutic doses, the greater the likelihood of withdrawal reactions when it is discontinued, especially abruptly. The most commonly reported withdrawal symptoms include: various gastrointestinal symptoms, diaphoresis, tremor,

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lethargy, dizziness, headaches, increased acuity for sound and smell, restlessness, insomnia, irritability, anxiety, tinnitus and depersonalization. These manifestations usually occur with mild intensity and fairly short in duration (from a few days to a few weeks). None is considered life-threatening or permanently debilitating and are thought to be simply manageable. However, in some patients, discontinuation, whether abrupt or gradual, may evoke highly distressing symptoms, including severe and prolonged depression, hallucinations, protracted tinnitus, opisthotonos, choreoathetosis, myoclonus, bizarre involuntary muscular movements, delirium with catatonic features, panic and agoraphobia[3-7].

**Abuse:** A great deal of BZD abuse is part of polydrug abuse, most commonly with opioids. Mostly, because of the rapidity of their onset of action, short-acting BZDs are considered as agents of choice among BZD addicts. Data suggest that highly lipophilic BZDs (e.g. those that cross the BBB more rapidly) and agents with a short half-life and high potency, are the most reinforcing BZDs and, therefore, the ones most likely to be associated with abuse[3-7].

**Adverse effects:** Comparing to other psychotropics, short-term BZD treatment is associated with fewer unwanted effects (e.g. fewer performance deficits); however, they may increase the chance of daytime anxiety in elderly patients. Sedation usually is the most prominent initial complication, subsiding in about a week as anxiolytic action emerges. Confusion, ataxia, excitement, agitation, transient hypotension, vertigo and gastrointestinal distress may also occur in a small number of patients[1,8,9].

**Behavioral disinhibition:** Studies have suggested that some BZD-treated patients experience increased hostility and aggressiveness, ranging from feelings to overt behavior. The phenomenon is difficult to characterize because it may include various manifestations including hostility, aggressiveness, rage reactions, paroxysmal excitement, irritability and behavioral dyscontrol[10,11].

**Psychomotor impairment:** BZDs may impair certain types of psychomotor functioning, such as coordination and sustained attention. Some patients have exhibited few or no decrements and it has been postulated that by reducing anxiety (which itself can impair functioning), a BZD may paradoxically improve performance[10,11].

**Cognitive impairment:** Even single doses of BZDs impair cognitive function. As well, dementia can be worsened by BZD side effects. It has also been demonstrated that psychological impairment occurs in normal subjects and after short courses of treatment in anxious patients. Patients taking high therapeutic doses for long periods of time perform poorly on tasks involving visuospatial ability and sustained attention, implying that these individuals may not be functioning well in everyday life. This is consistent with clinical evidence provided by patients who, after discontinuing a BZD, often report improved concentration and increased sensory perception and who only realized their functioning had been below par after stopping the drug[7,10,11].

**Seizures:** Although rare, seizures may occur after the abrupt discontinuation of both high and therapeutic doses of any BZD. It has been suggested that short-acting drugs are associated with increased seizure risk when compared with longer-acting compounds.

In almost all seizure cases, patients had abruptly stopped the drug and also at least one (and often more than one) of the following factors was present: high dose, extended duration of use (4 months to years), concomitant or immediately subsequent ingestion of other drugs associated with seizure induction and history of seizures[1,7,8].

**Respiratory depression:** All sedative agents are capable of depressing ventilation even in normal individuals. Dangerous respiratory depression is most likely to arise from postoperative analgesia and during the intravenous sedation which is now commonly used to cover minor surgeries[7,8].

**Sleep disorders:** Short-term use BZDs generally hastens onset of sleep, decrease nocturnal awakenings, increase total sleeping time and often impart a sense of deep and refreshing sleep. However, they produce alterations in the duration of the various sleep stages. Occasionally, BZDs produce paradoxical, apparently stimulant effects, particularly in anxious patients. On BZDs withdrawal after chronic use, the effects on sleep are reversed and a withdrawal syndrome which includes rebound insomnia, frequent awakenings, vivid dreams and nightmares is common and may be long-lasting[1,7,8,10,11].

**Anxiety:** Anxiety is a well-recognized feature of the BZDs withdrawal syndrome but can also occur as an adverse effect of acute or chronic usage. In addition, increasing anxiety with the onset of panic attacks, agoraphobia and

other phobias, may develop during long-term BZDs usage (as with alcohol), possibly as a result of drug tolerance[1,7,8].

**Depression:** Long-term use of BZDs can aggravate pre-existing depression and provoke suicide. Severe depression and suicidal ideas also occur in benzodiazepine withdrawal in dependent patients[7,8,10].

**Amnesia:** BZDs produce an anterograde amnesia, a property utilized, along with the sedative and anxiolytic actions, when the drugs are employed as premedication before surgery or for anaesthesia. The anterograde amnesia is secondary to disordered consolidation process that store information and is not impairment in the perception or retrieval information. It has been reported with most BZDs. The impairment of recent memory by BZDs (e.g. triazolam) may lead to memory lapses (transient global amnesia) many hours after the drug has been taken and it has sometimes led to charges of shoplifting. The elderly are particularly vulnerable to the amnesic effects of BZDs. Memory deficits are observed in patients who take BZDs regularly for a mean of 10 years[7,8,11].

**Delirium:** Intoxication with BZDs can cause drowsiness and delirium, often accompanied by ataxia, dysarthria and nystagmus. Occasionally there is an initial hyperactivity phase, but in overdosage a hypoactive delirium with clouded consciousness proceeding to coma occurs in elderly subjects even normal therapeutic doses can induce delirium, which may lead to bizarre behavior, falls and fractures. Withdrawal reactions of sedative and hypnotics in dependent subjects may include a hyperactive delirium[7,8,11] .

**Liver damage:** Hepatic injury from BZDs is a very uncommon incidence. Cholestasis or cholestatic hepatitis have been reported from chlordiazepoxide, diazepam and flurazepam. The onset of liver disease occurs from a few days to several weeks after starting treatment and signs of hypersensitivity may be present[1,7,8].

**Gynaecomastia:** Reduction in free testosterone concentration due to increased amount of sex-hormone-binding globulin and enhanced conversion of testosterone to estradiol could explain the gynecomastia due to diazepam[7,8].

**Eye movement:** The BZDs can affect the velocity of saccadic eye movements, although symptoms are not usually experienced by the patient[7-9].

**Coma:** The vast majority of drug-induced cases of coma are caused by overdose with drugs that are used therapeutically for their action on the central nervous system. They are principally psychoactive compounds, such as the BZDs. Intravenous flumazenil has emerged as a useful therapeutic and diagnostic tool in reversal of coma due to overdose in which BZDs might be implicated (even when a mixture of drugs has been taken)[7,8,10].

**Agranulocytosis:** Agranulocytosis and neutropenia, although rare, can be severe and even life threatening. Clearly there are a number of drugs, such as BZDs that produce predictable and usually reversible bone marrow aplasia which can particularly affect the granulocyte count[7,8].

**Sexual dysfunction:** Anxiolytic drugs and in particular, BZDs, seem to have little effect on sexual function. These drugs are sedative and this obviously may be a factor in reducing sexual activity. However, it is suggested that BZDs inhibit orgasm in female volunteers. In contrast, withdrawal of BZDs has been reported to increase sexual activity[7,8].

**Age effects:** Several cross-sectional studies of the elderly in hospital have indicated that they suffer from more adverse reactions than younger patients. Absorption appears to be substantially independent of age. An sage-related increase in body fat may well account for the greater volume of distribution of lipid-soluble medications such as long-acting BZDs. Drug elimination by the kidney may be considerably impaired in elderly subjects owning to age-related decline in renal function, although there is a large interindividual variability in such deterioration. Along with these changes in pharmacokinetic variables, certain pharmacodynamic variables also appear to be affected by age process.

**Fetal disorders:** Evidence that BZDs are teratogenic comes from retrospective studies showing a higher risk of cleft lip and palate and from case reported of babies with dysmorphic features and growth retardation. BZDs cross the placenta and may produce direct pharmacological effects on the fetus or give rise to a perinatal withdrawal syndrome, or produce both of these effects. A neonatal withdrawal syndrome may be seen, particularly if the maternal dosage has been high. The symptoms may take up to 2-3 weeks to appear and resemble those of opiate withdrawal; these include irritability, tremor, hypertonia, hyperactivity, tachypnoea, gastrointestinal disturbances, and vigorous sucking. BZDs are excreted in breast milk and thus are usually contraindicated in breast-feeding mothers[7,8].

**Xerostomia:** BZDs are capable of causing xerostomia in some patient and sialorrhoea in others[1,8,12,13].

**Galactorrhea:** Galactorrhea has been associated with BZDs though without hyperprolactinaemia[8].

In the following tables, the organs and functions which are influenced by chronic use of BZDs are classified under cardiovascular system, CNS, cognitive function, mood changes, endocrine/metabolic, gastrointestinal tract, blood and bone marrow, liver, eyes, respiratory system, skin, genitourinary tract, musculoskeletal system, ears and miscellaneous[7,8, 13-24].

| **Cardiovascular effects:** | |
|---|---|
| Arrhythmia | Diazepam, estazolam, midazolam |
| Bradycardia | Diazepam, halazepam |
| Chest pain | Flurazepam |
| Orthostatic hypotension | Adinazolam, alprazolam, bentazepam, bromazepam, clobazam, clorazepate, delorazepam, diazepam, etizolam, halazepam, medazepam, midazolam, pinazepam, temazepam |
| Palpitations | Alprazolam, clonazepam, estazolam, flurazepam, pinazepam, temazepam |
| Tachycardia | Adinazolam, alprazolam, bentazepam, etizolam, flunitrazepam, flurazepam, halazepam, midazolam, triazolam |

| **Central nervous system effects** | |
|---|---|
| Abnormal eye movement | Clonazepam |
| Akathisia | Clorazepate, etizolam, flurazepam, midazolam |
| Anxiety | Adinazolam, clobazam, diazepam, flurazepam, temazepam, tetrazepam |
| Ataxia | Alprazolam, bromazepam, clorazepate,delorazepam, diazepam, estazolam, flunitrazepam, flurazepam, ketazolam, loprazolam, medazepam, midazolam, prazepam, quazepam, temazepam, triazolam |
| Coma | Alprazolam, clonazepam |
| Delirium | Alprazolam |
| Diplopia | Clonazepam |
| Dizziness | Adinazolam, alprazolam, midazolam, bentazepam, bromazepam, lormetazepam, loprazolam, brotizolam, ketazolam, clobazam, clorazepate, clotiazepam, delorazepam, flurazepam, flunitrazepam, medazepam, metaclazepam, oxazepam, prazepam, quazepam, temazepam, tetrazepam |
| Drowsiness or sedation | Ketazolam, adinazolam, alprazolam, bentazepam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, clotiazepam, delorazepam, diazepam, estazolam, etizolam, flunitrazepam, flurazepam, halazepam, loprazolam, lormetazepam, medazepam, metaclazepam, midazolam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, tetrazepam, triazolam,temazepam |
| Dysarthria | Clonazepam, diazepam |
| Dysdiadochokinesis | Clonazepam |
| Dyskinesia | Alprazolam, metaclazepam |
| Dystonic reactions | Bromazepam, midazolam |
| Euphoria | Flurazepam, midazolam, Temazepam, triazolam |
| Faintness | Adinazolam, medazepam |
| Hallucinations | Adinazolam, chlordiazepoxide, clonazepam, Diazepam, etizolam, ketazolam, Metaclazepam, temazepam, tetrazepam |
| Headache | Adinazolam, alprazolam, brotizolam, Estazolam, flunitrazepam, clobazam, Diazepam, clonazepam, clorazepate, Flurazepam, ketazolam, loprazolam, Lormetazepam, medazepam, metaclazepam, Midazolam, oxazepam, prazepam, Quazepam, temazepam |
| Hemiparesis | Clonazepam |
| Hypotonia | Clonazepam, estazolam |
| Insomnia | Alprazolam, clobazam, clonazepam, clorazepate, clotiazepam, diazepam, etizolam, ketazolam, midazolam |
| Lightheadedness | Adinazolam, alprazolam, clobazam, flurazepam, ketazolam, midazolam, prazepam |
| Nervousness or agitation | Adinazolam, brotizolam, clonazepam, clorazepate, delorazepam, flurazepam, lormetazepam, metaclazepam, midazolam, oxazepam, temazepam, tetrazepam, triazolam |
| Nystagmus | Clonazepam, diazepam, medazepam, midazolam, temazepam |
| Paresthesia | Midazolam, nitrazepam |
| Seizures | Adinazolam, midazolam |
| Slurred speech | Clonazepam, clorazepate, diazepam, flurazepam, medazepam, metaclazepam, midazolam, prazepam, quazepam |
| Syncope | Alprazolam, clobazam, estazolam, oxazepam, prazepam |
| Tremor | Adinazolam, alprazolam, bentazepam, clonazepam, delorazepam, diazepam, etizolam, flunitrazepam, midazolam, Prazepam, temazepam |
| Vertigo | Clonazepam, clotiazepam, delorazepam, diazepam, etizolam, midazolam, oxazepam, temazepam |
| Vivid dreams | Adinazolam, brotizolam, flunitrazepam, loprazolam, metaclazepam, midazolam, nitrazepam, prazepam, temazepam |
| Weakness | Clobazam, clorazepate, clotiazepam, delorazepam, diazepam, etizolam, flurazepam, lormetazepam, medazepam, midazolam, prazepam, quazepam, temazepam, tetrazepam, triazolam |

| **Cognitive impairment** | |
|---|---|
| Confusion | Adinazolam, alprazolam, clonazepam, clorazepate, delorazepam, diazepam, flurazepam, ketazolam, loprazolam, medazepam, metaclazepam, midazolam, nitrazepam, prazepam,temazepam |
| Decreased concentration | Adinazolam, brotizolam, delorazepam, flurazepam, ketazolam, loprazolam, metaclazepam, temazepam |
| Depersonalization | Nitrazepam |
| Impairment of learning | Bromazepam, lormetazepam, temazepam |
| Memory impairment | Adinazolam, alprazolam, clonazepam, delorazepam, diazepam, loprazolam, flunitrazepam, medazepam, metaclazepam, midazolam, lormetazepam, pinazepam, temazepam, triazolam |

| **Mood disorders** | |
|---|---|
| Combativeness or aggressive behavior | Alprazolam, clorazepate, midazolam |
| Depression | Adinazolam, alprazolam, clobazam, clonazepam, clorazepate, diazepam, flurazepam, ketazolam, temazepam |
| Dysthimia | Clonazepam, alprazolam |
| Mania or hypomania | Adinazolam, alprazolam, clonazepam, flurazepam, midazolam, triazolam |
| Paranoid reactions | Triazolam |

| **Endocrine/metabolic effects** | |
|---|---|
| Galactorrhea | Chlordiazepoxide, clobazam, metaclazepam |
| Gynecomastia | Diazepam |
| Hypothermia | Lormetazepam, triazolam |
| Hypouricemia | Adinazolam |
| Increased cortisolsecretion | Midazolam |
| Increased growthhormone | Diazepam |
| Increased insulin secretion | Midazolam |
| Increases in growth hormone levels | Bromazepam |
| Menstrual disorders | Medazepam, metaclazepam, tetrazepam, bentazepam |
| Porphyria | Clonazepam, metaclazepam |
| Weight gain | Clobazam, clonazepam, ketazolam |

| **Gastrointestinal effects** | |
|---|---|
| Anorexia | Estazolam, flurazepam, loprazolam, lormetazepam, metaclazepam, nitrazepam, quazepam, temazepam Burning mouth syndromeClonazepam |
| Constipation | Adinazolam, alprazolam, clonazepam, delorazepam, diazepam, estazolam, flurazepam, metaclazepam, quazepam, tetrazepam |
| Diarrhea | Alprazolam, clobazam, medazepam, clonazepam, flunitrazepam, flurazepam, loprazolam, metaclazepam, tetrazepam |
| Dry mouth | Adinazolam, bentazepam, brotizolam, clobazam, clonazepam, clorazepate, estazolam, etizolam, flurazepam, flunitrazepam, halazepam, ketazolam, loprazolam, metaclazepam, prazepam, quazepam, temazepam, tetrazepam, triazolam |
| Dyspepsia | Bentazepam, quazepam, temazepam |
| Dysphagia | Nitrazepam, clobazam |
| Encopresis | Clonazepam |
| Epigastric pain | Bentazepam, flurazepam, loprazolam, metaclazepam |
| Flatulence | Estazolam |
| Gastritis | Clonazepam |
| Heartburn | Bentazepam, flurazepam, loprazolam |
| Increased salivation | Alprazolam, clonazepam, clobazam, diazepam, flurazepam, midazolam, nitrazepam, tetrazepam |
| Taste alterations | Alprazolam, flurazepam, midazolam |
| Vomiting and nausea | Adinazolam, alprazolam, temazepam, diazepam, quazepam, etizolam, brotizolam, clobazam, clonazepam Loprazolam, clotiazepam, delorazepam, estazolam, midazolam, flunitrazepam, flurazepam, halazepam, ketazolam, lormetazepam, medazepam, tetrazepam |
| Worsening GERD symptoms | Diazepam |

| **Hematologic effects** | |
|---|---|
| Agranolocytosis | Estazolam |
| Anemia | Chlordiazepoxide, diazepam |
| Granolocytopenia | Flurazepam |
| Leukocytosis | Alprazolam |
| Leukopenia | Estazolam, flurazepam, oxazepam |
| Neutropenia | Diazepam |
| Pancytopenia | Alprazolam, diazepam |
| Thrombocytopenia | Chlordiazepoxide, diazepam, clonazepam |
| Ttp | Chlordiazepoxide |

| **Hepatotoxicity** | |
|---|---|
| Cholestasis | Chlordiazepoxide, diazepam, flurazepam, triazolam |
| Elevated bilimbin | Alprazolam, chlordiazepoxide, clorazepate, flurazepam |
| Elevated hepatic enzymes | Alprazolam, bentazepam, chlordiazepoxide, clonazepam, flurazepam, medazepam,metaclazepam |
| Hepatitis | Clotiazepam |
| Hepatomegaly | Clonazepam |
| Jaundice | Alprazolam, chlordiazepoxide, clorazepate, diazepam, flurazepam, metaclazepam, oxazepam |

| **Ophthalmologic disturbances** | |
|---|---|
| Blurred vision | Alprazolam, bentazepam, temazepam, clonazepam, clorazepate, diazepam, flurazepam, medazepam, midazolam, triazolam |
| Brown opacification | Diazepam |
| Burning eyes | Flurazepam, temazepam |

| **Ophthalmologic disturbances** | |
|---|---|
| Decreased intra ocular pressure | Midazolam |
| Diplopia | Alprazolam, clorazepate, delorazepam, diazepam, medazepam, metaclazepam,midazolam |
| Induction or potentiation of increased IOP in closed-angle glaucoma | Diazepam |
| Induction of blepharospasm | Etizolam |
| Mydriasis | Alprazolam |

| **Respiratory system effects** | |
|---|---|
| Cough | Flunitrazepam, midazolam |
| Pulmonary edema | Chlordiazepoxide |
| Respiratory arrest (apnea) | Alprazolam, clonazepam, flurazepam, midazolam, nitrazepam |
| Respiratory depression | Alprazolam, clonazepam, delorazepam, diazepam, flunitrazepam, loprazolam, midazolam, nitrazepam |
| Rhinorrhea | Clonazepam |
| Shortness of breath | Clonazepam, flurazepam, midazolam, temazepam |
| Tachypnea | Midazolam |

| **Dermatologic effects** | |
|---|---|
| Bullous reactions | Alprazolam |
| chronic pigmented purpuric eruption | chlordiazepoxide |
| Dermatitis | Alprazolam |
| Edema | Clonazepam |
| Erythema annulare centrifugum | Etizolam |
| Erythematous rash | Alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, delorazepam, diazepam, etizolam, flurazepam, lormetazepam, medazepam, oxazepam, pinazepam, prazepam, quazepam, tetrazepamFixed eruption Chlordiazepoxide, lormetazepam, temazepam |
| Hair loss | Clonazepam |
| Hirsutism | Clonazepam |
| Hyperpigmentation | Diazepam |
| Morbilliform erythema | Chlordiazepoxide |
| Photosensitivity | Alprazolam, chlordiazepoxide, tetrazepam |
| Pmritus | Flurazepam, metaclazepam, prazepam, quazepam |
| SLE | Chlordiazepoxide |
| Sweating and flushing | Flurazepam |
| Sweet's syndrome | Diazepam |
| Utricaria | Clotiazepam, diazepam, chlordiazepoxide |

| **Genitourinary system effects** | |
|---|---|
| Fanconi syndrome | Clobazam |
| Incontinence | Clonazepam, delorazepam, diazepam, loprazolam |
| Precocious development | Clonazepam |
| Sexual dysfunction (impotence) | Bentazepam, chlordiazepoxide, diazepam, ketazolam, medazepam,metaclazepam, pinazepam, tetrazepam |
| Urinary retention | Diazepam |

| **Musculoskeletal system effects** | |
|---|---|
| Arthralgia | Estazolam, flurazepam |
| Asthenia | Bentazepam |
| Muscle spasm | Diazepam, estazolam, metaclazepam, tetrazepam |
| Myalgia Bentazepam, | estazolam, flurazepam |
| Rhabdomyolysis secondary to hypontremia | Temazepam |

| **Auditory system** | |
|---|---|
| Tinnitus | Brotizolam, chlordiazepoxide, flurazepam, oxazepam, triazolam |

| **Miscellaneous** | |
|---|---|
| Compartment syndrome | Diazepam, Triazolam |
| Death | Nitrazepam |
| Hiccups | Chlordiazepoxide, delorazepam, diazepam, flunitrazepam |
| Triazolam syndrome (reversible delirium, automatic movements and anterograde amnesia) | Triazolam |
| Thrombophlebitis | By all BZDs after iv injection |
| Vasculitis | Diazepam |

## REFERENCES


1. Davies, D.M., R.E. Ferner and H. DeGlanville (Eds.), 1998. Davies's Textbook of Adverse Drug Reactions. 5th Edn., London, Chapman and Hall Medical.
2. Fauci, A.S., 1998. Harrison's Principles of Internal Medicine. 14th Edn. Toronto, McGraw-Hill.
3. Gold, M.S., N.S. Miller, K. Stennie and C. Populla-Vardi, 1995. Epidemiology of benzodiazepine use and dependence. Psych. Ann., 25:146-8.
4. Janicak, P.G., 2001. Principles and Practice of Psychopharmacotherapy. 3rd Edn., Philadelphia, Lippincott Williams and Wilkins.
5. Wonsiewicz, M.J., 2001. Adams and Victor's Principles of Neurology. 7th Edn., Philadelphia, McGraw-Hill.
6. Roache, J.D. and R.A. Meisch, 1995. Finding from self-administration research on the addiction potential of benzodiazepines. Psych. Ann., 25: 153-7.
7. Longo, L. and B. Johnson, 2000. Addiction: Part 1. Benzodiazepines side effects, abuse risk and alternatives. Am. Fam. Physician, 61: 2121-8.
8. Moller, H., 1999. Effectiveness and safety of benzodiazepines. J. Clin. Pharmacol., 19: 2S-11S.
9. Epstein, D.L., 1997. Chandler and Grants Glaucoma. 4th Edn., Baltimore, Williams and Wilkins.
10. Janicak, P.G., J.M. Davis, S.H. Preskorn and Jr. F.J. Ayd, 2001. Treatment with Antianxiety and Sedative Hypnotic Agents. Principles and Practice of Psychotherapy. 3rd Edn., Philadelphia: Lippincott: Williams and Wilkins, pp: 471-512.
11. Greenblatt, D.J., 1991. Benzodiazepine hypnotics: Sorting the pharmacokinetic facts. J. Clin. Psychiatry, 52: 4-10.
12. Abdollahi, M., M. Rahbar-Haghighat and K. Soltaminejad, 2002. Prevention by flumazenil of benzodiazepines-suppressed of rat submandibular gland function. Ind. J. Pharmacol., 34: 164-171.
13. Abdollahi, M. and M. Radfar, 2003. A review of drug-induced oral reactions. J. Contemp. Dent. Pract., 4: 10-31.
14. Micromedex Healthcare Series, Drugdex. 2004. Vol(119).
15. Weinberg, D.S. and S.L. Kadish, 1996. The diagnosis and management of gastroesophageal reflux disease. Med. Clin. North Am., 80: 411-429.
16. Luton, E.F. and R.N. Finchum, 1965. Photosensitivity reaction to chlordiazepoxide. Arch. Dermatol., 91: 362-3.
17. Blair, H.M., 1974. Fixed drug eruption from chlordiazepoxide: Report of a case. Arch. Dermatol., 109:914.
18. Jafferany, M. and T.S. Haroon, 1988. Fixed drug eruption with lormetazepam (Noctamid). Dermatologica, 177: 386.
19. Archer, C.B. and J.S.C. English, 1988. Extensive fixed drug eruption induced by temazepam. Clin. Exp. Dermatol., 13: 336-8.
20. Nishioka, K., I. Katayama and M. Masuzawa *et al.*, 1989. Drug-induced chronic pigmented purpura. J. Dermatol. (Tokyo), 16: 220-2.
21. Almeyda, J., 1971. Drug reactions X III. Cutaneous reactions to imipramine and chlordiazepoxide. Br. J. Dermatol., 84: 298-9.
22. Fernandez-Real, J.M. *et al.*, 1994. Hyponatremia and benzodiazepines result in rhabdomyolysis. Ann. Pharmacother., 28: 1200-1.
23. Strohmaier, A. and M. Friedrich, 1991. Nicht-traumatisches Compartmentsyndrom beider Unterschenkel infolge einer akuten Rhabdomyolyse. Fortschr. Rontgenstr., 15: 277-279.
24. Abdollahi, M., H. Karimpour and S. Khalaj, 2003. Drug-induced skin reactions. J. Pharm. Pract. Res., 33: 12-15.
25. Wakakura, M., T. Subouchi and J. Inouye, 2004. Etizolam and benzodiazepine induced blepharospasm. J. Neurol. Neurosurg. Psych., 75:506-507.