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Management of Benzodiazepine Dependence and Toxicity

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ABSTRACT

The key target of this review is to compare the efficacies of the different adjuncts and methods used in the management of benzodiazepine dependence (tolerance and withdrawal) and poisoning. A systemic review of randomized controlled trials was carried out to determine which method of adjuvant therapy can be best used to overcome the withdrawal symptoms exhibited during benzodiazepine discontinuation. In addition, different tapering methods employed have also been presented in this review. Zolpidem in combination with cognitive behavioural therapy with a parallel gradual taper after conversion to long half-life Benzodiazepine seems to be a promising method among the several analysed. Finally the efficacies of the two available methods to combat benzodiazepine toxicity, namely flumazenil and naloxone have been discussed and compared.

INTRODUCTION

Benzodiazepines were introduced in the 1950s and became hugely popular as time went on. Especially in the 1970s their popularity reached a peak because of the versatility of their use in different disorders (Ashton, 2005). General practitioners prescribed about 80% benzodiazepines, which are the most frequently prescribed drugs after drugs used in heart and circulatory problems (Woods *et al*., 1992).

Benzodiazepines are used in both short and long term therapy. An average of 10% of the population used benzodiazepines as tranquilizer in sedation for minor surgical operations and/or hypnotics for insomnia, one-third on a regular basis and the rest for longer period of time (more than 180 days), who were called long-term users (Mellinger *et al*., 1984). Moreover, they are also used as anxiolytics against panic disorders and general anxiety. The use of the drug extends to as myorelaxant and also anticonvulsants to treat some forms of epilepsy and alcohol withdrawal symptoms. As their use widened, by the early 1980s long-term users had realized that the drugs tended to lose their efficacy over time and instead became associated with adverse effects. In particular, patients found it difficult to stop taking benzodiazepines because of addiction that caused withdrawal symptoms (Ashton, 2005).

This resulted in a phenomenon known as 'dependence' which is defined by the World Health Organization as a strong desire or sense of compulsion to take a substance, difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others (Lader, 2011).

Present criteria for substance dependence include tolerance, escalation of dosage, continued use despite efforts to stop and knowledge of adverse effects, other behavioural features, and withdrawal symptoms. Withdrawal symptom, as previously mentioned, has been described for patients who discontinue therapeutic doses of benzodiazepines administered on a long-term basis (Winokur *et al.*, 1980; Petursson and Lader, 1981; Rickels *et al.*, 1983; Busto *et al.*, 1986). Estimate of the occurrence rate for the benzodiazepine withdrawal symptoms range from 0% to 100%, based on discontinuation of benzodiazepines after long-term naturalistic treatment (Petursson and Lader, 1981; Bowden and Fisher, 1980). The table-1 assorts an array of common withdrawal symptoms:

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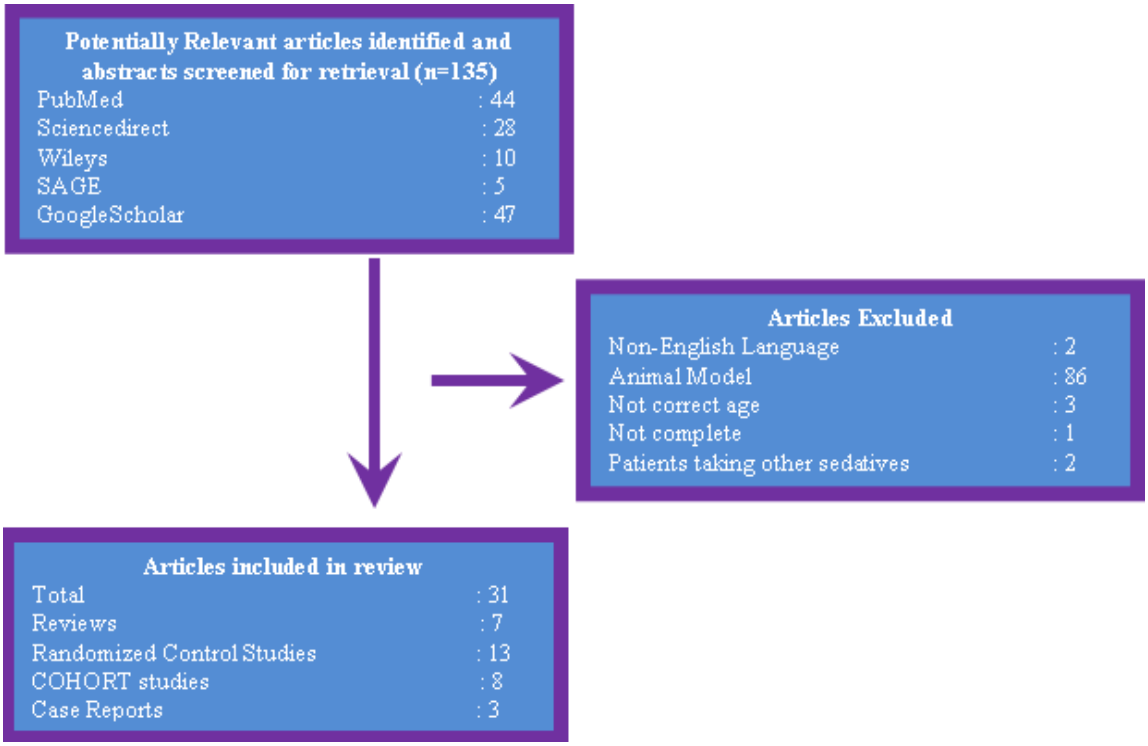

Fig. 1: Study selection flow diagram.

In sufficiently large doses of benzodiazepines can cause coma, respiratory depression (Abramowicz, 1991) and death (Caplehorn and Drummer, 1999). Severe toxicity is often related to co-ingestion, especially alcohol and opiates, and advanced age is an additional risk factor for severe toxicity (Buckley *et al.*, 1994).

METHODOLOGY

Aims and Objectives

The aim of this review was to compare the different adjuncts and tapering methods suggested for the management of dependence (tolerance and withdrawal) and toxicity arising from benzodiazepines. Each method was studied and the relative success rates of the different adjuncts were compared along with their relative efficacies. The main objective was to give a rational suggestion regarding preferable method for treating dependence and poisoning.

Data sources

Individual search strategy was employed by the authors after consultation with other co-workers. Title searches were made in relevant search engines including PubMed, Springerlink, ScienceDirect, MEDLINE, Google Scholar, SAGE Journal, and Wiley Interscience. Bibliographies of acquired articles were also investigated.

Study selection criteria

Inclusion criteria

Studies were selected which were (a) randomized controlled trials (RCTs), cohort studies. (b) evaluated at least 5 participants. (c) Enrolled a sizeable variety of participants that included both males and females (d) Age >13 years.

Exclusion criteria

Those studies were excluded that were (a) not written in English language (b) incorporated children (age < 13) or, animal models (c) included patients taking other sedatives.

Keywords used in searching

The searching was done based on the words or alternative words to ‘tolerance’, ‘dependence’, ‘benzodiazepine’, ‘withdrawal’, ‘toxicity’, ‘management’, ‘tapering’, ‘randomized controlled trial’, ‘poisoning’.

Data Extraction

Five authors vigorously analyzed the titles and abstracts retrieved through searches in relevant search engines. The following data were extracted: year of publication, population characteristics, population number, study design, outcome measured, and duration of the study.

RESULTS

The following Figure **1 and Tables (2 - 5)** summarize the results of article search. A total of 134 articles were studied via their abstracts. They were collected form websites like PubMed, Sciencedirect, Wileys, SAGE and Google Scholar. 13 were selected for final review and the rest were excluded since they met the exclusion criteria. Some cohort studies, case reports were also selected for additional information to support the review.

T**able 1:** Withdrawal Symptoms of Benzodiazepines.

Type	Symptoms
Adrenergic	Anxiety, nervousness, restlessness, agitation, loss of appetite, diaphoresis, nausea
Lethargy	Irritability, fatigue, loss of drive, lethargy, dysphoric mood, constipation
Disequilibrium	Lightheadedness, dizziness, poor coordination, tinnitus, perceptual distortions
Confusional	Increased acuity for sound and smell, difficulty with concentrating, Depersonali-zation, difficulty with expressing thoughts, confusion, nightmares
Neurasthenia	Weakness, tremor, tremulousness
Muscular	Muscle cramps, muscle fasciculations
Individual	Insomnia, headaches, diarrhoea

(Ashton, 2005; Rickels *et al.*, 1990; Lader *et al.*, 1984; Ashton, 2002)

Table. 2: Characteristics of the selected studies & target population.

Reference	Study characteristics	Demographic Data	
		Age (years)	Sex (M/F)
Isbister *et al.*, 2003	Randomized controlled trial	14 – 73	3081
Gerra *et al.*, 2002	Single blinded randomized trial	19–44	26/24
Vissers *et al.*, 2006	Randomized placebo-controlled discontinuation trial	≥80	16/22
Garfinkel *et al.*, 1999	In period 1, subjects were randomized (double-blinded) and in period 2, they were single blinded	40-90	9/25
Peles *et al.*, 2007	Double blind randomized clinical trial	42.6 ± 1.2	43/18
Solhi *et al.*, 2010	Randomized clinical trial	28±11	43/73
Hojer *et al.*, 1988	A Double-blind Controlled Study	19-92	21/31
Allain *et al.*, 1998	Randomized, double-blind, placebo-controlled clinical trial	32-84	27/57
Closser *et al.*, 1994	Randomized clinical trial	43-72	1/5
Otto *et al.*, 1993	Randomized controlled trial	27-55	11/22
Weinbroum *et al.*,1996	Double blind, randomized controlled study followed by a prospective, open study.	110	Not Given
Spivey *et al.*, 1993	Double blind, randomized controlled study	170	
Hojer *et al.*, 1990	Double blind, randomized controlled study	17-83	46/59

Table. 3: Different adjuncts for benzodiazepine withdrawal management & their outcomes.

Adjunct used		Results (Discontinuation of benzodiazepines)
Melatonin	Garfinkel *et al*., 1999	Melatonin group (77.7%), Placebo group (25%)
	Vissers *et al*., 2006	Melatonin group (60%), placebo group (50%). Although only 40% of the patients could stay away from benzodiazepines after 1 year.
	Peles *et al*., 2007	Melatonin (35.48%), placebo group (36.66%).
Zolpidem	Allain *et al*., 1998	Zolpidem group (94.44%), Placebo group (87.5%)
Flumazenil	Gerra *et al.*, 2002	Oxazepam plus flumazenil group (60%), Oxazepam plus placebo group (30%)
Chlodiazepoxide	Closser *et al.*, 1994	High rate of benzodiazepine discontinuation of therapy due to less withdrawal symptoms (60%)
Cognitive behavioral therapy	Otto *et al.*, 1993	Cognitive-behavioral program group (76%), Slow taper group alone (25%)
	O'Connor *et al.*, 2008	Group Support group (85%), Cognitive Behavioral group (82.6%), normal tapering group (39%)

Table. 4: Different tapering protocols of benzodiazepines and their outcomes.

Article	Tapering protocol	Outcome (Discontinuation of benzodiazepine)
Garfinkel *et al*., 1999	Dosage reduced 50% during week 2, 75% during weeks 3 and 4, and then 100% during weeks 5 and 6.	Study group – 25% (4 out of 16)
Vissers *et al*., 2007	Benzodiazepine was converted to an equivalent dose of diazepam that was stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose.	Study group – 50% (9 out of 18)
Schweizer *et al.*, 1990	25% per week taper.	Long half-life – 68% , Short half-life – 58%

Table 5: The tapering protocol of diazepam:

Week	Method 1 (mg)	Method 2 (mg)	Method 3 (mg)
1	10mg	10mg	10mg
2	5mg	10mg	7.5mg
3	3.75mg	7.5mg	5.6mg
4	2.81mg	7.5mg	4.2mg
5	0mg	3.75mg	3.2mg
6	0mg	3.75mg	2.4mg
11		0mg	0.56mg
18			0mg

Tapering protocols

Method - 1 (Garfinkel *et al*., 1999)

Patients were encouraged to reduce their usual benzodiazepine therapy dosage 50% during week 2, 75% during weeks 3 and 4, and then to discontinue benzodiazepine completely during weeks 5 and 6.

Method – 2 (Vissers *et al*., 2006)

Their Benzodiazepine was converted to an equivalent dose of diazepam that was stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose.

Method – 3 (Schweizer *et al*., 1990)

Tapering of 25% per week of short half-life vs Long half-life benzodiazepines in 63 benzodiazepine-dependent patients was employed. For example: dose reduction of diazepam 10mg in the aforementioned methods:

Toxicity

Two studies show that Modified Glasgow Coma Scale score before administering flumazenil or placebo were 6.4, but after administration of placebo and flumazenil to their respective group, there was a significant change in the flumazenil group. The Modified Glasgow Coma Scale score in flumazenil group averaged 13, whereas the Modified Glasgow Coma Scale score of placebo group averaged 7.3. (Hojer and Baeerendtz, 1988)

However, two case studies showed that after administration of flumazenil, patients developed serious side effects like tachycardia, severe convulsions and bradycardia (Burr *et al.*, 1989; Merchant *et al.*, 1989).

But in case of naloxone injection, all signs and symptoms significantly improved in all drug types in comparison to control groups except nystagmus. In addition, level of consciousness significantly improved in case groups in all drug types except lorazepam (Solhi *et al.*, 2010).

DISCUSSION

Melatonin therapy significantly facilitates the discontinuation of benzodiazepine therapy for long-term users compared with placebo. Despite the high rate of benzodiazepine therapy discontinuation in the CRM (Controlled Release Melatonin) therapy group, sleep quality did not diminish. Some patients who could not stop benzodiazepine therapy completely reduced their dosages while receiving melatonin. Long-term benzodiazepine therapy may impair the endogenous melatonin rhythm, which may in turn induce or aggravate sleep disturbances. Administration of melatonin may break this vicious cycle by normalizing the night peak of melatonin and reinstating a robust nocturnal melatonin signal that results in improved night sleep (Garfinkel et al., 1999). In a separate trial, the positive outcome of Garfinkel et al could not be confirmed. In general, readiness to stop using benzodiazepine sleeping medication was low. In contrast to that of Garfinkel et al., at the end only 9% still used melatonin. Four participants changed their use to a homeopathic or phytotherapeutic medication, which indicates a basic need to use something for their sleeping problem (Vissers *et al.*, 2006). In another study the outcome of Garfinkel was contrasted. This study showed that there was no significant difference between the 'melatonin' and 'placebo' group except a slight increase in sleep quality in the melatonin group. Hence the effectiveness of melatonin in assisting the withdrawal of benzodiazepines remains doubtful (Peles *et al.*, 2007).

Another study showed that zolpidem, 10 mg once daily dose at bed time, reduced the occurrence of withdrawal symptoms induced by the abrupt or gradual discontinuation of long term triazolam treatment in outpatients with insomnia. The rational pharmacological explanation of how a non-benzodiazepine hypnotic can safely antagonize withdrawal from long-term triazolam treatment has still to be determined (Allain *et al.*, 1998).

Flumazenil treatment, associated with low doses of oxazepam, was found more effective in the treatment of the withdrawal syndrome in BZD tolerant patients. These preliminary data, obtained with a single blind protocol in a small sample of subjects, need to be interpreted with great caution. However, flumazenil may be regarded as a therapeutic option in the treatment of BZD withdrawal particularly in subjects who have developed severe dependence and tolerance with a history of prolonged BZD abuse who cannot cope with the withdrawal symptoms provoked by tapering treatment (Gerra *et al.*, 2002). On the other hand inpatients on a chemical dependency unit successfully tolerated rapid withdrawal from alprazolam in doses of 2-6 mg daily when chlordiazepoxide was substituted in adequate doses and then tapered over l-2 weeks. When the amount of chlordiazepoxide was individualized, cross-dependence occurred, and seizures were prevented. The mean follow-up period (2 weeks) was too short to observe the full course of withdrawal (2-4 weeks) (Mary *et al.*, 1994).

Cognitive behavioral program as an adjunct to the conservative taper and regular monitoring is recommended for benzodiazepine discontinuation. It was found that cognitive behavioral therapy decreased occurrence of panic disorders. Interceptive exposure (exposure to somatic sensations of anxiety) and cognitive interventions were used to decrease fears and catastrophic misinterpretations of emergent panic sensations and withdrawal symptom, preparing patients for symptoms they might encounter during and after the discontinuation procedure. Symptom management skills, i.e., breathing retraining and relaxation procedures were taught to help patients decrease the intensity of these symptoms. The findings suggest that a brief, focused trial of cognitive behavioral therapy may permit successful discontinuation of benzodiazepine treatment without a general or sustained exacerbation of symptoms in patients with panic disorder (Otto *et al.*, 1993). These findings were also confirmed by the study of O'Connor *et al.*, 2008. Thus the efficacy

of cognitive therapy as an important adjuvant to benzodiazepine discontinuation have been established. The main findings of the tapering studies can be summarized as follows: (1) a gradual tapering of long-term therapeutic doses of benzodiazepines was well tolerated in all patients when judged by the absence of precipitated seizures, psychosis, or other serious withdrawal symptoms, or the need for inpatient management. Yet, physicians judged that almost 90% of both Long half-life and Short half-life benzodiazepine-treated patients experienced at least some benzodiazepine withdrawal symptoms. Clearly, therefore, a gradual taper did not prevent the occurrence of withdrawal symptoms in the patient sample, with the majority of withdrawal symptoms occurring during the last half of benzodiazepine taper. (2) Use of a gradual taper schedule minimized the contribution of benzodiazepine daily dose and half-life to withdrawal severity, which was observed with abrupt benzodiazepine discontinuation (Garfinkel *et al*., 1999; Vissers *et al*., 2006; Schweizer *et al.,* 1990). The longer weeks taken by Vissers *et al.,* 2007 to taper resulted in twice as better an outcome than Garfinkel *et al.,* 1999. Moreover, the longer half-life taper yielded slightly better results than the short half-life taper in Schweizer *et al.,* 1990. So, although gradual taper, with longer weeks and long half-life benzodiazepines, is seen to be superior over abrupt discontinuation of benzodiazepines, no particular tapering method proved significantly more efficacious than the other.

The clinical effects of benzodiazepine overdose were minor in the majority of cases, but alprazolam was significantly more toxic than other benzodiazepines. A previous study suggested that the variable toxicity of benzodiazepines may be related to different rates of absorption (Isbister *et al.,* 2003). The sedation produced by benzodiazepines in therapeutic doses and overdose has a poor correlation with measured drug concentration but is increased with rapid absorption. Temazepam is more rapidly absorbed and oxazepam is more slowly absorbed than most other benzodiazepines. Further research is required to determine if the rate of absorption is different in overdose and is sufficient to explain the differences in sedation (Buckley *et al.,* 1994). Similar to other poisonings, supportive therapy has the main role in management of this poisoning; however, we can use flumazenil, too. Although flumazenil is a specific antagonist of benzodiazepine receptors and has a rapid effect, it has some side effects such as cardiac complications and seizure, especially in mixed poisoning of benzodiazepins with other drugs. So, it has limited indications and its risk-benefit ratio must be considered in each patient individually. On the other hand, flumazenil is an expensive drug and since benzodiazepines are generally categorized as low-risk drugs and their pure poisoning seldom leads to death, in many centres, especially in developing countries, these poisonings are managed supportive and it seems that more low-priced and safer drug(s) must be considered in benzodiazepine poisoning (Hojer and Baeerendtz, 1988; Spivey *et al.,* 1993; Weinbroum *et al.,* 1996; Höjer *et al.,* 1990; Burr *et al.,* 1989; Merchant *et al.,* 1989). On the other hand, naloxone is a low priced drug that has been used in narcotic overdose for many years. Moreover, it is a low-risk drug, which has made it a very common drug in cases of coma due to poisoning. Because of its short half-life and rapid response, it has low side effects. Naloxone has been used limited and experimentally in some other drugs poisoning, too (Malin *et al.,* 1988). Since the effect of benzodiazepine on gamma-aminobutyric acid (GABA) receptors is well known, the beneficial effects of naloxone may be through blockage of GABAergic neurons (Solhi *et al*., 2010).

CONCLUSION

The conclusions of the review cannot be definite because of the lack of ample work on the subject. The use of melatonin, as shown by a latest work nullifies the suggestion of the work of other researchers and renders it dubious for assisting benzodiazepine withdrawal. The works of chlordiazepoxide and flumazenil are not conclusive either because the researches were conducted on a relatively small number of subjects for a short period of time. On the other hand, zolpidem can be considered as a useful adjunct in benzodiazepine withdrawal alongside cognitive behavioral therapy which also seems promising to be used in escape from benzodiazepine dependence.

Moreover, we are unable to suggest any particularly preferable taper protocol other than that it should be done slowly with the maximum allowable number of weeks and that the dose should be converted to long half-life benzodiazepines for a slightly better discontinuation rate of the drug. Nonetheless, withdrawal symptoms seem to be prevalent, especially in the later stages of the taper, nonetheless. The safety of benzodiazepines in overdose should be given enough consideration when they are prescribed. It can be concluded that although flumazenil is considered as useful tool in the treatment of drug overdose when benzodiazepines are involved. Its side-effects, limited indications and high price as well as other considerations call for another more efficient antidote. Naloxone could be another alternative owing to its proven efficacy in the management of benzodiazepine poisoning. However, future clinical trials comparing the efficacy among flumazenil and naloxone in the management of benzodiazepine overdose with greater sample size will be required for precise conclusion.

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