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Deprescribing of benzodiazepines and Z-drugs amongst the psychiatric patients of a tertiary care Hospital

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ABSTRACT

Background: In current clinical practice, regardless of the clinical guidelines, BZDs and Z drugs are used beyond the period of indication, resulting in undesirable effects. This study aimed to assess feasibility of deprescribing amongst patients utilizing BZDs and Z drugs inappropriately for longer duration than the prescribed period. The study also analysed the Quality of Sleep (QoS) and Cost Savings incurred amongst deprescribed patients.
Methods: It was a prospective interventional study conducted in IP and OP settings of Psychiatry Department, Bangalore, India. Based on inclusion criteria, 109 patients were recruited for the study for a period of 7 months. Deprescribing was advised to inappropriate BZD and Z-drug users by clinical pharmacist after discussing with the prescribing psychiatrist. The patients were followed-up twice in a month after deprescribing. QoS was assessed by using Pittsburg Sleep Quality Index (PSQI) scale. The total medications cost incurred per patient/month before and after the intervention among both the groups was measured.
Results: Post-intervention, 40(30.69%) BZD users were deprescribed i.e, either dose tapered 6(5.5%), completely ceased 27(24.8%) or on *si opus sit* (SOS) BZDs prescription 7(6.4%). A majority of 44(40.36%) patients continued BZDs according to the algorithm. Clonazepam 35(87.5%) was the most deprescribed BZD. Deprescribing of BZDs showed an association with QoS of patients, p-value (< 0.05). A statistically significant cost reduction was observed after deprescribing BZDs, ($Z = 5.465$, $p = < 0.001$).
Discussion: Deprescribing BZDs was associated with decline in its usage; implementing deprescribing practice amongst the inappropriate BZD users is feasible, provides an improved QoS and an economic benefit.

1. Background

Deprescribing is a relatively new term coined to describe the process of cessation or tapering of a medication or prescribing in an SOS basis that are not providing benefit to the patient or are exposing them to unacceptable risks (Reeve & Wiese, 2014; Reeve, Shakib, Hendrix, Roberts, & Wiese, 2014). Deprescribing mandates parallel monitoring and periodic review based on the medication and patient related factors (McKean, Pillans, and Scott (2016)); Page, Clifford, Potter, Schwartz, & Etherton-Beer, 2016). Benzodiazepines (BZDs) and Z drugs are group of compounds that belong to the hypnotic – sedative class with wide therapeutic applications in the treatment of anxiety, insomnia, panic disorder, social phobia, obsessive-compulsive disorder, drug withdrawal and the adverse effects induced by antidepressants and antipsychotics. Also, utilized as skeletal muscle relaxant and as anti-epileptic (Mehdi, 2012; Singh & Sarkar, 2016).

Inappropriate medication use in the form of over or under-prescribing increases morbidity and even death (Jhaveri, Patel, Barvaliya, & Tripathi, 2014). As per the clinical guidelines, BZD and Z-drugs should be prescribed for a limited duration as possible, with the maximum of four weeks and must be used as indicated, i.e. at standard therapeutic doses with only one type of BZD or Z-drug at a time for short-term relief of severe anxiety or insomnia. When BZD and Z-drugs are used accordingly, treatment is usually without potential side effects (Manthey, van Veen, & Giltay, 2011; Kurko & Saastamoinen, 2015).

Commonly reported ADRs of BZDs and related drugs include

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cognitive decline, physical dependence (58-100%) and psychomotor impairments like daytime fatigue, ataxia, hip fractures and road traffic accidents due to falls or postural instability (60%). Recently, there is an increased concern on premature mortality (OR > 1 in 33 studies) and increased risk of overdose (29.4%) (Paterniti, Dufouil, & Alperovitch, 2002; Van Der Hooft, Schoofs, Ziere, and Hofman (2008)); Pariente, Dartigues, & Benichou, 2008; Belleville, 2010).

A study conducted in India, has revealed that due to health illiteracy, patients are consuming medications for longer durations than required (Kamath & Kamath, 2017). Thus it is truism to state that prevention of chronic use (more than a month) is an essential part of BZD and Z-drug prescribing and, if strictly adhered to, dependency and withdrawal will be a theoretical rather than a practical issue. Nonetheless, a great number of patients continue to use BZDs and Z-drugs on a long-term basis and it is necessary to plan withdrawal programmes very carefully (Ferguson, 2012).

According to a review on deprescribing, the barriers of patient willingness to deprescribe includes fear i.e psychological issues related to cessation, fear of return of condition, fear of withdrawal effects (Reeve et al., 2013). Also, the commonly cited barriers towards deprescribing amongst the physicians were unwillingness to stop medications prescribed by another doctor, lack of time and insufficient knowledge to deprescribe (Nadarajan, Balakrishnan, Yee, & Soong, 2018).

Clinical pharmacists and psychiatrists play an important role in educating the patients on deprescribing practices thereby increasing the patient's medication knowledge, patient engagement in medication management and resolution of Drug Related Problems (DRPs), promote life style modifications and also reduce the financial burden (Kamath & Kamath, 2017; Reeve & Wiese, 2014).

Current studies are focussed on assessing the feasibility of introduction of deprescribing practices and study the factors influencing the deprescribing practices (Reeve et al., 2014).The literature reveals that very few studies are conducted on the concept of deprescribing and this is the first study that has looked upon assessing the feasibility of deprescribing among the inappropriate BZDs and Z-drug users in India. Hence the current study was conducted to assess the feasibility of BZDs and Z drug deprescribing among patients of the Department of Psychiatry.

2. Methods

2.1. Study design and ethics

This is a prospective, interventional study carried out for a period of 7 months from August 2017 to February 2018 in the inpatient and outpatient settings of the Department of Psychiatry at a tertiary care Hospital, Bangalore, Karnataka. The study protocol was reviewed and approved by the Institutional Ethics Committee.

2.2. Participants

All patients above 18yrs who were already prescribed with BZD or Z-drugs were included for the study. Elderly patients aged above 85yrs, patients on antiepileptic medications for seizure disorder and patients with history of alcohol dependence were excluded from the study.

A total of 109 patients were recruited based on the inclusion criteria. The study was performed by collecting relevant data from the patient's prescription forms, case records and by interviewing the patients or care takers. The BZD and Z-drug deprescribing was initiated after obtaining consent from the prescribing psychiatrist and patient based on Benzodiazepine and Z-drug (BZRA) Deprescribing algorithm (Pottie et al., 2018). The data was collected employing well-designed patient data collection form. Withdrawal symptoms after tapering or cessation of BZDs and Z-drugs were assessed using the Benzodiazepine Withdrawal Symptom Questionnaire [BWSQ] (Tyrer, Murphy, & Riley, 1990). The difference in sleep quality of patients using BZD and Z-drug before and after deprescribing was assessed by the Pittsburg Sleep Quality Index (PSQI) scale.

2.3. Intervention

Deprescribing process was performed in the following steps:

(1) Comprehensive medical and medication history: Patient history was taken which includes the signs and symptoms, history, past psychiatric consultation, laboratory data, social history, family history, prescription and non-prescription medications, dose, frequency, formulation, route of administration, duration of use and patient reported indication, specific allergies, intolerances and ADRs. Patients with primary or secondary insomnia with underlying comorbidities, sleeping disorders (eg., restless legs), anxiety and depression, physical or mental condition that may be causing or aggravating insomnia, were identified and maintained on BZDs or Z-drugs.

(2) Potentially inappropriate BZD or Z-drug (more than 4weeks) use was identified.

(3) Shared decision making for facilitation of deprescribing was done by involving patients and the psychiatrist in discussions regarding potential risks, benefits, withdrawal plan, symptoms and duration. If any contraindications for withdrawal exist, the reasons for the same were documented.

(4) Withdrawal plan and initiation: BZD or Z-drug dose was tapered and then stopped (in collaboration with patient) and advised on good practices to improve sleep.

(5) Monitoring and Documentation - The patients were monitored for rebound symptoms twice a month depending on the duration of tapering and discontinuation of BZDs or Z-drugs. In case of occurrence of withdrawal symptoms, current BZD or Z-drug dose was maintained for 1-2 weeks then continued to taper at slow rate or alternate drugs were chosen.

2.4. Statistical analysis

The categorical variables were presented using frequencies and percentages. Chi-square test was employed to compare the differences in QoS with deprescribing and continuing BZDs or Z-drugs groups. The total medications cost per patient before and after the intervention among both the continuing and deprescribed groups of BZDs or Z-drugs were calculated. The median medications cost and interquartile range among both groups were compared. Wilcoxson signed rank test was applied to test the statistical significance of cost reduction among both the groups. P-value < 0.05 was considered as statistically significant. Data was coded and analysed using IBM SPSS Statistics version 21.0 for windows.

3. Results

3.1. Study population characteristics and demographic information

(Table 1)

A total of 109 BZD or Z-drug users were enrolled in the study of which 62(56.88%) were males and 47(43.11%) were females. Amongst all age groups, prevalence of BZD use, were found to be higher 59(54.12%) among patients between18-35years, followed by 38(34.86%) among patients in the range of 36-55years. 34(31.19%) were admitted in Inpatient (IPD) whereas 75(68.80%) were treated on Outpatient Department (OPD) basis.76(69.72%)were married whereas 32(29.35%) were unmarried. 39(35.77%) were employed whereas 48(44.03%) were unemployed. Clonazepam 91(83.5%) was the most commonly prescribed BZD followed by lorazepam 13(11.9%). The remaining 5 patients were prescribed with alprazolam 1(0.9%), diazepam 1(0.9%) and zolpidem 3(2.8%). 10(9.2%), 36(33%) and 63(57.7%) were found to use BZDs < 4weeks, < 3months and > 3months

Table 1
Study population characteristics and demographic information.

Characteristics	N (%)
Age	59 (54.12%)
18-35yrs	
36-55yrs	38 (34.86%)
56-65yrs	4 (3.66%)
66-85yrs	8 (7.33%)
Sex	62 (56.88%)
Male	
Female	47 (43.11%)
Category	34 (31.19%)
Inpatient	
Outpatient	75 (68.80%)
Marital Status	76 (69.72%)
Married	
Unmarried	32 (29.35%)
Others(widower, remarried, separated, divorced)	1 (0.917%)
Employment	39 (35.77%)
Employed	
Unemployed	48 (44.03%)
Self employed	22 (20.18%)
Type of BZD prescribed	91(83.5%)
Clonazepam	
Lorazepam	13 (11.9%)
Alprazolam	1 (0.9%)
Diazepam	1 (0.9%)
Zolpidem	3 (2.8%)
Duration of Use	10 (9.2%)
< 4 weeks	
< 3months	36 (33%)
3 -6months	34 (31.2%)
6-12 months	19 (17.4%)
> 1 year	5 (4.6%)
> 2years	5 (4.6%)

respectively.

3.2. Deprescribing of benzodiazepines study flow chart

(Fig. 1)

A total of 109 patients utilizing BZDs were screened, of which 109 patients consented for the assessment of BZD use. On assessment we found, 10 patients were using BZDs as appropriate (rational utilization) i.e, less than 4 weeks duration. Whereas, 36 and 63 patients utilizing BZDs for short term (less than 3 months duration) and long term (more than 3months duration) respectively were considered inappropriate. These 99 inappropriate BZD users were potentially suitable candidates for withdrawal. Of the 99 patients, 2 self-discontinued, 10 were lost during follow up, 3 changed physician and 44 continued BZD use. BZDs were continued by 44 patients as feasibility of deprescribing was not attained as per the algorithm. Henceforth, of the 99 inappropriate BZD users, 40 patients approached to consent for deprescribing. Dose tapering was started for 33 patients and 7 were prescribed on SOS basis. Amongst the 33 patients who were started on dose tapering, 27 were completely ceased and 6 were advised to continue the tapered use. Clonazepam 36(32%) was the most deprescribed BZD followed by lorazepam 4(4%).

3.3. Age distribution of benzodiazepine deprescription

(Fig. 2)

A total of 4(50%) BZD users in the age group of 66-85 years followed by 14(36.84%) in the age group of 36-55 years and 21(35.59%) in the age group of 18-35 years were deprescribed.

3.4. Disease and type of benzodiazepines deprescribed

(Table 2)

Most common diagnosis (according to ICD-10) for which the BZDs were deprescribed among the inappropriate BZD users was found to be (F-41.0) Panic Disorder 6(5.50%).

Also, the PSQI questionnaire was employed for assessing the QoS. QoS of 84 subjects was assessed, since 10 subjects were lost during follow up, 3 subjects changed physician, 2 subjects self-discontinued and 10 were rationally deprescribed. In the deprescribed group of 40 subjects, a total of 38(95%) subjects had good sleep quality whereas 2(5%) had poor sleep quality.

3.5. Deprescription and benzodiazepines withdrawal symptoms

(Table 3)

The withdrawal symptom among the deprescribed patients was also assessed as per the BWSQ. Amongst the deprescribed group, 2(50%) and 36(100%) patients prescribed with lorazepam and clonazepam respectively had no withdrawal symptoms whereas the remaining 2(50%) of 4(100%) patients using lorazepam had moderate withdrawal symptoms.

3.6. Cost analysis of benzodiazepines continuation and deprescription

(Table 4)

Post intervention amongst the continuing group the median cost incurred was 244.92 (35.40-1606.60) and amongst the deprescribed group the median cost incurred was 230.39 (0.00-1101.30). Statistically significant cost reduction was observed after deprescribing BZDs ($Z = 5.465, p < 0.001$).

4. Discussion

In the present study a total of 109 BZD users were identified and their prescriptions were analysed. Of the entire study population, males 62(56.8%) were predominant BZD users as compared to the females 47(43.11%). This finding is similar to a study conducted by Meagher et al where males 88(56%) used BZDs predominantly than females 70(44%) (Raju & Meagher, 2005). Amongst all age groups, prevalence of BZD use, was highest in 18-35years, 59(54.12%) followed by 36-55 years, 38(34.86%). This is in contrast to a study conducted by Fourier et al which showed that elderly were heavy BZD users and its use was found to increase with age among both males (26%) and females (74%) (Fourrier, Letenneur, & Dartigues, 2001). Our study observed that 10(9.1%) subjects were appropriate BZD users (< 4weeks), 36(33%) subjects were short term users (< 3months) and 63(57.7%) subjects were long term users (> 3months).

Following intervention, of the 109 study participants, 10(9.2%) was lost during follow up. A total of 40 (30.69%) BZD users were deprescribed. The patients were dose tapered 6(5.5%), completely ceased 27(24.8%) and 7(6.4%) patients frequency of drug intake was converted to SOS basis. A total of 44 (40.36%) patients were advised to continue BZDs use due to various conditions like sleeping disorders (eg. Restless legs), unmanaged anxiety, depression, physical or mental condition that may be causing or aggravating insomnia, BZDs effective specifically for anxiety, as mentioned in the BZRA algorithm (Pottie et al., 2018). The remaining 2(1.8%) patients self-discontinued BZDs due to fear of dependence, 3(2.8%) changed physician and 10(9.2%) patients were deprescribed rationally (i.e. within 4 weeks duration).

According to another study conducted by Naono-Nagatomo et al., patients are prescribed with long term BZDs due to difficulty in reduction of BZDs. This study observed a gradual dose reduction of BZDs by adding ramelteon therapy for patients with long term insomnia. Addition of ramelteon containing regimens showed improvement in the patient symptoms and quality of life (Naono-Nagatomo et al., 2018).

A total of 4(50%) BZD users in the age group of 66-85 years followed by 14(36.84%) in the age group of 36-55 years and 21(35.59%) in the age group of 18-35 years were deprescribed. This implies

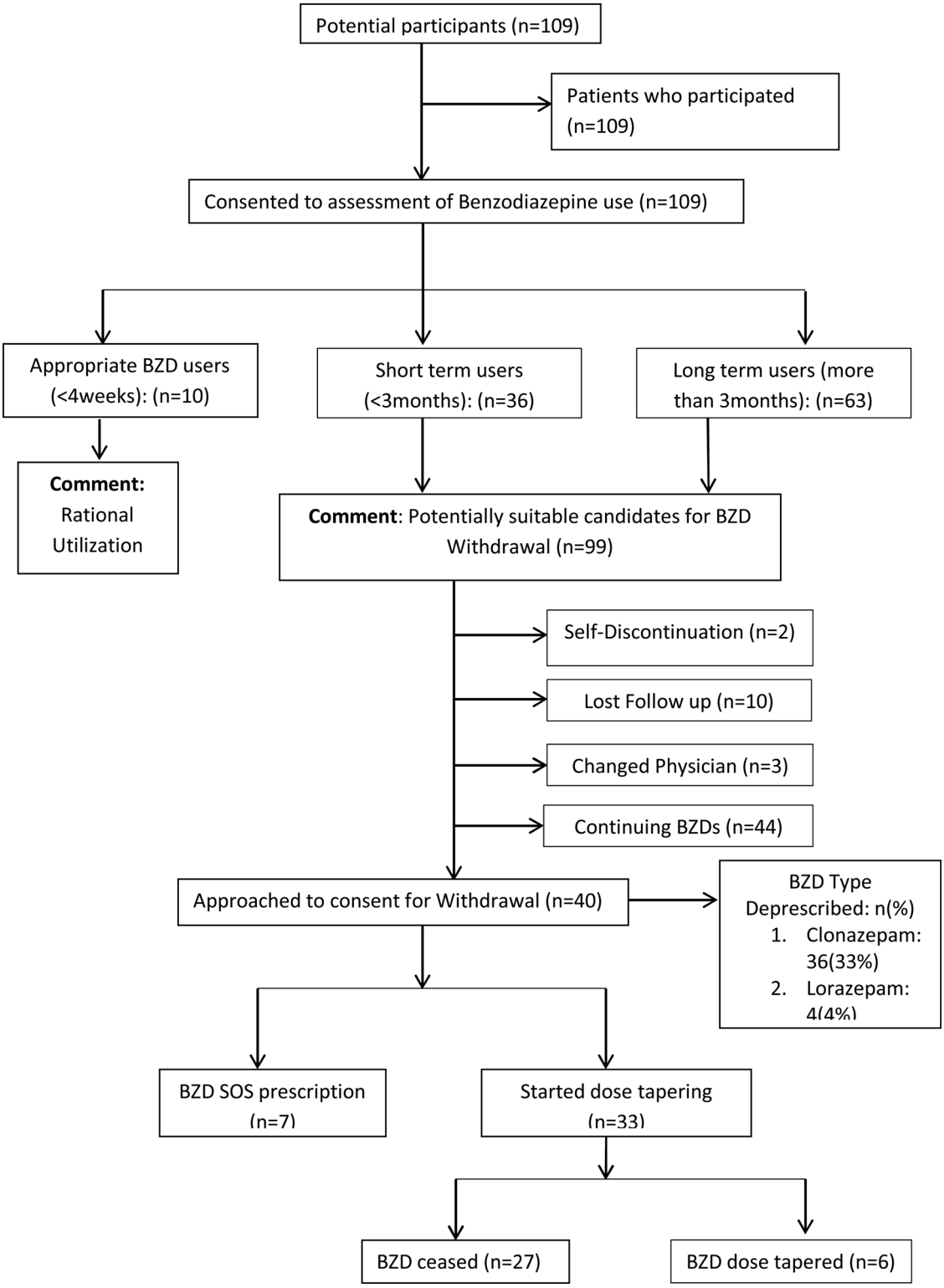

Fig. 1. Deprescribing of Benzodiazepines Study Flow Chart.

deprescription was relatively higher among elderly patients compared to adults.

A majority of 6(5.50%) patients who were deprescribed had panic disorder and 4(3.66%) patients had Bipolar Affective Disorder (BPAD) with current episode mania without psychotic symptoms and Obsessive Compulsive Disorder (OCD).Clonazepam 36(32%) was the most deprescribed BZD followed by lorazepam 4(4%).

The QoS of patients among deprescribed and continuing BZD use was assessed using the Pittsburg Sleep Quality Index (PSQI).In the deprescribed group of 40 subjects, a total of 38(95%) subjects had good QoS whereas 2(5%) had poor QoS. Among the patients who continued BZDs, 15(32%) had good QoS and 29(65%) had poor QoS. On applying Chi-Square test statistics to analyse the association of QoS between the deprescribed group and continuing group, the p-value was found to be < 0.05. It implies that there is an association of QoS with deprescribing BZDs and there can be improvements in QoS following

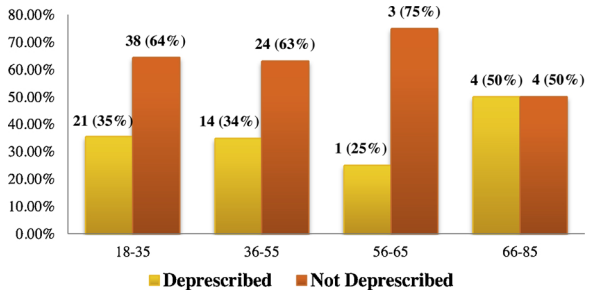

Fig. 2. Age distribution of BZD deprescription.

deprescription. This finding is similar to a study conducted by Wilson et al, where in the participants did not report significant worsening in their quality of sleep after BZD cessation (Wilson, Lee, & Hass, 2018).

BZD dependence was observed in 3(2.8%) patients. This is similar to a study conducted by Lader, 2011 where 3-4% of patients on BZDs showed clear signs of dependence (Lader, 2011).Upon follow up of the 40 deprescribed patients, the patients on clonazepam 36(100%) had no withdrawal symptoms when compared to the patients using lorazepam 2(50%) i.e, the other 2(50%) of 4 patients prescribed with lorazepam had moderate withdrawal symptoms following deprescribing when assessed through Benzodiazepine Withdrawal Symptom Questionnaire [BWSQ] (Tyrer et al., 1990). This is in contrast to another study conducted by Lader (2011) which showed that about 15-30% of patients after 4-6weeks of BZD use reported some sort of withdrawal symptoms when tried to discontinue BZDs (Lader, 2011). Also, the data from our study findings implies that the patients prescribed with an intermediate half-life BZD like clonazepam ($t_{1/2}$ = 18-39 hrs) or lorazepam ($t_{1/2}$ = 10-20 hrs) have relatively none or moderate withdrawal symptoms upon withdrawal when compared to short ($t_{1/2}$ = 1-4 hrs) or long half-life BZDs (30-210 hrs).

Cost savings of BZDs pre and post intervention was compared among the patients continuing and deprescribed of BZDs. Amongst the continuing group in the first quadrant the median cost incurred pre-intervention was found to be 245.36(35.40-2097.60), post intervention 0.44 INR/month/patient was reduced and the median cost incurred was 244.92 (35.40-1606.60).Similarly, amongst the deprescribed group in the first quadrant the median cost incurred pre-intervention was found to be 283.90(35.40-1722.89), post-intervention 53.51 INR/month/patient was reduced and the median cost incurred was 230.39 (0.00-1101.30). Wilcoxson signed rank test showed that deprescribing of BZDs among potential candidates who were eligible for deprescribing did elicit a statistically significant reduction in cost ($Z = 5.465, p < 0.001$). A cost reduction of approximately 54 INR/month/patient was observed among deprescribed study group. We have also analysed the non-deprescribed study group to understand the change in cost, however it was not statistically significant ($Z = 1.069, p = 0.285$). The cost saving addressed in this study should be considered as the least amount saved as we haven't measured the indirect cost incurred for the study subjects.

In conclusion, deprescribing of BZDs and Z-drugs among the inappropriate BZD and Z-drug users was pragmatic. This study highlights the importance of deprescribing based on shared decision model involving physician, pharmacist and patients to deprescribe inappropriate BZDs use. Implementation of deprescribing practice among long term BZDs and Z-drug users improves QoS and moderates the financial burden of patients. Enlightening of patients and doctors by clinical pharmacist about the benefits of deprescribing could help in implementation of better deprescribing practices.

5. Financial Disclosure

This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

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Table 2
Disease and type of BZDs deprescribed.

ICD-10 Diagnosis	Type of Benzodiazepines Deprescribed			Total
	Not Deprescribed	Clonazepam	Lorazepam	
F-11.2-Opioid dependence syndrome & withdrawal	1	0	0	1
F-31.1-BPAD current episode mania without psychotic symptoms	7	4	0	11
F31.2-BPAD current episode mania with psychotic symptom	4	0	0	4
F32.11-Moderate depression with somatic symptoms	6	3	0	9
F32.3-Severe depression without psychotic symptoms	1	0	1	2
F33-RDD	2	1	0	3
F34.1-Dysthymia	0	1	0	1
F40.01-Agoraphobia with panic disorder	0	1	0	1
F-12.2-Cannabis dependence syndrome	0	2	0	2
F40.1-Social phobia	3	1	0	4
F.41.0-Panic disorder	4	5	1	10
F-41.1-GAD	0	2	0	2
F-41.2-Mixed anxiety depression	4	1	0	5
F.42-OCD	4	4	0	8
F43.2-Adjustment disorder	4	2	0	6
F45.2- Hypochondriasis	2	0	0	2
F.99-Psychosis NOS	2	1	0	3
F.51.Insomnia	2	2	0	4
F13.2-BZD dependence syndrome	3	0	0	3
F20.0-Paranoid schizophrenia	8	2	0	10
F.20.3-Undifferentiated schizophrenia	6	2	1	9
F23.2-Acute schizophrenia like psychotic disorder	5	2	1	8
F.25-Schizoaffective disorder	1	0	0	1
Total	**69**	**36**	**4**	**109**

Table 3
Deprescription and Benzodiazepine Withdrawal Symptoms..

BZD type	Prescribed	Deprescribed	No	Moderate	Severe
Clonazepam	91(83.5%)	withdrawal		Withdrawal	Withdrawal
Lorazepam	13 (11.9%)		Symptoms	Symptoms	Symptoms

Table 4
Cost Analysis of BZDs Continuation and Deprescription.

Category		Continuing (N = 44)		Deprescribed (N = 40)	
		Pre -Intervention	Post -Intervention	Pre – Intervention	Post – Intervention
Median		245.365	244.920	283.900	230.390
Minimum		35.400	35.400	35.40	0.00
Maximum		2097.600	1606.600	1722.89	1101.30
Percentiles	**25**	146.700	146.700	94.500	8.500
	50	245.365	244.920	283.900	230.390
	75	359.475	359.475	465.150	356.250

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