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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Long-term prescribing of benzodiazepines in community psychiatry clinics in the Johannesburg Health District

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A research report submitted in partial fulfilment of the of the requirements for the degree of Master of Medicine in Psychiatry, in the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa, in June 2021.

Declaration

I, Dr. Machipi Alice Tau, 0502164X, declare that this research report is my unaided work. It is being submitted for the Master of Medicine degree in Psychiatry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination at any other University.

It is submitted in “submissible format” as an article for submission to an academic journal. The journal chosen for submission is the South African Journal of Psychiatry (SAJP), and the report follows guidelines provided by the SAJP.

_____ _____

Machipi Alice Tau **Date**

Dedication

This work is dedicated to Godfrey, Naledi, Asante' and the rest of my family members and friends who have been my source of strength and support.

Presentations and Publications from this Study

None

Abstract

Background

Anecdotal evidence indicates that the prevalence of long-term benzodiazepine prescription in the Johannesburg health district is high and not in accordance with accepted prescribing guidelines.

Aim

This study aimed to determine the prevalence of long-term prescriptions of benzodiazepines in community psychiatry clinics in Johannesburg during 1st January to 30th June 2019 and to determine, if any, associations between demographic and clinical variables and long-term prescriptions.

Setting

Five of the 27 community psychiatry clinics in the Johannesburg Health District were randomly selected. The clinics included in the study were Discoverers, Eldorado Park Ext 8, Crosby, Zola, and Hillbrow.

Methods

A descriptive, retrospective and cross-sectional record review was conducted. Clinical records of 126 adult patients above 18 years were reviewed. Descriptive statistics were presented as proportions and percentages. Odds Ratios calculated from Fischer's exact tests described the association between long-term benzodiazepines and the demographic and clinical variables.

Results

The study population comprised of 126 patients. Approximately one out of every four patients (23.8%; n=30) were prescribed benzodiazepines. Most of the patients were males (56.7%) aged between 18 and 50 years (56.7%), single (60.0%), and unemployed (63.3%). The most common psychiatric diagnoses were bipolar disorders (33.3%) and psychotic disorders (23.3%). The majority had no comorbid medical illnesses (56.7%) nor substance use (80.0%). The most common benzodiazepine prescribed was clonazepam at relatively low dosages. Ninety-three percent of the

patients had been prescribed benzodiazepines for the long-term (more than 180 days). There were no statistically significant associations between this prescribing pattern and any sociodemographic and clinical factors ($p>0.05$).

Conclusion

This study found that approximately one in four patients (23.8%) attending community psychiatry clinics in the Johannesburg Health District were prescribed benzodiazepines. Nearly all these prescriptions were long-term (over 180 days), and no statistically significant associations between this practice and any sociodemographic and clinical factors could be established.

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Submissible Paper

Introduction

International treatment and good practice guidelines recommend that before prescribing benzodiazepines in any patient, clinicians should first exclude any physical illness and determine the benefit to risk ratio (1). The guidelines also recommend that benzodiazepines may be prescribed as a short-term treatment for severe insomnia (2;3) to counter any side effects of co-prescribed medication (1) while waiting for the full effect of other treatment modalities to occur (3;4;5), and to alleviate withdrawal symptoms in patients with substance abuse (1;6;7). Benzodiazepines should not be used routinely in patients with anxiety disorders (2;5;7) except for symptomatic relief of severe anxiety and during crises. They should be prescribed for only two weeks and after that reviewed (1). The South African Society of Psychiatrists' guidelines (8) are remarkably similar to these international guidelines.

Worldwide, variable rates in the prescribing of benzodiazepines have been reported (9-14). Maust, Blow, and Lin (15) said that, in the United States, 30.6 million adults (12.6%) used benzodiazepines in 2016, although Agarwal and Landon (16) reported a slightly lower rate of 7.4 percent in 2019. The European study of the epidemiology of mental disorders reported a prescribing rate of 18.4 percent across Europe (12), while in South Africa, a study comparing prescribing patterns in Gauteng and the Northern Cape found rates of 7.9-8.5 and 9-9.5 percent respectively (17). The variation in published rates by different countries may be attributed, at least in part, to different methodological approaches and clinical settings.

Despite not being recommended as first-line treatment by all guidelines (1;2;4;17), benzodiazepines in actual clinical practice tend to be prescribed for a broad range of psychiatric conditions, including anxiety, mood, psychotic, personality, and sleep disorders (10;18-20), and in patients with comorbid medical illnesses (19-22). They are also frequently prescribed for older patients (23-26), females (27-29), patients with lower education and socioeconomic status (24), and those with perceived low levels of support (24;30).

Although the guidelines recommend that benzodiazepines be prescribed for short periods of two weeks initially and then reviewed, several studies have reported a high rate of prescribing of benzodiazepines for long-term periods (18;19;31-33). The World Health Organization (WHO) defined long-term benzodiazepine use as exceeding 180 days (34), while others have suggested between four and twelve weeks (33). The WHO definition is the most frequently used in research and was the definition used in this study.

Inappropriate and long-term prescribing of benzodiazepines by healthcare professionals is one of the leading causes of iatrogenic benzodiazepine use disorders (31). The adverse health effects of benzodiazepine use disorder include psychomotor impairment, impairment in judgment and dexterity, forgetfulness, confusion, irritability, aggression, and paradoxical disinhibition (35). Tolerance, dependence, and withdrawal symptoms may also occur (35;36). Long-term benzodiazepine use may be appropriate in cases such as terminally ill or severely handicapped patients, where the benefits outweigh the risks and side effects (1;37).

There is a paucity of research in the South African public health sector, especially in district clinics, where anecdotally it appears that long-benzodiazepine prescribing is a common practice, hence the need for this study. Establishing the prescribing patterns of benzodiazepines at the clinic level may help detect and prevent long-term use and subsequent adverse health consequences. Such findings would also help district managers develop systems for monitoring benzodiazepine prescribing patterns and ensuring that the recommendations of approved guidelines are correctly implemented.

This study aimed to determine the rate of long-term prescribing of benzodiazepine and to determine any associations between demographic and clinical variables and this prescribing pattern at community psychiatry clinics in the Johannesburg health district.

Method

Study design and setting

The study was a descriptive retrospective and cross-sectional record review. Five of the 27 community psychiatry clinics in the Johannesburg health district were randomly

selected. The clinics included in the study were Discoverers, Eldorado Park Ext 8, Crosby, Zola, and Hillbrow.

Study population and sample

The records of all patients aged 18 years and older who attended the community psychiatry clinic and were seen by a doctor from 1st January to 30th June 2019 were eligible for inclusion**.** Anyone below the age of 18 was excluded**.** If the patient had several clinic visits within the study period, only the first visit was considered. Systematic sampling of every fifth name in each clinic's register was used to draw 25 or 26 patients from each of the five clinics, making a sample of 126 patient records, which were sourced from the registry.

Data collection and analysis

The relevant sociodemographic and clinical data was obtained from the patients' clinical notes and prescription sheets. It was recorded on the data sheet and then captured on a Microsoft Excel spreadsheet. Based on the literature review of factor associated with benzodiazepine use, sociodemographic data included age, gender, marital status, occupational status, and the highest level of education. Clinical data included primary psychiatric diagnosis, the presence of comorbid medical illness or substance use/ abuse, psychotropic medication prescribed, and the type, dose, indication, and duration of the benzodiazepine prescribed. A review of clinic notes prior to the study indicated that it was not possible to distinguish whether patients were either using or abusing substances and hence it was considered as one variable. For each variable, the category of "unknown" was recorded if the data was missing from the clinical notes".

Frequencies and percentages were calculated for all variables. Association between long-term prescribing of benzodiazepines and sociodemographic variables was determined by the use of contingency tables. Because of the retrospective nature of the study and poor record keeping by the treating doctors, some categories within certain variables had very small numbers. For the purpose of meaningful statistical analyses of the data, the categories were first collapsed into fewer categories e.g., age (18-50 years and > 50 years), occupational status (employed or unemployed),

highest level of education achieved (matric or below or above matric), marital status (single or married) etc. before analysis. Unknown values are shown for the socio-demographic variables for inclusivity but were not statistically analysed. Odds Ratios (OR), confidence intervals (CI) and p-values were generated using Chi squared and Fisher's exact test to determine any significant associations (instead of cross-classification tables). All tests were two-tailed and p -values was set at 0.05. All analysis was done using the R (version 3.6.1) statistical software.

Ethical considerations

Ethical approval was granted by the Human Research and Ethics Committee of the University of the Witwatersrand (Certificate number M190116). The study was registered with the National Health Research Department (NHRD_201904_015). Permission to conduct the study in the chosen clinics was obtained from the Johannesburg District Research Committee. No identifying data were captured, and each record was given a unique number known only to the researcher.

Results

Demographic and clinical characteristics of the study population

The study population comprised 126 patients, 25 from each of Discoverers, Crosby, Zola, and Hillbrow, and 26 from Eldorado Park Ext 8 psychiatric clinics. The demographic and clinical characteristics are presented in Table 1.

Most of the participants were males (53.2%; n=67), in the age group 18-50 years (66.7%; n=84), single (67.5%; n=85) and unemployed (52.4%; n=66). Just below half of the participants had achieved a matric or lower level of education (46.8%; n=59). The commonest primary diagnosis was psychotic disorder (31.0%; n=39), followed by bipolar disorder (29.4%; n=37). Personality disorders accounted for only 4.8% (n=6) of the patients. The psychotropic medication was co-prescribed in 84.1% (n=106) of patients. 63.5% (n=80) of the patients had no comorbid medical illness and 73.0% (n=92) had no comorbid substance use.

Demographic and clinical characteristics of all patients prescribed benzodiazepines.

Approximately one out of every four patients in the study population were prescribed a benzodiazepine (23.8%; n=30), as shown in Table 1. The majority of the patients in this group were males (56.7%; n=17), in the 18–50-year age group (56.7%; n=17), unemployed (63.3%; n=19) and single (60.0%; n=18). Just below half (46.7%; n=14) had only achieved a matric or lower education level. There were no statistically significant differences between this group and the group that was not prescribed benzodiazepines with respect to gender (p=0.675), age group (p=0.192), employment status (p=0.313), marital status (p=0.585), and level of education achieved (p=0.719).

The primary psychiatric diagnosis in the group that was prescribed benzodiazepines was bipolar disorder (33.3%; n=10), followed by psychotic disorder (23.3%; n=7) and depressive disorder (13.3%; n=4). Personality and anxiety disorders accounted for only 6.7% (n=2). More than half (56.7%; n=17) of the patients had no comorbid medical illness and comorbid substance use (80%; n=24). Psychotropic and other medications were co-prescribed for 86.7% (n=26) of patients. There were no statistically significant differences between this group and the group that was not prescribed benzodiazepines with respect to primary psychiatric diagnosis, co-prescribing of psychotropic and other medication (p=0,781), absence of comorbid medical illness (p=0.392), and absence of comorbid substance use disorder (p=0.358).

The benzodiazepine most prescribed was clonazepam (96.7%; n=29), and only one patient (3.3%) was prescribed oxazepam. The mean dose of clonazepam prescribed was 0.8 mg (SD ± 0.61) and the actual doses were 0.25mg (18.5%; n=5); 0.5mg (44.4%; n=12); 1mg (33.3%; n=9); 2mg (7.4%; n=2) and 3mg (3.7%; n=1). The dose of oxazepam prescribed was 15mg.

Only three patients (10.0%) had a clear indication for the initiation of a benzodiazepine prescription, two for sedation and one for insomnia.

Table 1: Frequency distribution of demographic and clinical characteristics of the study population, the group that was prescribed benzodiazepines, and those who were not.

Variables		Sample (n=126) n (%)	Benzodiazepine prescribed. (n=30) n (%)	Benzodiazepine not prescribed. (n=96) n (%)	Fisher's exact (OR CI; p-value)
Gender	Male	67 (53.2)	17 (56.7)	50 (52.0)	OR:1.22, CI:0.48-3.13, p=0.675
	Female	55 (43.7)	12 (40.0)	43 (44.8)	
	Unknown	4 (3.2)	1 (3.33)	3 (3.1)	
Age group	18-50 years	84 (66.7)	17 (56.7)	67 (70.0)	OR:0.57, CI: 0.23-1.45, p=0.192
	> 50 years	42 (33.3)	13 (43.3)	29 (30.2)	
Occupational status	Employed	9 (7.14)	1 (3.33)	8 (8.33)	OR:0.43, CI: 0.01-2.62, p=0.313
	Unemployed	66 (52.4)	19 (63.3)	47 (49.0)	
	Unknown	51 (40.5)	10 (33.3)	41 (42.7)	
Highest level of education achieved	Matric or below	59 (46.8)	14 (46.7)	45 (46.9)	OR:1.70, CI:0.31-17.61, p= 0.719
	Above matric	13 (10.3)	2 (6.67)	11 (11.4)	
	Unknown	54 (42.9)	14 (46.7)	40 (42.7)	
Marital status	Single	85 (67.5)	18 (60.0)	67 (70.0)	OR:0.76, CI:0.24-2.71, p=0.585
	Married	23 (18.3)	6 (20.0)	17 (17.7)	
	Unknown	18 (14.3)	6 (20.0)	12 (12.5)	
History of Medical comorbidity	Yes	46 (36.5)	13 (43.3)	33 (34.4)	OR:1.46, CI:0.57-3.63, p=0.392
	No	80 (63.5)	17 (56.7)	63 (65.6)	
History of Substance use/abuse	Yes	34 (27.0)	6 (20.0)	28 (29.2)	OR:0.61, CI: 0.18-1.75, p=0.358
	No	92 (73.0)	24 (80.0	68 (70.8)	
Other Psychotropic medication prescribed	Yes	106 (84.1)	26 (86.7)	80 (83.3)	OR:1.20, CI: 0.37-5.81, p= 0.781
	No	20 (15.9)	4 (13.3)	16 (16.7)	
Primary psychiatric disorder diagnosis	Psychotic	39 (31.0)	7 (23.3)	32 (33.3)	OR:0.6, CI: 0.20-1.67, p=0.370
	Bipolar	37 (29.4)	10 (33.3)	27 (28.1)	OR:1.28, CI:0.47-3.31, p= 0.648,
	Depressive	21 (16.7)	4 (13.3)	17 (17.7)	OR:0.72, CI:0.16-2.48, p=0.781
	Personality	6 (4.8)	2 (6.67)	4 (4.17)	OR:1.64, CI: 0.14-12.12, p=0.628
	Anxiety	10 (7.9)	2 (6.67)	8 (8.33)	OR:0.79, CI: 0.08-4.28, p=1.000
	Other	13 (10.3)	5 (16.7)	8 (8.33)	OR:0.22, CI: 0.52-8.39, p=0.299

Demographic and clinical characteristics of patients prescribed long-term benzodiazepines.

Figure 1 shows that 27 (90%) of the 30 patients in the study sample who were prescribed benzodiazepines met the WHO criterion of over 180 days for long-term benzodiazepine prescriptions. Only two patients were prescribed benzodiazepines for one to six months, and one patient for six to twelve months. Therefore, no meaningful comparisons could be made between patients who were prescribed long-term benzodiazepines and those who were not.

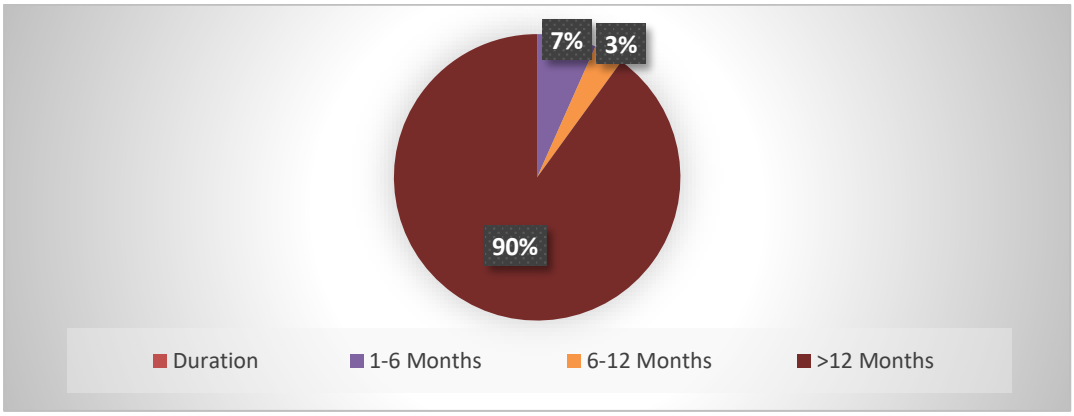

Figure 1: Duration of benzodiazepine prescription

There was no statistically significant association between gender, age, occupational status, level of education, marital status, medical comorbidity, substance use/abuse, psychotropic medication co-prescribed, primary psychiatric diagnosis and long term benzodiazepine use ($p>0.05$).

However, there was a positive association (OR>1) with respect to males (OR=1.255; CI=0.527-2.987; p=0.666), having a less than matric level of education (OR=1.021; CI=0.248-4.206; p=1.000), having medical comorbidity (OR=1.707; CI=0.728-4.006; p=0.267), and being co-prescribed with other psychotropic medication (OR=1.171; CI=0.357-3.835; p=1.000). There was negative association (OR<1) with respect to the 18-50 year age group (OR=0.441; CI=0.187-1.039; p=0.073), being employed (OR=0.386; CI=0.0460-3.243; p=0.683), being single (OR= 0.760; CI=0.262-2.212; p=0.585), and having a comorbid substance use (OR=0.877; CI=0.334-2.300; p=1.000). With respect to the primary psychiatric diagnosis there was a positive association with personality disorders (OR=1.798; CI=0.158-4.134; p=0.614) and

bipolar disorders (OR=1.456; CI=0.530-3.842; p=0.481) and a negative association with anxiety disorders (OR=0.866, CI=0.085-4.726; p=1.000) depressive disorders (OR=0.795;CI=0.178-2.769;p=1.000) and psychotic (OR=0.689; CI=0.224-1.909; p=0.495). However, the small sample size for most categories and the wide confidence intervals demonstrated a lack of statistical power and non-significance in the above.

Discussion

Approximately one out of every four patients (23.8%) in the Johannesburg Health district community psychiatric clinics were prescribed a benzodiazepine. While similar high prescribing rates of 18.7 to 24.0 percent have been reported (10;32;38), lower rates of 3.8 to 12.6 percent have also been reported (13-15). The variation in reported prescribing rates could be due to differences in the methodology employed, such as study design, settings, and inclusion and exclusion criteria. The high rates in the studies of Ghosh-Nodia and Ahuja (38) and Haw and Stubbs (11) may have been due to much larger sample sizes, whereas in the Haw and Stubbs (11) and Johnson et al. (32) studies they may have been because the prescription was initiated during hospital admission and continued in the community clinics where the studies were conducted soon after discharge. The high prescribing rates in the current study may in part be due to clinicians' lack of knowledge of benzodiazepine prescribing guidelines (39), lack of capacity and time for the re-evaluation of benefits and risks associated with benzodiazepines (40), and failure to provide patient psychoeducation on non-pharmacological interventions to manage symptoms (15). In addition, there may have been inadequate monitoring of prescriptions by pharmacists, who are required to serve as gatekeepers (41). In South Africa, benzodiazepines are classified as schedule five (S5) drugs by the Medicines and Related Substances Control Act No 101 of 1965, which serves as a control measure to prevent inappropriate prescribing and limiting misuse of these drugs (42). However, these control measures have not been entirely effective (21).

Benzodiazepines are divided into four groups based on their elimination half-life. They include ultra-short acting (midazolam, triazolam), short-acting (oxazepam, temazepam), intermediate-acting (alprazolam, bromazepam, lorazepam), and long-acting (clonazepam, diazepam, nitrazepam) (6). The most frequently prescribed benzodiazepine (96.7.0%) by the clinicians in this study was clonazepam. Singh and

Oosthuizen (18) also reported that clonazepam was the most commonly prescribed in their patients, followed by diazepam. However, Summers, Schutte, and Summers (43) reported a preference for the longer-acting benzodiazepines in their public sector study. Generally, in the South African public health care sector, clinicians' choice depends on what is available on the country's essential medicine list and in the central pharmacy stocks at the time of prescribing (21;44). During this study, the benzodiazepines available on the essential medicine list were diazepam, lorazepam, oxazepam, and clonazepam. However as there are no limitations in the South African private health sector; there is a preference for intermediate-acting benzodiazepines such as alprazolam and bromazepam (14;29). Other countries have also shown variation in the choice of benzodiazepine prescribed between the public and private sectors. In Lebanon, Ramadaan, Sheik-Taha, and Deep (10) reported that the most used intermediate-acting benzodiazepines were alprazolam (34.6%) and bromazepam (33.6%). It is unclear what guides and informs the choice of one benzodiazepine over another in the public and private health care sectors of different countries. The mean dose of clonazepam was like that of other studies (10;20) and within the manufacturers' recommendations (45). There was also no progressive increase in the benzodiazepine dosage, as might be expected with the development of tolerance (46).

This study found that in almost all the patients (90%), the benzodiazepines were prescribed for a long-term period exceeding 180 days. This rate was considerably higher than the range of 10 to 19 percent reported in most other studies (18;32;33). However, it must be noted that the Johnson et al. (32) study had a small sample size, and the benzodiazepines were initiated during admission to a hospital, with only those still on benzodiazepines at community clinics soon after discharge included in the study. The Bernard et al. (18) review was an observational study at primary health care clinics with a larger sample size and included only adult patients with anxiety disorders. Although higher rates of between 60 and 70% have been reported (12;47), the Lagnaoui et al. (12) study included only patients with mood and anxiety disorders, while the Valenstein et al. (47) study included only depressed patients on antidepressants.

Notwithstanding the wide variation in published long-term benzodiazepine prescribing rates, which may be attributed to differing methodologies, the rate found in the present study was still significantly high. It is therefore important to determine what factors may be associated with this long-term benzodiazepine prescribing habit. Several studies have reported that the long-term prescribing of benzodiazepines has been more common for female rather than male patients (47-50). Females tend to have better help-seeking behaviours than males, which may account for their consulting doctors more often and being on medication for more extended periods (51). However, Zandstra et al. (34) and Sjostedt et al. (24) reported no gender differences to support this. Contrary to the above, although not statistically significant, this study found a slight preponderance of males. Franken et al. (52) also reported most males among their participants. It is likely that the present study population, at the outset, consisted of more males. This male preponderance may be attributed to the observation that males tend to have medication non-compliance and poor social reintegration after discharge (52), which necessitates regular and ongoing follow up at community clinics.

The current study also found that almost half of the patients on long-term benzodiazepine use (43.3%) were older than 50 years of age, like findings in the French study of the long-term prevalence of benzodiazepine use (53). Patients of advancing age generally have comorbid medical conditions that may warrant benzodiazepine initiation and possible subsequent prolonged use (54;55). Chronic medical conditions in the older population have been associated with increasing psychosocial stressors that might precipitate or exacerbate anxiety and depression (16;56). However, more than half of the patients in the current sample (56.7%) had no medical comorbidities to support this argument. Gerlarch et al. (56) reported that low quality of sleep in the elderly is also a predictor for long-term benzodiazepine use. However, this was not a clear indication for prescribing benzodiazepine for the patients in the current study. Although this study did not show statistically significant associations between age and long-term prescribing of benzodiazepines, the studies that have demonstrated this have focused primarily on individuals older than 60 years with chronic diseases and with depressive, anxiety, or insomnia disorders (12;22;28).

Being single with perceived poor social support has also been associated with long-term benzodiazepine use because of an increased likelihood of anxiety and related

disorders (9;30;48;52). Similarly, a lower socioeconomic status due to a lower level of education and unemployment may add to the anxiety of low social support and perpetuate long-term benzodiazepine use (9;21;30). The settings of these studies were similar to our research. Many participants who were prescribed benzodiazepine for long-term use in the current study were also either unmarried, divorced, or widowed, had a level of matric or below education, or were unemployed. This may be because they were generally from a relatively poor socioeconomic community with a lower level of education, unemployment, and lower income or disability grants (53).

The origins of substance use disorders are complex and multifactorial, and there is evidence of a correlation with poor mental health, poverty, low level of education, unemployment, lack of social amenities, and social exclusion (57). The increasing level of discomfort relating to anxiety may lead to prolonged periods of individuals being prescribed and misusing benzodiazepines. Benzodiazepines may be taken inappropriately to treat the undesirable effects of substance abuse, enhance or augment other drugs' euphorigenic effects, or induce intoxication (58). Several studies have reported that comorbid substance use is also associated with long-term benzodiazepine use (9;20;22). A South African study (59) reported a high prevalence rate of substance use disorders in psychiatric patients; however, no studies reported an association between comorbid substance use and prolonged benzodiazepine use. The current research found that most patients (80%) had no comorbid substance use disorder, similar to Aragaines et al. (53). This may be due to the patients' under-reporting, poor documentation by the doctors, or the small sample size.

Despite it not being recommended by approved guidelines, common mental disorders such as depression, anxiety, and sleep disorders are often associated with long-term benzodiazepine use (9;26). Johnson et al. (32), in their study, also reported that borderline personality and bipolar disorders were significantly associated with long-term benzodiazepine use. It is likely that because our patients have been attending the clinics for a very long time, the benzodiazepines initiated during their psychiatric admissions may have been gradually discontinued (52) and hence the lack of any association.

Surprisingly, the current study found that having anxiety, depressive, psychotic or other psychiatric disorders was protective (OR<1) from being prescribed long-term

benzodiazepines. However, the wide confidence intervals demonstrated non-significance in this observation, as would be expected.

Only three patients on long-term benzodiazepines had documented reasons for a benzodiazepine being prescribed. It is possible that there were clinical grounds for prescribing a benzodiazepine; however, because of poor record-keeping, the prescribers did not document it. Agarwal and Landon (16) also reported poor record keeping. It may be that clinicians failed to record the indications for the use of these drugs because they were not familiar with accepted prescribing guidelines due to limited training or lack of confidence in correctly prescribing these drugs (39;60).

Limitations

There were some limitations to this study. The study population comprised patients from only five out of the twenty-seven community psychiatry clinics in the Johannesburg health district, and therefore may not be truly representative. The generalisation of the findings should be made with caution, as there is a likely variation in prescribing patterns between clinics and other districts. The relatively small sample size may have limited the ability to detect statistically meaningful differences in the various categories' analyses. The exceedingly small group of short-term benzodiazepine prescriptions has defaulted this study to merely a description of long-term benzodiazepine prescriptions without any comparisons possible. As in any retrospective study design, some data were missing due to possible poor record keeping. Other reported factors associated with long-term benzodiazepine prescribing were not considered in this study and should be included in the design of future studies. Notwithstanding the limitations, this study does provide useful insights into the prescribing patterns of benzodiazepines.

Recommendations

It is recommended that further studies be conducted with larger sample sizes and across the various districts in Gauteng and the rest of South Africa. The studies should also include some of the reported factors associated with long-term benzodiazepine use, but not included in this study.

According to accepted guidelines, clinicians at community clinics should attend regular training on responsible prescribing and reviewing of prescriptions of these drugs. They should be encouraged to psycho-educate patients with respect to the advantages and disadvantages of benzodiazepines before initiation and during the process of de-prescribing. District clinical managers and pharmacists should also establish monitoring systems for continuous reviewing of the prescription of benzodiazepines with respect to dosage and duration.

Conclusion

This study found that approximately one in four patients (23.8%) attending community psychiatry clinics in the Johannesburg Health District were prescribed benzodiazepines. Nearly all these patients (90%) were prescribed these benzodiazepines long-term, for longer than 180 days. No statistically significant associations could be established between this practice and any sociodemographic and clinical factors. Proper records of the indications for benzodiazepine prescribing were not evident, and the recommendations of accepted prescribing guidelines were not being adhered to. It is recommended that regular training on guidelines be carried out and that proper clinical monitoring systems be established.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author contributions

The first author undertook this study for an MMed degree. The second author supervised this study. Both authors contributed to the design and implementation of the research, the analysis of the results, and the manuscript's writing.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclaimer

The views expressed in the submitted article are the author’s views and not an official position of the institution.

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Appendix A: Approved Research Protocol

Long-term prescribing of benzodiazepines in community psychiatry clinics in the Johannesburg Health District.

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1. Introduction

Benzodiazepines were introduced in the late fifties to replace barbiturates and meprobamate due to their safety profile, efficacy, and tolerability. They were soon widely prescribed medication. By the late 1970s, safety concerns had arisen about their use (Haw & Stubbs, 2000). Side effects include psychomotor impairment and increased risk of motor vehicle accidents and falls, impairment in judgement, dexterity, forgetfulness, confusion, irritability, aggression, paradoxical disinhibition as well as tolerance, dependence, and withdrawal symptoms, increasing the risk of abuse and addiction potential, especially in patients with other substance use disorders and personality disorders (Johnson et al.,2016).

Inappropriate use of these psychotropic medications in health care facilities is a growing threat to public health. It is one of the leading causes of iatrogenic substance (benzodiazepine) use disorders and other adverse health outcomes (Ahmer et al., 2009).

It would appear from the anecdotal evidence that there is also a remarkably high prevalence of benzodiazepines prescription in the community psychiatry clinics in Johannesburg and that these prescriptions are for an exceptionally long duration. Hence the need for this study to confirm this assumption and to propose strategies on how to manage this problem if it exists.

2. Literature Review

Primary indications for benzodiazepine use include insomnia disorders, anxiety disorders, seizure disorders, muscle spasms, and spasticity (Haw & Stubbs, 2007).

Benzodiazepines are also used for acute sedation in emergency rooms and psychiatric settings, anaesthetic induction, and maintenance, preoperative medication to provide sedation, muscle relaxation, anterograde amnesia, and the management of alcohol withdrawal (Davis, 2017).

The National Institute for Health and Care (NICE) guidelines (Taylor et al., 2015), which are the most common and widely used guidelines, recommend that:

- benzodiazepines should not be routinely used in patients with anxiety disorders, except as a short-term measure during the crisis.
- use of benzodiazepines as a hypnotic should be used for, and that physical causes and substance misuse should be excluded first.
- benzodiazepine use in depression may be helpful for up to 2 weeks early in the treatment, particularly with SSRI (to help with sleep and SSRI induced agitation). Use beyond this period is discouraged.

2.2 Prevalence of benzodiazepine use

The European study of the epidemiology of mental disorders (ESEMeD) investigated psychotropic drug use across six European countries (Belgium, France, Italy, Germany, Netherlands, and Spain) involving 22 000 adults within communities. They found that benzodiazepines were the most used psychotropic drugs in these countries, with an overall prevalence of 9.8% (Alonso et al., 2004). In South Africa, a comparative study by Visser (2010) between two provinces on the prescribing patterns of benzodiazepines, the author reports that the prevalence of benzodiazepine use ranged between 1.4% and 38%, and the prevalence rate was higher in Gauteng province and lowest in Northern Cape province.

2.3 Type of benzodiazepines commonly prescribed.

A systematic review by Kurko et al. (2015), assessing twenty studies for the association between characteristics of benzodiazepines and long-term use, found that in eleven studies, the use of short-acting high potency benzodiazepines such as alprazolam, lorazepam, or oxazepam was the significant predictor of long-term benzodiazepine use.

A retrospective review of data from three multicentres in Korea involving patients at 41 tertiary university hospitals and eight secondary hospitals reported that the highest co-prescription rates with antipsychotics included benzodiazepines (30.3%), anticholinergics (28.8%), antidepressants (13.3%), Beta-blockers (10.1%) and mood stabilizers (8.7%) (Kim et al., 2014).

2.4 Long-term benzodiazepine use

The World Health Organization (WHO), using the standardized classification system for drugs, defines long-term benzodiazepine use as having prescriptions for more than or equal to 180 days (6 months). Other researchers have used cut-off duration of above four weeks and 12 weeks (Zandstra et al., 2002). The WHO definition is the most used in most research and used in this study.

Despite generally accepted advice to keep treatment short, benzodiazepines are often prescribed for more than six months. Prevention of long-term benzodiazepine use could be facilitated by the utilization of risk indicators for long-term use (Zandstra et al., 2002).

2.5 Factors associated with long-term benzodiazepine use.

Factors commonly associated with long-term benzodiazepine use include older age, female gender, and low socioeconomic status. Other factors include clinical factors, such as the presence of a psychiatric/medical condition as well as the use of other psychotropic medication.

2.5.1 Sociodemographic

2.5.1.1 age

A retrospective observational study of benzodiazepine uses in the United States using data from Lifeline and medical expenditure panel survey covering 60% of all retail prescriptions in the U.S., found that approximately 5.2% of U.S. adults aged 18 to 80 years used benzodiazepines. The percentage who used benzodiazepines increased with age: 2.6% (18-35 years); 5.4% (36-50 years); 7.4% (51-64 years) and 8.7% (65-80 years) (Olfonso et al., 2014). A study by Zandstra et al. (2002) provided the following profile of long-term benzodiazepine users: older, had a more severe

psychiatric history, and had many other prescriptions psychotropics, and poorer mental health status, with more common chronic diseases and more visits to medical specialists.

2.5.1.2 Gender

According to Canadian Centre on Substance Use and Addiction and the Canadian Tobacco, Alcohol and Drugs Survey in 2015, the prevalence of prescription sedative use was significantly higher among females (13.6%) compared to males (7.3%) (CCSA, 2017).

In a study examining the trends in the prescription of benzodiazepines for the elderly (aged >65 years) in Korea, it was found that females are 10% more likely to be prescribed benzodiazepines than males (Hwang et al., 2017).

2.5.1.3 Socioeconomic status

A study by Sjostedt et al., (2017) on sociodemographic factors and long-term benzodiazepine use in patients with depression, anxiety, and insomnia showed that individuals with high income, compared to individuals with middle to low income, had 30% higher odds of long-term use. Those with middle to lower education status had higher odds of long-term use as compared to those with the highest education. Social welfare recipients have the highest odds. The study also found that being married and social support have been shown to be associated with decreased benzodiazepine use.

2.5.2 Clinical Factors

2.5.2.1 Nature of psychiatric illness

Zandstra et al., (2002) compared the differences in health status between long-term and short-term benzodiazepine users. They found that 48% of long-term benzodiazepine users as compared to 42% of short-term users had a history of mental illness. Paton et al., (2000) reported that almost 10% of patients occupying psychiatric rehabilitation beds had a diagnosis of schizophrenia and received long-term benzodiazepine. A study by Peritogiannis et al., (2016) in rural mental health clinics in Greece also found that 39% of patients with psychotic disorders were regularly prescribed benzodiazepines as part of their treatment regimen. Ramadaan et al.,2016)

also found a more significant association between long-term benzodiazepine use and cluster B personality disorders. The study also noted that the prescribing physician was primarily a psychiatrist (43.2%), general practitioner (29.7%) or a surgeon (2.3%).

From the review of studies above it is evident that mentally or psychologically vulnerable are more likely to use benzodiazepines. However, there is no significant difference in the prevalence or duration of prescriptions by the specific nature of the psychiatric illness.

2.5.2.2 Family history of benzodiazepine use

2.5.2.3 Comorbid substance use disorder

Substance use disorders encompass substance abuse and dependence as they are referred to in the diagnostic and statistical manual of mental disorders (DSM 5, 2013). Benzodiazepine (anxiolytic, sedative & hypnotic) use disorder most commonly occurs in conjunction with other drugs. They are typically secondary drugs of abuse for most, and a much smaller number report benzodiazepines as the primary drug of abuse. Approximately 1 in 5 individuals are abusing alcohol also abuse benzodiazepines. Benzodiazepines are used to enhance the euphoric effects of other drugs; reduce the unwanted effects of drugs, such as insomnia due to stimulant use; and alleviate withdrawal (Schimitz, 2016).

2.5.2.4 Comorbid medical illness

A longitudinal study by Sonnenberg et al. (2012) assessing the ten-year trend in benzodiazepine use found that there is an increase in the prevalence of physical health problems with benzodiazepine users. The data that was derived from the Longitudinal Aging Study of Amsterdam (LASA) consisted of 3107 adults aging between 55 and 85 years.

The cross-sectional prospective observational study in which 5201 community-dwelling elderly were studied to determine the correlates and prevalence of benzodiazepine users it was found that there is significantly higher prevalence of coronary heart diseases, congestive heart failure, renal diseases, and cerebrovascular diseases (Gleason et al.,1998).

This review of published international and limited local literature indicates that the prevalence of benzodiazepine prescription is high, despite guidelines to the contrary, and that they are often prescribed for exceptionally long periods. Long-term benzodiazepine use is associated amongst others, with increasing age, female gender, alcohol use disorder, and a diagnosis of anxiety and depressive disorders. Benzodiazepines are commonly prescribed in individuals with medical comorbidities, especially in the elderly population and with other psychotropic medication drugs, especially antidepressants. There is a paucity of research in the South African public health care sector, especially in community psychiatric clinics, where benzodiazepines are frequently prescribed for long periods. Establishing the prevalence of long-term prescribing of benzodiazepines and some of the factors associated with this pattern in this sector may help with limiting its overuse. It may also prevent the subsequent adverse health consequences and cost implications. The findings may assist District Mental Health managers in implementing systems for monitoring the prescription of benzodiazepine and developing training programs on the judicious use of these medications.

3. Hypotheses

The hypotheses for this study are as follows:

3.1 There is a high prevalence of benzodiazepine prescribing.

3.2 Benzodiazepines are prescribed long-term (more than or equal to 180 days)

3.3 There is an association between long-term benzodiazepine prescriptions and female gender, increasing age and patients with a history of substance use disorders.

4. Aim:

To describe the long-term prescribing of benzodiazepines in community psychiatric clinics in the Johannesburg Health District

5. Objectives:

The specific objectives are to:

5.1 To describe the demographic characteristics of patients in the study population.

5.2 To describe the clinical characteristics of the study population.

5.3. To determine the prevalence of long-term (exceeding 180 days) prescribing of benzodiazepines

5.4. To determine, if any, demographic and clinical variables that are associated with the long-term prescribing of benzodiazepines.

6. Methodology

6.1 Study Design

The study is a descriptive, retrospective, and cross-sectional record review.

6.2 Study setting.

There are twenty-seven secondary level psychiatric clinics in the district. All the clinics names were written on pieces of paper, placed in a hat, and shaken. Five pieces were blindly removed, and the five clinics selected in this randomized fashion were Discoverers, Eldorado Park, Hillbrow, Zola and Crosby.

6.3 Study population

The study population will include all patients, 18 years and above, who attended the clinic in the previous 6 months and prescribed medication by a doctor. There are no exclusion criteria except that a patient will only be used once if he had more than one visit during the six-month period.

6.4 Sample size

The sample size for this study is 125. The following formula was used to calculate the sample size: $n \geq (Z_{\alpha}/E)^2 \cdot p(1-p)$ where p is the expected proportion who have the characteristic of interest, E is the margin of error, and Z_{α} is a value from the normal distribution related to the significant level α. As the 5% significant level is used in this study, $Z_{\alpha} = 1,96$. One of the hypotheses to be tested in this study is, there seems to be a high prevalence of benzodiazepine use in psychiatry district clinics. So, considering the null hypothesis of equal proportion (Prevalence), the value of 0.5 is

used for p to calculate the sample size. Z_α is approximated to 2 and ±10% margin of error. Therefore, n ≥ (2/0,10) ^2·0,5·0,5 = 100 (Hulley et al., 2013). To increase the power of the study, the sample size was set at 125.

6.5 Data collection

The register of patients consulted by a doctor in the previous six months will be obtained from the psychiatric nurse in charge of each of the five clinics. The 25 patients' names will be randomly (every fifth name) selected from the patient register at each clinic. Another patient will be chosen if already selected. The patients' clinic files, including the prescription sheets, will be obtained from the clinic's registry. The researcher will then get the relevant information from the clinical notes in the file and prescription sheet and record it on the data-capturing sheet (addendum 1).

The data will include:

a) **Socio-demographic variables:** Age (in years), Gender (male/female); Marital status (single; married/ cohabiting/ divorced/ widow/er/ unknown); Occupational status (employed/ unemployed/ on a grant/ unknown); Highest level of education attained.
b) **Clinical variables:** Psychiatric diagnosis (Psychotic disorder; Mood disorder; Anxiety disorder; other); Medical comorbidities (yes/no) and type of medical comorbidity (if applicable); Substance use/abuse (yes/no) and type of substance (if applicable); Psychotropic medication co-prescribed (yes/no) and medication group (if applicable)
c) Details of benzodiazepine prescribed: Indication for use; name of benzodiazepine; date of first prescription; date of last prescription; initial dose; current dose.

7. Data Analysis

Data will be collected using a specially designed form, processed, and analysed using the statistical software Stata version 14.2. As all the variables are categorical, frequencies and percentages (proportions) will be provided to describe them. Sociodemographic variables will be presented in a pie chart or bar graph formats, while clinical and benzodiazepine variables will be presented in Table format. To

determine whether sociodemographic and clinical variables are associated with long-term use of benzodiazepine use, cross-classification tables will be carried out followed by the chi-square test of independence, to check the statistical significance of the association. Confidence intervals for the prevalence rate will be calculated using the reasonable approximation of the binomial distribution.

8. Limitations

The study is limited to the Johannesburg Health district; thus, the results might not be generalizable to communities in other districts. By including five clinics serviced by different doctors, prescriber bias is limited. As this is a retrospective record review, the patient's records might be incomplete or missing some information.

9. Ethical considerations

The study will be conducted according to Wits University's research committee and the National Health Research Ethics Council (NHREC) of the department of health. Permission to conduct the study will be obtained from relevant clinic authorities. To ensure the patients' privacy and confidentiality, the identifying data will not be part of the sociodemographic profile to be collected and analysed.

10. Funding:

A minimum of R1000-00 will be required for the printing of questionnaires. Personal funds will cover the costs.

11. Time Frames

	May–Dec 2018	Jan 2018	Mar –Apr 2019	May-Jun 2019	Jul-Dec 2019
Preparing Protocol					
Submission to Postgrad and Ethics Committees					
Collecting Data					
Data Analysis					
Writing up Thesis					

12. References

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Data Collection Sheet

Patient Ref No: _____

1. Socio-demographic variables:

(a) Age (in years): _____

18-35	36-55	56 -65	65+

(b) Gender

Male	Female	Unknown

(c) Marital status

Single	Married	Divorced/separated	cohabiting	Widow/er

(d) Occupational status

Employed	Unemployed	On grant	Unknown

(e)Highest level of education attained.

Primary	Secondary	Tertiary	Other	

2. Clinical variables:

(a) Primary psychiatric diagnosis (DSM 5),

Psychotic disorders	Substance related disorders	Sleep-wake disorders	Depressive disorders	Anxiety disorders
Bipolar disorders	Neurocognitive disorders	Personality disorders	Trauma and stressor-related disorders	Others

(b) Medical comorbidities (yes/no) and type of medical comorbidity (if applicable)

Endocrine	Cardiovascular	GIT	Musculoskeletal	Autoimmune

Nutritional	Malignancy	Infections	Neurological	Other

(c) Substance use/abuse (yes/no) and type of substance (if applicable)

Alcohol	Cannabis	Stimulants	Other prescribed/OTC	Other

(d) Psychotropic medication co-prescribed (yes/no) and type of medication (if applicable)

Antidepressants	Antipsychotics	Mood-stabilisers	Anticholinergics	Other

3. Details of benzodiazepine prescribed:

(a) Name of benzodiazepine

Clonazepam	Diazepam	Lorazepam	Oxazepam	Other

(b) Indication

Sedative	Hypnotic	Other	Not stated	

(c) Date of the first prescription:

_____

(d) Duration of prescription

< 1month	1-3months	3-6 months	6-12 months	Above 12 months

Appendix B: Ethical Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr M Tau

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190116

NAME: (Principal Investigator)	Dr M Tau
DEPARTMENT:	School of Clinical Medicine Department of Psychiatry Medical School University
PROJECT TITLE:	Long term prescribing of benzodiazepines in community psychiatric clinics in the Johannesburg Health District
DATE CONSIDERED:	2019/01/25
DECISION:	Approved unconditionally
CONDITIONS:	Title amended on 30 April 2019
SUPERVISOR:	Professor MYH Moosa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/04/17

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case the study was initially reviewed in January and will therefore reports and re-certification will be due early in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix C: Permission to carry out the study.

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JOHANNESBURG HEALTH DISTRICT

Faculty Of Health Sciences
Research Ethics Committee,
University of The Witwatersrand
Johannesburg, South Africa
0302164X@students.wits.ac.za

Enquiries: Dr EM Ohaju
Tel: 011 694 3888 Cell: 078 8831559
Email: Elizabeth.Ohaju@gauteng.gov.za
Hillbrow CHC: Administration Building
Cr Smith Str. & Klein Street
Private Bag X21, Johannesburg
South Africa, 2017

DRC Ref: 2019-04-007

NHRD Ref no: GP_201904_015

Dear: Dr Machipi Tau

TITLE: *Long term prescribing of benzodiazepines in community psychiatry clinics in the Johannesburg Health District*

Your application for research approval refers.

The District Research Committee has reviewed your application. This letter serves as an in-principle approval to access the Districts Health facilities (mentioned below) for the above project subject to following conditions:

- The facility to be visited: CROSBY CLINIC, DISCOVERERS CHC, ELDORADO PARK EXT 9 CLINIC, HILLBROW CHC, ZOLA CHC
- This facility will be visited from **09/04/2019 to 09/04/2020**
- The research can only commence after you submit an ethics clearance certificate from a recognized institution.
- You will report to the Facility Manager before initiating the study.

Region	Regional Health Manager	Contact No.	Cell phone
ABCEP	Ms Matlala	011 440 1259	082 307 0267
E (L A)	Dupa Montsioa	011 681 8130	082 467 9423
D (L A)	Mabel Ngcobo	011 986 0164	082 467 9316
D	Ms. Maria Mazibuko	011 674 1200	082 781 9919

The following conditions must be observed:

- Participants' rights and confidentiality will be maintained all the time.

- The study will comply with Publicly Financed Research and Development Act, 2008 (Act 51 of 2008) and its related Regulations.
- You will submit a copy (electronic and hard copy) of your final report. In addition, you will submit a six-monthly progress report to the District Research Committee.
- Your supervisor and University of The Witwatersrand will ensure that these reports are being submitted timeously to the District Research Committee.
- The District must be acknowledged in all the reports/publications generated from the research and a copy of these reports/publications must be submitted to the District Research Committee.

We reserve our right to withdraw our approval, if you breach any of the conditions mentioned above.

Please feel free to contact us, if you have any further queries. On behalf of the District Research Committee, we would like to thank you for choosing our District to conduct such an important study.

Regards,

Dr E.M Ohaju
Chairperson: District Research Committee
Johannesburg Health District
Date 11/04/2019

Mrs M.L Morewane
Chief Director
Johannesburg Health District
Date: 11/04/2019

Dr R Bismilla
Executive Director
Johannesburg Health District
Date: 2/5/19

Appendix D: Turnitin Report Cover Page

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