Pharmacotherapeutic Implications and Prescribing Pattern of Benzodiazepines (BZD) by Psychiatrists and Neurologists

الاستنتاجات العلاجية والدوائية ونمط وصف مشتقات البنزوديازيبين عند الأطباء النفسيين وأخصائيي الأمراض العصبية

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Abstract

The aim of this study is to explore and investigate benzodiazepine (BZD) prescribing pattern by neurologists and psychiatrists. Randomly selected five hundred and five neurologists and psychiatrists prescriptions were collected throughout West-Bank and analyzed using SPSS 10 for windows. Approximately half of the prescriptions contain BZD with alprozolam being the most commonly prescribed BZD followed by clonazepam. More than half of the BZD prescriptions were missing important patient and dispensing information. Gender of the patient and physician's specialty were not a determining factor in choosing or prescribing BZD. Antidepressants were commonly co-prescribed with BZD (57%). BZD were more commonly co-prescribed with tricylic antidepressants (TCA) antidepressants than selective serotonin reuptake inhibitors (SSRIs). Approximately 20% of antipsychotic prescriptions contained BZD especially clonazepam. In conclusion, although our study is not based on complete clinical investigation of patients disease and drug history, it is clear that there is some irrational BZD prescribing practices based on the general requirements for BZD prescriptions.

ملخص

هدفت هذه الدراسة الى فحص استعمال مشتقات BZD بين أخصائي الأمراض العصبية والنفسية. تمت الدراسة على ٥٠٥ وصفات من أطباء نفسانيين وأطباء أعصاب، تم اختيارها عشوائيا "من جميع مناطق الضفة الغربية وتم تحليلها بواسطة برنامج SPSS-10 – تقريبا" نصف الوصفات كانت تحتوي على مشتقات BZD بالذات دواء البرازولام يتبعة دواء كلونازيبام. أكثر من نصف وصفات BZD كانت ناقصة من حيث المعلومات الخاصة بالمريض أو معلومات آخرى ضرورية للصرف. لم يكن هنالك تأثير لجنس المريض أو تخصص الطبيب على صرف البنزوديازيبين. في حوالي ٥٧% من الوصفات كان هنالك أدوية مضادة للكآبة TCA موصوفة مع أدوية البنزوديازيبين. أدوية الكآبة من نوع TCA كانت موصوفة أكثر من SSRI. في حوالي

٢٠% من وصفات أدوية انفصام الشخصية كان هنالك أدوية BZD وبالذات دواء كلونازيبام. في المحصلة، بالرغم من ان هذه الدراسة غير مبنية على حالات مرضية معروفة من حيث تاريخها المرضي والدوائي الا أن هذه الدراسة تبين أن هنالك ممارسات غير دقيقة في وصف البنزوديازيبين.

Introduction

Benzodiazepines (BZD) are among the most widely prescribed anxiolytic and hypnotic medications due to their effectiveness in relieving anxiety and insomnia [1]. When they were introduced into clinical use in early 1961, BZD appeared to be a safer alternative to barbiturates with regard to long term use. However, reported side effects like impaired psychomotor performance and cognitive function, especially memory, withdrawal symptoms, dependence and abuse were of concern to people in the medical field [2]. Concern about BZD use is further increased because: first, most BZD use is based on personal and social circumstances rather than on truly physiological processes or needs [3]; and second, there is no evidence of benzodiazepines being effective for more than 3-4 months [2].

No studies were carried out to investigate the prevalence of BZD use among the Palestinian population. Such a project is of great importance given the loose health system and lack of law enforcement in Palestine. Furthermore, the misuse of BZD could add a new disease or new problem to the already existing problems regarding irrational drug use in Palestine. Studies in other countries have indicated that benzodiazepine use varies from 2-10% of the adult population. That use increases with age and is more common among women than men. Of the total users of benzodiazepines 15-30% were reported to be continuous users and have, in most cases, developed a physical dependence [4 – 8].

One important aspect in evaluating population based BZD use is to focus on physicians perspective of BZD prescribing. Such studies are also lacking in Palestine. BjoÈrndal and Fugelli found good theoretical knowledge about when and how to prescribe benzodiazepines among physicians, despite this, they found a great variation in prescription practices with respect to benzodiazepines [9]. Isacson (1997) found that female and younger physicians prescribed psychotropics to female patients more often than to male patients, and did so more frequently than male and older physicians did [4]. Differences among various specializations of physicians have not shown any consistent pattern [4, 10] and hence, the great variation among physicians with regard to prescribing benzodiazepines is not clearly understood.

There are currently no accepted guidelines for the safe and effective prescribing of BZD [11-12]. In several other countries various steps have been taken to control the prescription of benzodiazepines [11-12]. In Europe, the *Swedish Medical Board* has published recommendations about how to prescribe BZD as e.g. never prescribe benzodiazepine at the first visit or to an unknown patient, offer non pharmacological support or psychotherapy as the first choice and restrict the use of benzodiazepine to more severe cases of anxiety or insomnia [11-12]. In addition, many countries have introduced special numbered prescriptions, sometimes in duplicate or triplicate, for registration and follow-up [13]. The present study was undertaken in order to explore the BZD prescribing pattern among psychiatrists and neurologists, to investigate the effect of gender on BZD prescribing and to investigate the drugs co-prescribed with BZD.

Methodology

The goal of this paper is to investigate the BZD prescribing based on out-patient prescriptions dispensed at community pharmacies in Palestine. The community pharmacies refer to private pharmacies that are open to the public and sell and dispense medications. The prescriptions collected were those prescribed by psychiatrists or neurologists. The categorization of a psychiatrist or neurologist was based on the title appearing on the top of the prescription. The collected prescriptions from all the students in all areas were pooled and organized by the authors. The authors have no prior knowledge of the prescribing physicians or areas from which the prescriptions were collected. The collection process was meant to be random and unbiased. The students collecting the prescriptions were not told about the study or the purpose of the study until the end of the collection process. The data contained in the prescriptions were analyzed using SPSS version 10 for windows. The data entered and analyzed include the source of the prescription, the age and gender of the patient, number of drugs, class and type of drugs prescribed and finally whether the drugs are locally manufactured or imported.

The overall purpose of prescription collection is to create an annual prescription database that will serve:

1. In studying prescribing pattern and prescribing rational in Palestine and,
2. In doing pharmacoepidemiological surveys for major and specific drugs in Palestine. Such studies, to the best of author's knowledge, have not been carried out in Palestine before.

The current work is based on five hundred and five (505) prescriptions. These out-patient prescriptions were collected by An-Najah third, fourth and fifth grade pharmacy students who spend their summer courses in the third and fourth year training in community pharmacies. The collection period was roughly between January 2000 and May 2001. The prescriptions included for this current study were not collected from a particular area in the West-Bank of Palestine. In fact, the prescriptions for this current work and for our ongoing project were being collected from community pharmacies located everywhere in West-Bank of Palestine. In this current work, the data was collected and analysed based on proprietary names and was aggregated by individual medication as well as by central nervous system drug class. Finally, the current work is based on prescription analysis and not on direct patient or physician contacts. Nevertheless, this work will be the first step for studies to be based on either patient review or retrospective complete drug profile review.

Results

1. Descriptive Statistics of the Prescription Sample:

The 505 randomly collected prescriptions were prescribed by (256/505; 50.7%) neurologists and by (249/505; 49.3%) psychiatrists. The prescriptions belong to 267 male patients (52.9%) and to 238 female patients (47.1%). The age distribution of the patients to whom the prescriptions were dispensed was not clear. In three hundred and one (301) prescriptions, the patient age was not specified. For the rest of the prescriptions (204/505; 40.4%), the age disribution of the patients was as follows: 85/204 (41.6%) were less than 30 years old; 87/204 (42.6%) were between 30 and 50 years old and finally 34/204 (16.6%) were above 50 years old. Regarding the number of drugs present in the prescriptions, there was a total of 1006 drugs in the 505 prescriptions giving an average of approximately 2 medications per prescription. Less than 5% of the prescriptions contained 4 or more drugs per prescriptions.

2. Benzodiazepine Prescribing Pattern:

Approximately 48 % (244/505) of the prescription contained BZD suggesting that every other patient attending a psychiatric or neurologist clinic was prescribed a BZD drug. The most commonly prescribed BZD was alprazolam (15.6%) followed by clonazepam (12.1%) and lorazepam (8.5%) as seen in table 1.

Table (1): Frequency and distribution of various types of BZD in the 505 prescriptions.

BZD

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no BZD	261	51.7	51.7	51.7
	Diazepam	26	5.1	5.1	56.8
	Alprazolam	79	15.6	15.6	72.5
	Lorazepam	43	8.5	8.5	81.0
	Clonazepam	61	12.1	12.1	93.1
	Bromazepam	31	6.1	6.1	99.2
	Chlordiazepoxide	1	.2	.2	99.4
	Triazolam	2	.4	.4	99.8
	Clobazam	1	.2	.2	100.0
	Total	**502**	**100.0**	**100.0**	

Analysis of gender or physicians speciality on BZD prescribing shows that there is no statistically significant effect of gender and BZD prescribing ($P > 0.05$) suggesting that prescibing of BZD is not influnced by sex of the patient as seen in table 2. One hundred and twenty three male patients were prescribed BZD (123 / 267; 46%) while one hundred and twenty one female patients were prescribed BZD (121/238; 50.8%).

Table (2): correlation between gender and BZD prescribing.

Crosstab

Count

		Gender		Total
		Male	female	
BZD	no BZD	144	117	261
	Diazepam	12	14	26
	Alprazolam	37	42	79
	Lorazepam	31	12	43
	Clonazepam	27	34	61
	Bromazepam	16	15	31
	Chlordiazepoxide		1	1
	Triazolam		2	2
	Clobazam		1	1
	Total	**267**	**238**	**505**

Analysis of BZD prescribing with respect to physicians specialty shows that there is no statistical significance between being a psychiatric or neurologist and prescribing BZD. However there is a strong statistical

significance between the specialization (neurologist vs. psychiatrist) and the type of BZD prescribed. Neurologists prescribe mostly clonazepam followed by alprazolam while psychiatrists prescribe mostly alprazolam followed by lorazepam as seen in table 3. Such differences could be explained on the pharmacological basis of the therapeutic use of alprozaolam versus clonazepam. Alprazoplam is used mostly for treatment of generalized anxiety and no surprise that it is very commonly prescribed by psychiatrists for anxiety disorders. On the other hand, clonazepam is mostly used as sedative hypnotic. Neurologists who encounter many neurological conditions that my include painful attacks like migraine or epilepsy might need to prescribe such drugs to sedate the patient.

Table (3): Neurologists vs. Psychiatrists BZD prescribing choices

Crosstab

Count

		Specilty		Total
		Neurologist	**Psychiatriat**	
BZD	no BZD	133	128	261
	Diazepam	13	13	26
	Alprazolam	31	48	79
	Lorazepam	11	32	43
	Clonazepam	45	16	61
	Bromazepam	22	9	31
	Chlordiazepoxide	1		1
	Triazolam		2	2
	Clobazam		1	1
	Total	**256**	**249**	**505**

3. BZD co-prescription with Anti-depressants and anti-psychotics:

Analysis of BZD medications co-prescribed with anti-depressants by neurologists or psychiatrists shows that 160 prescriptions (160/505; 31.7%) contained neither BZD nor anti-depressant medications. One hundred and thirty six of the prescriptions containing anti-depressant medications (136/237; ~57 %) have BZD in the prescription as seen in table 4. The most common anti-depressant / BZD combination were clomipramine / clonazepam followed by imipramine / alprazolam.

Table (4): BZD medications co-prescribed with anti-depressants.

Crosstab

Count

	BZD									
	No BZD	**Diaze-pam**	**Alpra-zolam**	**Loraz-epam**	**Clona-zepam**	**Broma-zepam**	**Chlord-iazepo-xide**	**Triaz-olam**	**Cloba-zam**	**Total**
ANTIDEIno.	160	22	36	18	24	7			1	**268**
Fluox	18		14	4	8	10				**54**
Clomip	3	1	2	1	20	4				**31**
Amitripty	43	2	8	8	2	1				**64**
Trazadone	1			1	1					**3**
Maprotiline	9			1	1					**12**
paroxitine	6		2	2	4	3				**17**
Imipramine	18	1	16	9	1	5				**50**
Citalopram	2		1					2		**5**
Fluvozamir	1									**1**
Total	**261**	**26**	**79**	**43**	**61**	**31**	**1**	**2**	**1**	**505**

Analysis of BZD medications co-prescribed with anti-psychotics shows that among the 505 prescriptions, one hundred and nine (109/505; 21.6%) prescriptions contained antipsychotic medications and that among those 109 prescriptions, twenty two (22/109; 20%) contain BZD co-prescribed with the anti-psychotic medications. The most common anti-psychotic / BZD combination was haloperidol / clonazepam as can be seen in table 5.

Table (5): BZD medications co-prescribed with anti-depressants.

ANTIPSY* BZD Crosstabulation

	BZD									
	No BZD	**Diaze-pam**	**Alpra-zolam**	**Loraz-epam**	**Clona-zepam**	**Broma-zepam**	**Chlord-iazepo-xide**	**Triaz-olam**	**Cloba-zam**	**Total**
ANTIPS'no	174	22	76	41	50	29	1	2	1	**396**
Haloperidol	16				5					**21**
Sulpiride	6	3	2	1	3	2				**17**
Thioridazine	11			2						**13**
Chloropromazir	10				1					**11**
Thioxanthene	23									**23**
Trifluperazine	14			1						**15**
Risperazine	3	1								**4**
Clozapine	4		1							**5**
Total	**261**	**26**	**79**	**43**	**61**	**31**	**1**	**2**	**1**	**505**

The various types of benzodiazepines available in the Palestinian market is shown in table 6. The table lists the BZD generics with trade names, half life (duration of action), therapeutic aim and equivalent oral dose.

Table (6): BZD Pharmacological Characterstics[31]

Benzodiazepines[5]	**Half-life (hrs) [active metabolite]**	**Market Aim**	**Approximately Equivalent Oral dosages (mg)**
Alprazolam (Xanax®)	6-12	a	0.5
Bromazepam (Lexotan, Lexomil)	10-20	a	5-6
Clobazam (Frisium®)	12-60	a,e	20
Clonazepam (Rivotril®)	18-50	a,e	0.5
Clorazepate (Tranxene®)	[36-200]	a	15
Diazepam (Valium®)	20-100 [36-200]	a	10
Estazolam (ProSom®)	10-24	h	1-2
Flunitrazepam (Rohypnol®)	18-26 [36-200]	h	1
Flurazepam (Dalmane®)	[40-250]	h	15-30
Halazepam (Paxipam®)	[30-100]	a	20
Ketazolam (Anxon®)	2	a	15-30
Loprazolam (Dormonoct®)	6-12	h	1-2
Lorazepam (Ativan®)	10-20	a	1
Lormetazepam (Noctamid®)	10-12	h	1-2
Medazepam (Nobrium®)	36-200	a	10
Nitrazepam (Mogadon®)	15-38	h	10
Oxazepam (Serax®)	4-15	a	20
Prazepam (Centrax®)	[36-200]	a	10-20
Quazepam (Doral®)	25-100	h	20
Temazepam (Restoril®)	8-22	h	20
Triazolam (Halcion®)	2	h	0.5

The speed of elimination of a benzodiazepine is obviously important in determining the duration of its effects. The effect of the duration of action of the BZD may become apparent during continued use or may appear as withdrawal symptoms when dosage is reduced or the drug is stopped. Although all BZD have similar actions, they are usually marketed as anxiolytics (a), hypnotics (h) or anticonvulsants (e). There are major differences in potency between different benzodiazepines, so that equivalent doses vary as much as 20-fold. For example, 0.5 milligrams (mg) of alprazolam (Xanax®) is approximately equivalent to 10mg of diazepam (Valium®). Thus a person on 6mg of alprazolam daily, is taking the equivalent of about 120mg of diazepam, a very high dose These differences in strength have not always been fully appreciated by doctors, and some would not agree with the equivalents given here. Nevertheless, people on potent benzodiazepines such as alprazolam, lorazepam (Ativan®) or clonazepam (Klonopin®) tend to be using relatively large doses. This difference in potency is important when switching from one benzodiazepine to another, for example changing to diazepam during withdrawal, as described in the next chapter.

Discussion

From this study of 505 randomly selected out-patient prescriptions throughout West-Bank, we can see that BZD are commonly prescribed by psychiatrists and neurologists. Based on the data and information available in our hand, it is difficult to judge whether BZD in the prescriptions studied was justifiable or not. However, few points deserve attention:

1. More than half of the BZD prescriptions were not complete: patient's age, date and duration of therapy were missing from the prescription.
2. More than 90% of the prescriptions did not specify the number of re-fills.
3. Very few BZD prescriptions (< 5%) were stamped by the dispensing pharmacist and finally.
4. In approximately 103 / 244 (42%), the dose or strength of the BZD were not clearly specified. These irrational practices on the behalf of the prescribing physicians and dispensing pharmacists as well might lead to serious clinical and legal consequences. Since no information is available on the prevalence and prescribing pattern of BZD by general practitioners and other specialist in Palestine, we can not extrapolate the previous points to the whole medical situation in Palestine. However, we strongly recommend that the Ministry of Health (MOH) issues special prescription

format for BZD and demand pharmacists to keep these prescription for inspection purposes. Such prescription format may be available in three copy format such that the physician keeps one copy and the second copy is kept by the pharmacist while the third copy is to be sent by the pharmacist to the department of Pharmacy at the MOH on a monthly basis.

In our study, we also found that the patient's gender has no influence on BZD prescribing. Similarly, no differences were found among psychiatrists and neurologists with regard to BZD prescribing in general, although differences were found with regard to the type of BZD being prescribed.

Our data also showed that BZD were commonly prescribed with antidepressant drugs. The data also showed that Tricyclic and other nonselective amine reuptake inhibitor antidepressants were more commonly prescribed than selective serotonin re-uptake inhibitors (SSRIs). Choosing appropriate antidepressant therapy is not an easy task [(14)]. Particular attention has been given to the adverse effects of these drugs. Side effects associated with the use of (TCAs) include postural hypotension, anticholinergic effects, and extrapyramidal symptoms [(15)]. Adverse effects of selective (SSRIs) include syndrome of inappropriate antidiuretic hormone secretion, gastrointestinal disturbances, and insomnia [(15)]. As a result of the unwanted effects of TCAs, the use of SSRIs is increasing [(14)]. However, the preferential use of the more expensive SSRIs is still under debate [(16-18)]. The need for concomitant benzodiazepines during antidepressant therapy has also been debated [(19– 23)]. BZD drugs decrease the nonspecific symptoms of depression, such as insomnia, agitation, and anxiety, and are often used during the initiation of antidepressant treatment. After 4–6 weeks of treatment, benzodiazepine is usually discontinued [(24)]. Drug utilization studies has suggested that concomitant prescribing of benzodiazepines may occur more frequently in users of SSRIs than in users of TCAs, and this may be partly due to the less sedative effects of SSRIs [(20-21)]. In our study, BZD were more commonly co-prescribed with TCA (69%) than SSRIs (43%). This might be questionable given the additive sedative effects of BZD and TCAs. However, we can not confirm that the prescribed TCA were actually used as anti-depressant and not as an analgesic for chronic pain.

Our study also shows that anti-psychotics were also co-prescribed with BZD. Benzodiazepine are used in acute psychotic state to reduce hyperarousal and prevent further exhaustion and harm, however, long term use of benzodiazepine has not been adequately researched. Wolkowitz has reported the

successful use of alprazolam combination to neuroleptics after 37 months of follow – up [25]. The correct choice of benzodiazepine to be co-prescribed with antipsychotic is not clear. Although the low potency diazepam and lorazepam are the most frequently used benzodiazepines for rapid tranquilization [26]. Alprazolam and clonazepam have been reported to be more potent and effective in neuroleptic augmentation [27]. In our study, clonazepam was the most frequently co-prescribed BZD with the anti-psychotic medications. The preference of low potency BZD (e.g. lorazepam and diazepam) is for successful and easy withdrawal in the long term use [28]. Major disadvantages for the use of BZD in psychosis include tolerance, rebound psychosis and withdrawal [29]. Worsening of the baseline psychotic symptoms in long term benzodiazepine users would mean increase in benzodiazepine dose and increase or change of the antipsychotic medication. Given these potential problems, there is a questionable need for co-prescribing BZD with antipsychotics in long term use. Research evidence recommend benzodiazepines only for short term relief of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia, short-term psychosomatic, organic or psychotic illness[30].

In conclusion, although our study is not based on complete clinical investigation of patients disease and drug history, it is clear that there is some irrational BZD practices that require further investigation.

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