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ASSESSMENT OF PHARMACISTS' AND PATIENTS' KNOWLEDGE AND ATTITUDE TOWARDS IRRATIONAL USE OF CHLORDIAZEPOXIDE-CLIDINIUM BROMIDE COMBINATION IN KHARTOUM STATE

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ABSTRACT

This study was conducted to evaluate the knowledge and attitude of community pharmacists in controlling Chlordiazepoxide-Clidinium bromide (CC) dispensing and to assess the potential of irrational use of this combination product. Self-administered questionnaire was used as the study tool and distributed among 200 community pharmacist and 200 CC users. The majority of pharmacists [176/200 (88%)] were shown to dispense CC as OTC. Although the vast majority of respondent pharmacists [192/200 (96%)] mentioned frequent dispensing of CC for certain patients without prescription, but [196/200 (98%)] revealed no patient counseling regarding the presence of concomitant diseases and/or the use of other medications before dispensing CC. Concerning the pharmacist's knowledge about CC, only [60/200 (29.7%)] correctly mentioned the chemical group to which chlordiazepoxide belonged. Sedation was the most side effect of CC that reported by [114/200 (57%)] of pharmacist, followed by addiction [50/200 (25%)], constipation [48/200 (24%)] and tolerance [18 (9%)]. Regarding patients, most of them [141/200 (70.5%) reported purchasing of CC as OTC with the vast majority of them [195/200 (97.5%)] mentioned continued use beyond the prescribed course. The majority of patients announced the use of CC for 4-6 years. Only six (3%) women had used CC during pregnancy with three (50%) of them been aborted their pregnancies, two (33%) delivered children with thalidomide-like deformities and one (17%) had no problem.

KEYWORDS: Chlordiazepoxide, Clidinium bromide, prescription, dispensing, patient counseling.

1. INTRODUCTION

Chlordiazepoxide-Hcl/Clidinium-bromide (CC) is a fixed drug combination (5/2.5 mg) that combines the anticholinergic effects of clidinium bromide and the anxiolytic properties of the chlordiazepoxide hydrochloride. It's commonly used in the treatment of irritable bowel syndrome and in peptic ulcer as adjunctive therapy.[1] Clidinium bromide might be used for smooth muscle relaxation or to decrease the biliary tract secretions.[2] Chlordiazepoxide belongs to the least restrictive Schedule IV controlled drug under the convention on psychotropic substances.[3] Like other benzodiazepines, chlordiazepoxide has skeletal muscle relaxation effect, hypnotic properties and could be used for its anxiolytic effect.[4] It binds to the benzodiazepine allosteric sites of the gamma-aminoputyric acid (GABA)/ion-channel receptor complex, potentiating the inhibitory effects of neurotransmitter GABA on the central nervous system and the body.[5] It is thought that the activation of the benzodiazepine-GABA-chloride ionophor complex responsible from the anxiolytic effect of benzodiazepines and their side effects. Dependence and withdrawal from these drugs also might be attributed to the same mechanism.[6] In addition to its anxiolytic properties, chlordiazepoxide alone is also indicated for the treatment of the withdrawal symptoms of the alcohol.[7] The high rate of prescription of benzodiazepines over barbiturates might be due to the fact that they are relatively safer, but they are potentially addictive drugs.[8] Therapeutic doses of Benzodiazepines might lead to dependence and cause withdrawal symptoms if the drug discontinued suddenly. Dose tapering or medication switching generally used to avoid the withdrawal symptoms.[9] However, moderate dosage for short period of time (1-2 weeks) doesn't induce dependence or withdrawal symptoms.[10] On the other hand, long term use of benzodiazepines at therapeutic doses will lead to physical dependence and the users will

experience withdrawal symptoms.[11] Benzodiazepines differ in their dependence potential.[12] Increase the dose of some benzodiazepines may not add therapeutic value to the patients taking benzodiazepine on a daily basis.[13] A previous study showed that if the elderly people stop taking benzodiazepines, their doctor visits per year will be reduced.[14] Benzodiazepines may aggravate substance abuse and its prescription for the patients with severe mental disorders is controversial.[15, 16] Although benzodiazepines are prescription only drugs, but their irrational use was reported.[17]

Chlordiazepoxide is a long acting benzodiazepine that accumulates in the body during repeated administration. Its metabolite (desmethyldiazepam) which is also active has a longer half-life than the parent compound and its clearance decreases in individuals with liver disease or the elderly patients.[18, 19] It is recommended that chlordiazepoxide should not be prescribed to the elderly, [20] during pregnancy or for children.[21] However, chlordiazepoxide and diazepam relatively safer than the other benzodiazepines and their prescription during breastfeeding or pregnancy should be based on the benefits/risks ratio.[22-24]

Intensive patient counseling and education is required for patients taking benzodiazepine, for instance, if there is a hypersensitivity or allergy to any drug in the benzodiazepine class or the patient suffering from acute narrow-angle glaucoma, severe hypoventilation, severe sleep apnea, myasthenia gravis and severe liver deficiencies.[25] Chlordiazepoxide has been found to increase the risk of addictive behavior in animals, [26] and substituted for the behavioral effects of barbiturates.[27] In addition, it was detected in the urine of drug users without medical prescription, which indicating irrational use of the drug.[28]

Therefore, this study was conducted to assess the knowledge of both community pharmacist and patients about CC and to evaluate the role of community pharmacist in controlling the irrational use of this drug.

2. METHODOLOGY

2.1. Study design, population and area

The study was conducted as non intervention, descriptive cross sectional survey. Self-administered questionnaire was designed and used as study tool. The study population comprised 204 community pharmacist and 200 CC users in Khartoum state, Sudan. Verbal consent was taken from all pharmacists and patients participated in this study.

2.2. Sampling techniques

The total number of pharmacies in Khartoum state was 1225, the list was provided by Directorate of Pharmacy, Ministry of Health, Khartoum state, Sudan. The distribution of pharmacies in the 3 cities of Khartoum state was: 513 pharmacies in Khartoum city, 417 in Omdurman city and 295 pharmacies in Khartoum North city.

The sampling size was calculated according to the following equation

$$n = \frac{N z^2 P q}{(N-1) d^2 + z^2 P q}$$

$$n = \frac{1225 \times (1.96)^2 \times 0.5 \times 0.5}{1224 \times (0.06)^2 + (1.96) \times 0.5 \times 0.5} = 240$$

Where
N = Population under study
n= Sample size
Z= Value of normal curve corresponding to level of confidence (95% = 1.96).
P= Proportion of target group
q= 1 – p
d= Desired margin of error 6%

Hundred (42%) Pharmacies were selected from Khartoum city, 80 (34%) Pharmacies from Omdurman city and 60 (24%) Pharmacies from Khartoum North city. Two hundred pharmacists and 200 patients within these pharmacies received the questionnaire.

2.3. Systematic random sampling

Sampling was carried out as follows

Sample interval= total number of pharmacies in the group/number of pharmacies to be included in the sample. e.g. in Khartoum city : 513/ 100 = 5.13.

The random number containing three digits was selected to be 0.195. Sample interval = 5.13 x 0.19 = 1 (represent the first number of pharmacy from the list to be chosen).

The same procedure was carried out to choose the remaining 100 pharmacies in Khartoum city which done as follows

The second chosen pharmacy = 1 + 5.13 = 6.13, approximately pharmacy No. 7.
The third chosen pharmacy = 6.13 + 5.13 = 11.26, approx. pharmacy No. 12

The same selection procedure was applied for the pharmacies of the remaining cities (Omdurman and Khartoum North) to be included in the study.

Finally, 1 pharmacist and 1 patient from the specified pharmacies were included in the study.

2.4. Study questionnaire: Two questionnaires were especially created for the purpose of this study and a pilot survey was conducted to identify the variables of the study. The first questionnaire was designed to assess the knowledge of community pharmacist about CC and its irrational use, the number of CC strips sold as OTC or as prescriptions per day and to assess the pharmaceutical care provided by community pharmacists

to patients taking this drug. The second questionnaire was directed towards patients and designed to evaluate their knowledge about CC and its irrational use, and to identify the categories of people using CC.

3. RESULTS

The response rate was found to be 100% for the patients and 99% for the community pharmacists. Most of community pharmacists participants (74%) and patients (55%) were female. Most of the Pharmacists holding B.pharm (82%). The vast majority of pharmacist's ages range between 22 - 40 years and there were only 8 participants above 40 years, however those between 22 – 26 years constitute (46%) of the pharmacists participants. While (45%) of the patients with age range from 31- 40 years "Fig. 1". On the other hand (55%) of patients were female, (45%) hold University degrees, (40%) below University degree, (15%) postgraduate and (25%) were manual labor. The detailed occupations of patients taking CC were summarized in "Fig. 2."

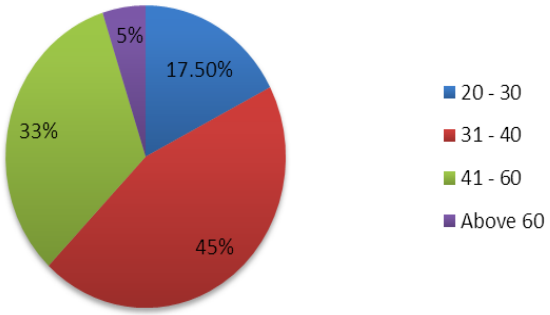

Figure 1: Ages (years) of patients using CC (n = 200)

It was found that 98% of Pharmacist dispensed CC as OTC and (75%) of them think that CC should be dispensed as OTC. For the number of strips that normally dispensed as OTC per day, we found that (67%) dispense 1-10 strips, (25%) dispense 11-20 strip, (4%) dispense 21-30 strips, (2%) dispense more than 30 strips per day while only (2%) didn't dispense CC as OTC. The vast majority of pharmacists (95%) dispense CC frequently for certain patient. It has been found that almost all pharmacist dispense CC daily by prescription and a large proportion of them (72%) dispense (1-5) strips of CC by prescription per day.

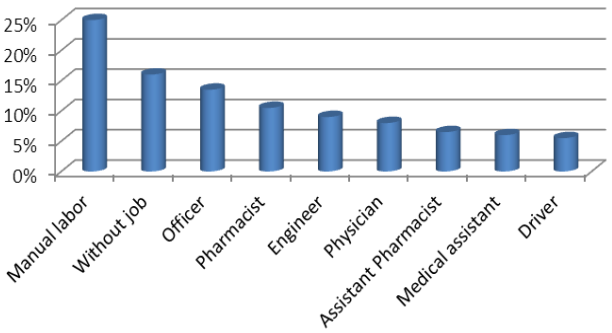

Figure 2: Occupations of patients using CC (n = 200)

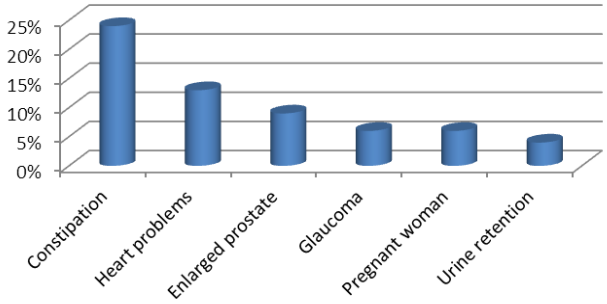

Figure 3: Pharmacists dispensed CC with one or more of these diseases

The majority of pharmacists (97%) not asked patients from other concomitant diseases "Fig. 3" or drugs "Fig. 4" before dispensing CC and also (97%) of the patients confirmed that pharmacists didn't ask them questions before dispensing CC. Most of pharmacists not remember if they dispense CC while the patients suffering from some diseases such as enlarged prostate, glaucoma and constipation or using central nervous system medicines.

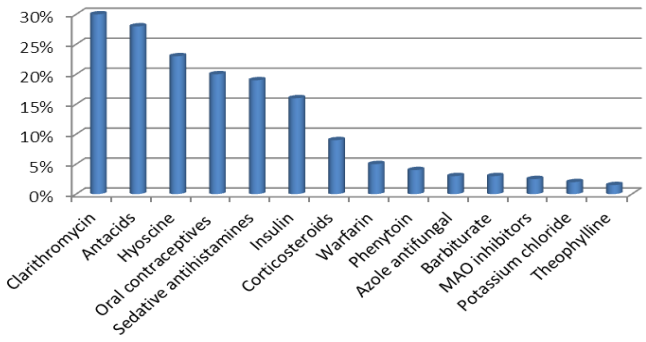

Figure 4: Drugs dispensed with CC by Pharmacists

Regarding the knowledge of pharmacists about CC side effect, (57%) mentioned sedation as one of the side effects, (25%) mentioned addiction, (24%) mentioned constipation and (10%) mentioned tolerance as one of the side effects of CC "Fig. 5".

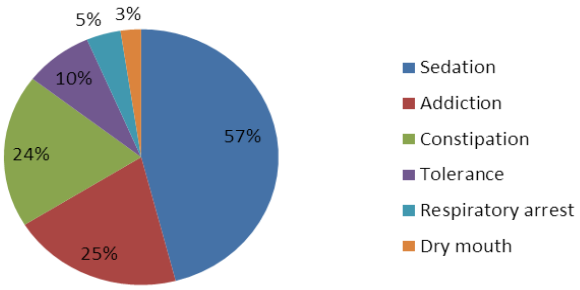

Figure 5: Side effects of CC mentioned by Pharmacists participants

Seventy percent of patients stated that they are using CC as OTC and the vast majority of patients (97%) continued CC after finishing the prescribed course, (41%) used CC for (4-6) years "Fig. 6", (95%) mentioned that they were not asked by pharmacists from prescription to buy CC, while all patients stated that pharmacists never dispense CC with prescription only.

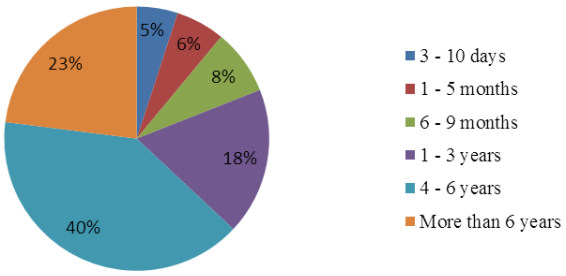

Figure 6: Duration of CC usage

Patients using CC as OTC were asked about the sources of their information and (32%) said that they knew it from doctors, (24%) from pharmacists, (34%) from their friends and (10%) from their relatives. Forty percent of the patients said that they can't stay for 10 days without using CC and (59%) stated that they observed some changes in their behaviors such as nervousness or some side effects such as sedation after long use of CC.

Although (57%) of patients didn't specify when they used CC but (28%) of them used it before meal. In this survey we found that 3% of patients participants used CC while they were pregnant. Although some of pregnant women used CC didn't face any problems, but half of them had an abortion and there were 2 mothers gave birth to babies with significant birth defects such as thalidomide-defects and their babies died. It is worth noting that one of the later cases used CC together with mefenamic acid when pregnant.

The reasons for using CC specified by patients were summarized in "Fig. 7". Ninety percent of the patients stated that they are using CC for irritable bowel syndrome.

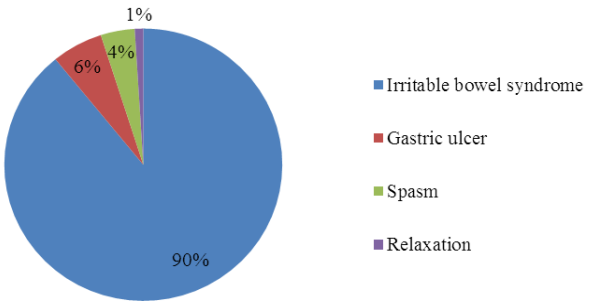

Figure 7: Reasons for using CC specified by patients

4. DISCUSSION

The irrational use of drugs continues to increase despite interventions by health care professionals and regulatory agencies. Drugs containing benzodiazepines such as CC are the leading class of irrationally used drugs. In our region and most developing countries where there is no proper implications of drug policies, we believe that the actual impact of irrational use of these drugs is beyond the expectations of health care professionals. However, in some developed countries such as USA where there is a proper drug-monitoring programs, a 5-fold increase in deaths attributed to benzodiazepines occurred from 1999 to 2009.[29]

In this study most of the community pharmacists participants (74%) were female. The gender profile of pharmacist is due to the fact that most of the graduates of the faculties of pharmacy in Sudan are female. Also most of the patients (55%) using CC were female and this higher usage rates among female is in accordance with what were described in the literature.[30-32] Ironically, 32% of the patients using CC in this study were health personnel and 45% of them hold University degrees "Fig. 2". The reason behind this high usage among educated people is unknown, however, most health personnel believed that CC in general is relatively safe and, with overdose, rarely result in death. It is known that used chronically, drugs containing benzodiazepines can be addicting.[14]

Despite the fact that widespread concerns surrounding the CC use have abounded for long time, but this study revealed that this drug is still widely dispensed by pharmacist (98%) as OTC and (75%) of these pharmacist think that CC should be dispensed as OTC, while 70% of patients stated that they are using CC as OTC. Major clinical problems may arise from the fact that 40% of patients in this study said that they can't stay for 10 days without using CC which may prone them to side effects of chronic use such as physical and psychological dependence. In addition, there is no obvious therapeutic benefit from its chronic use and people may develop tolerance to it.[9, 11] Also in most industrialized countries CC and benzodiazepines in general are still widely prescribed drugs of all time, [33] although there is a doubt of their clinical effectiveness and their chronic prescription is a matter of great concern for those committed to global health.[34, 35] Irrational use of drugs remains a major concern worldwide, therefore, pharmacists should have the knowledge and skills needed to take up their responsibilities and find some alternatives to the dispensing of CC.

This study also highlighted the knowledge of pharmacists towards CC side effects "Fig. 5". Although there is a considerable number of pharmacists didn't know the side effect of CC such as sedation, addiction, constipation, blurred vision, dry eyes, dry mouth and tolerance, but in general their knowledge about CC was intermediate. This level of pharmacist's knowledge was reported in the literature. Pharmacists working in community settings are less knowledgeable than those who work in the hospital or clinical settings.[35, 36]

We believed that pharmacists should always be an accessible and trusted source of advice and treatment, but in this study, a large proportion of pharmacists (97%) not asked patients from other concomitant diseases "Fig. 3" or drugs "Fig. 4" before dispensing CC, and also (97%) of the patients confirmed that pharmacists didn't ask them questions before dispensing CC. Furthermore, a substantial number of pharmacists did not remember if they dispense CC while the patients suffering from some diseases or taking other medications that might be contraindicated. What was truly frustrated is that (30%) of pharmacists only was known the drug group of

Chlordiazepoxide, including 7 Pharmacists holding M. Pharm. This may be attributed to the fact that the vast majority of pharmacists participants in this study were holding B.pharm (82%) and with ages range between 22 - 40 years. However, other study reported that younger pharmacists performed better than older pharmacist and age had a negative relationship to knowledge.[36] It's clear that there is an urgent need for professional training that offers the pharmacists deep knowledge to play an expanded role in optimizing the use of all drugs, including CC, and reducing their inappropriate use.

It's known that CC and all other drugs containing benzodiazepines should not be used for long time, [18-20] however, in this study we found that (41%) of the patients used CC for (4-6) years and (23%) used it for more than 6 years "Fig. 6". Some countries have issued prescribing guidelines for benzodiazepines. The benzodiazepine committees of Ireland, [37] UK, [38] Denmark and Norway [39] recommending that these drugs should not be prescribed for longer than 2–4 weeks. Existence of such guidelines in addition to drug consultation behavior will improve therapeutic outcomes and patients' quality of life.

CC may harm a fetus, therefore it's not recommended for use during pregnancy. In addition, it passes into breast milk and may have undesirable effects on a nursing infant, so breast-feeding while using this drug is not recommended too.[22-24] However, in this survey we found that 3% of the patient participants used CC while they were pregnant and half of them had an abortion, and there were 2 mothers gave birth to babies with significant birth defects.

Based on these findings there is an urgent need for intensive educational and continues training programs, workshops and seminars for the pharmacists to provide appropriate patient education, counseling and other activities revolving around professional practice and health care ethics. Nevertheless irrational patient demand has to be addressed by well-planned health education, and to the best of our knowledge there are no such programmes available in our region.

5. CONCLUSION

Results in this study showed inappropriate use of CC among patients with various educational levels including health personnel. Although it's recommended that benzodiazepines should not be prescribed for longer than 2–4 weeks, but we found that patients used CC for very long time, even years. In addition, the majority of pharmacists participants in this study dispensed CC as OTC and there was not enough patients counseling. CC could serve as a useful model for examining the role of the pharmacist in optimizing drug use since its chronic use is prevalent in our region.

CONFLICTS OF INTEREST

The authors declares no conflict of interest.

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