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Original Research

A snapshot on the usage pattern of gabapentinoids in Oman

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Abstract

Background: Since their introduction as adjunct anticonvulsants, the use of gabapentinoids (gabapentin and pregabalin) has increased substantially worldwide to include a wide range of clinical conditions. Various reports have demonstrated that they possess addiction liability and can produce effects similar to traditional recreational drugs, such as significant euphoric effects, enhanced sociability, and relaxation. However, there is limited information on the use of these agents in the Middle East. Objectives: Here, we describe the usage pattern of gabapentinoids at Sultan Qaboos University Hospital, a tertiary care medical institution in Oman. Methods: Adult patients (≥18 years) who were prescribed gabapentinoids for six months (March–August 2019) were included in this retrospective cross-sectional study. Indications and dosing regimens were reviewed according to the Food and Drug Administration labeling. Controlled and restricted drugs were reviewed using Oman National Formulary. Institutional ethical approval was obtained before conducting the study. Results: We analyzed 291 prescriptions. The mean (standard deviation, SD) age was 60.5 years (SD = 13.0) with the age group of ≥60 years being the most common (190, 65.3%). Most of patients were females (178, 61.2%). The majority of prescriptions were for outpatients (85.8%). Drugs were prescribed as refill and follow-up in 116 (40.0%) and 97 (33.4%) of prescriptions, respectively. Diabetic peripheral neuropathy (50, 79.4%) was the most labeled indication for both. Off-label use was 128 (51.8%) and 31 (70.5%) for pregabalin and gabapentin, respectively, with lower back pain as being the most common indication for both drugs. A total of 54 (19.0%) patients were using at least one of the psychotropic drugs. Conclusions: Our findings indicate that gabapentinoids are frequently prescribed for off-label use. Awareness programs and the establishment of policy for the use of these drugs are required to ensure their rational use and prevent misuse and/or abuse.

Keywords: pregabalin; gabapentin; abuse; misuse; off-label use

INTRODUCTION

The use of gabapentinoids has increased substantially worldwide since their introduction to the market in 1994, a trend that is expected to continue.[1] In the US the use of gabapentinoids increased from 1.2% in 2002 to 3.9% in 2015, while in the United Kingdom (UK), the use of gabapentin and pregabalin has increased by 350% and 150% over five years, respectively.[2,3]

There are multiple factors responsible for the increase in the use of these drugs such as an increase in off-label indications and clinician preference.[1,4,5] Clinicians prefer alternatives to opioid analgesics for chronic pain management due to potential opioid abuse.[5]

The increase in the use of these drugs was associated with the potential for their misuse and/or abuse and of causing harm to different patient populations. Smith et al. reported in 2016 that one–fifth of opioid abusers misuse gabapentin.[6] Similarly, another study showed that about 20% of opioid users have misused a gabapentinoids drug.[7] Moreover, gabapentin was found to be associated with a potential risk of suicidal ideation, aggressive behavior, and depression, especially in patients with underlying psychiatric conditions.[8] A population-based cohort study conducted in France in 2019 revealed that misuse, defined as the use of daily doses higher than the daily recommended dose, was more frequent in new users of pregabalin (12.8%) than in new users of gabapentin (6.6%) or duloxetine (9.7%; used as control).[9] Misuse was significantly associated with pregabalin use, younger age, having cancer, multiple sclerosis, neuropathy, and depressive disorder.[9] Furthermore, an analysis of the database EudraVigilance showed that misuse/abuse/dependence associated with pregabalin and gabapentin from 2004 to 2015 were 6.6% of 115,616 and 4.8% of 90,166, respectively.[10] In addition, the analysis reported a total of 27 and 86 identified fatalities, associated with pregabalin and gabapentin, respectively. In the UK, in a recent postmortem study on death due to drug use, gabapentin, and pregabalin were identified in 3.1% and 6.1% of all cases, respectively, compared to 3.2% for tramadol which was used as a control.[11]

This growing body of evidence regarding the potential for misuse and associated mortality of gabapentinoids has raised concerns about their use, especially with the increase in their prescription numbers. In response, gabapentinoids in the UK were reclassified as class C controlled substances (substances associated with the least amount of harm) in 2019.[12] As a result, there was an increase in studies on the utilization, prescribing

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patterns, and predictors of misuse and abuse of these drugs.

Information on the utilization pattern for the use of these drugs is scarce in the Middle East. Therefore, this study was performed to assess the utilization pattern of gabapentinoids in Oman.

METHOD

Setting and design

This retrospective cross-sectional study was conducted at the Sultan Qaboos University Hospital, a tertiary care and an educational medical hospital with a 700-bed capacity. All adult patients (≥18 years) who were prescribed gabapentinoids as in- or out-patient prescriptions between 1st of March 2019 and 31st of August 2019 were included. Ethical approval for this study was obtained from the Medical Research and Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University (MREC #2029).

Data collection

The data such as demographics, diagnosis, number of drugs per prescription, comorbidities and the prescribers' ranks and specialty, was collected from the electronic patient record, system used by the university hospital for storing patients' information. The latest prescription was considered for patients who had multiple prescriptions.

Drug indication and dosage

Indications for both drugs and dosing regimens were reviewed in accordance with Food and Drug Administration (FDA) labeling.[13,14] The indication was classified into labeled, off-label, others, and undocumented. A dose was considered within the dosage regimen if it did not exceed the maximum daily dose which is 600 mg/day and 3.6 g/day for pregabalin and gabapentin, respectively.

Controlled drugs

Controlled and restricted drugs were reviewed using Oman National Formulary as a reference. Controlled drugs can only be prescribed on special prescription (e.g., narcotic with red color Rx, psychotropic with green color Rx) while restricted drugs can only be prescribed by consultant and specialist or be used in specialized units. The use of controlled drugs by patients and their primary diagnosis were recorded.

Statistical analysis

The data were analyzed using Statistical Package for Social Science program version 26 (SPSS™, Chicago, IL, USA). Descriptive statistics were used to describe the data. Continuous variables were presented as means and standard deviation (SD) if normally distributed or as medians and interquartile range if not normally distributed.

RESULTS

Demographic and clinical data

Table 1 shows the demographic and clinical characteristics of patients (N = 291). Most of the patients were females (178, 61.2%). The mean (±SD) age was 60.5 years (SD = 13.0) with most patients in the ≥60 years' age group (190, 65.3%), followed by the 51–60 years (21.6%) and 41–50 years (10.7%). The majority of the prescriptions were for out–patients (85.8%).

Table 1. The demographic and clinical characteristics of the studied population, n=291

		Cohort	Pregabalin	Gabapentin
N (%)		291	247 (85.0)	44 (15.0)
Female gender		178 (61.2)	149 (60.0)	29 (66.0)
Age	Mean (±SD)	60.5 (13.0)	60.1 (12.7)	62.9 (13.4)
	18-30	2 (0.8)	2 (0.8)	-
	31-40	5 (2.0)	5 (2.0)	-
	41-50	31 (10.7)	26 (10.5)	5 (11.4)
	51-60	63 (21.6)	52 (21.0)	11 (25.0)
	>60	190 (65.3)	162 (66.0)	28 (64.0)
Comorbidities				
	Cardiovascular diseases - Hypertension - Dyslipidemia - Ischemic heart disease	230 (79.0) 137 (47.1) 62 (21.3) 14 (4.8)	191 (77.3) 113 (45.7) 52 (21.1) 10 (4.0)	39 (88.6.) 24 (54.5) 10 (22.7) 4 (9.1)
	Endocrine - Diabetes mellitus - Thyroid diseases	137 (47.1) 124 (42.6) 11 (3.8)	113 (45.7) 104 (42.1) 7 (2.8)	24 (54.5) 20 (45.5) 4 (9.1)

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	Rheumatology - Osteoporosis - Osteoarthritis - Rheumatoid arthritis	72 (24.7) 21 (7.2) 17 (5.8) 8 (3.2)	62 (21.3) 16 (6.5) 15 (6.1) 8 (3.2)	10 (22.7) 5 (11.4) 2 (4.5) -
	Neurology	47 (16.4)	40 (16.2)	7 (15.9)
	Orthopedic	40 (13.7)	35 (14.2)	5 (11.4)
	Others	109 (37.4)	88 (35.6)	21 (47.4)
Setting				
	Outpatient	264 (91.0)	223 (90.0)	41 (93.0)
Prescription type (N = 216)				
	Follow up visit	116 (53.7)	96 (52.5)	20 (60.6)
	Refill	97 (44.9)	84 (45.9)	13 (39.4)
	New	3 (1.4)	3 (1.6)	-
Prescriber's specialty (N = 247)				
	Endocrinology	41 (16.6)	37 (17.6)	4 (10.8)
	Family medicine	30 (12.1)	25 (11.9)	5 (13.5)
	Medicine	28 (11.3)	24 (11.4)	4 (10.8)
	Neurology	24 (9.7)	17 (8.1)	7 (18.9)
	Hematology	21 (8.5)	19 (9.0)	2 (5.4)
	Others	103 (41.7)	88 (41.9)	15 (40.5)
Prescriber's rank (N = 174)				
	Consultant	57 (32.8)	49 (32.9)	8 (32.0)
	Specialist	55 (31.6)	50 (33.6)	5 (20.0)
	Resident	44 (25.3)	36 (24.2)	8 (32.0)
	Intern/senior medical officer	18 (10.3)	14 (9.4)	4 (16.0)

Some data do not add up to 100% as some were missing

Drugs were prescribed as refill and follow–up in 97 (44.9%) and 116 (53.7%) prescriptions, respectively.

Cardiovascular conditions (hypertension (137, 47.1%), dyslipidemia (62, 21.3%) and ischemic heart disease (14, 4.8%)) were the most common comorbidities followed by endocrine and metabolic disorders (diabetes mellitus (124, 42.6%) and thyroid diseases (11, 3.8%)) and rheumatic disorders (osteoporosis (21, 7.2%), osteoarthritis (17, 5.8%) and rheumatoid arthritis (8, 3.2%)).

Prescriber information was available for 174 (59.8%) prescriptions. Among the four physician ranks, consultants were the most common prescribers (57, 32.8%), followed by specialists (55, 31.6%) and residents (44, 25.3%). Endocrinology (41, 16.6%) was the most common specialty among prescribers followed by family medicine (30, 12.1%) and medicine (28, 11.3%).

Drug–related data

Drug–related data are summarized in Table 2. Indications were available for 222 prescriptions. Labeled indications accounted for 61 (24.7%) and two (4.5%) of pregabalin and gabapentin, respectively. Diabetic peripheral neuropathy (50, 79.4%) was the most common labeled indication. The off-label use was 128 (51.8%) and 31 (70.5%) for pregabalin and gabapentin, respectively, with lower back pain as the most common indication for both drugs.

The dosing regimen for labeled and off-label indications was found to be within FDA–recommended doses in all prescriptions.

Cardiovascular agents were the most frequently co-prescribed classes of drugs (34.4%), followed by pain management agents (15.0%) and antidiabetic agents (12.5%). Aspirin was the most frequently co-prescribed drug 78 (26.8%) followed by metformin 68 (23,4%) and esomeprazole 63 (21.6%).

The controlled drugs used by the studied cohort were opioid analgesics (co-codamol and tramadol), anti-depressants (escitalopram, fluoxetine, paroxetine, and duloxetine), and anxiolytic agent (clonazepam). A total of 54 (19.0%) patients were using at least one of these controlled drugs. The most commonly used controlled drug was tramadol (18, 6.2%), followed by co-codamol (12, 4.1%) and duloxetine (9, 3.1%).

DISCUSSION

The potential for misuse and/or abuse of gabapentinoids is a global concern. Despite recommendations from health associations, the prescription rate is increasing globally. [15-18] Several health authorities have classified pregabalin

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Table 2. Drugs' indication, dosage appropriateness and co-prescribed drugs, n=291

		Cohort	Pregabalin	Gabapentin
N (%)		291	247 (84.8)	44 (15.1)
Indications labelled		63 (21.6)	61 (24.7)	2 (4.5)
	Diabetic peripheral neuropathy	50 (79.4)	49 (80.3)	1 (50.0)
	Fibromyalgia	10 (15.9)	10 (16.4)	
	Postherpetic neuralgia	3 (4.7)	2 (3.3)	1 (50.0)
Off-label		159 (54.6)	128 (51.8)	31(70.5)
	Lower back pain	47 (29.6)	43 (33.6)	4 (12.9)
	Spinal cord injury	16 (10.1)	13 (10.2)	3 (9.7)
	Others	83 (52.2)	72 (56.3)	11 (35.5)
undocumented		69 (23.7)	58 (23.5)	11 (25.0)
Dosage appropriateness		291 (100)	247 (100)	44 (100)
Co-prescribed drugs				
	Aspirin	78 (26.8)	70 (28.3)	8 (18.2)
	Metformin	68 (23.4)	58 (23.5)	10 (22.7)
	Esomeprazole	63 (21.6)	54 (21.9)	9 (20.5)
	Paracetamol	61 (21.0)	49 (19.8)	12 (27.3)
	Rosuvastatin	59 (20.3)	50 (20.2)	9 (20.5)
	Atorvastatin	44 (15.1)	44 (17.8)	
	Celecoxib	34 (11.7)	34 (13.8)	
Co-prescribed controlled drugs				
	Tramadol	18 (6.2)	16 (6.5)	2 (4.5)
	Co-codamol	12 (4.1)	10 (4.0)	2 (4.5)
	Duloxetine	9 (3.1)	7 (2.8)	2 (4.5)
	Fluoxetine	5 (1.7)	3 (1.2)	2 (4.5)
	Others	10 (3.4)	8 (3.2)	2 (4.5)

Some data do not add up to 100% as some were missing

and gabapentin as controlled substances.[12] Therefore, pharmacovigilance studies are required to monitor the use of gabapentinoids.

In this study, pregabalin was the most frequently prescribed drug 247 (84.8%). A similar result was reported in a retrospective study conducted in the UK, where pregabalin was prescribed in 66 (61.0%) cases.[19] In contrast, a Pakistani study revealed that gabapentin was the most prescribed gabapentinoids, followed by pregabalin.[20] The reported potency of pregabalin and more favorable pharmacokinetic profile including better solubility and bioavailability than gabapentin may account for its high utilization rate.[19] However, pregabalin is more expensive than gabapentin, which may explain why gabapentin is more commonly used in underdeveloped and developing countries than in developed countries.

In our study, females were found to be the most frequent users of pregabalin (149, 51.2%) and gabapentin (29, 10.0%), which is consistent with the findings of studies conducted in other populations.[21-23] The high prevalence of gabapentinoids use among females might be due to high pain sensitivity, reduced pain inhibition and other genetic factors.[24-26] However, further research is required to determine the reasons for this trend.

The most frequent users were found to be those older than 60 years, which is consistent with previous reports.[22,27] The high use of these drugs in this age group might be due to the high prevalence of chronic pain.[26]

We found that specialists and consultants are the most common prescribers of gabapentioinds. Among specialists, endocrinologists followed by family physicians and medicine physicians are the most common prescribers. In Oman, there are no restrictions on the use of gabapentiniods, and physicians from different specialties can prescribe them. In a response to several global reports and documented cases of misuse and abuse of these drugs, the Ministry of Health in Oman issued a circular (No. 79/2019) stating that gabapentinoids can be prescribed only by family medicine, neurology, endocrinology,

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internal medicine, orthopedics, and psychiatry specialists and/or consultants. However, such circular require time to show their results.

In line with the findings of Montastruc et al., the two most common labeled use for gabapentinoids were orthopedic and neurologic conditions in this study.[28] Moreover, 51.8% and 70.5% of pregabalin and gabapentin prescriptions were found as off–label indications, respectively. Back pain was the most common off-label indication for both. Similar findings have been reported in other studies. A study from the US conducted by Zhou et al., found that 96.6% of gabapentinoids visits were for unapproved indications.[23] Two studies in the UK observed that off-label and unlicensed indications accounted for 50% and 33% of gabapentinoids prescriptions, respectively.[19,28]

Despite the limited supporting evidence, the off–label use of gabapentinoids is still widespread.[29-32] In the US, 83% of gabapentin prescriptions were addressed as off–label indications, and only 5% of patients used gabapentin for labeled indications.[31,33] In addition, among the 15 drugs with the highest off–label use; gabapentin was ranked second (99.2% of prescriptions).[29] Some of the speculated reasons behind the off–label use of gabapentinoids are the lack of efficacious alternatives and a false sense of safety regarding the addiction potential of these drugs.[16,34] Furthermore, the global effort to decrease opioid epidemic misuse by using other analgesics has placed gabapentinoids at the top of the list of alternatives due to the belief that they have a low risk, when used appropriately.

In our cohort, 54 (19.0%) patients were prescribed gabapentinoids in combination with opioids or antidepressants. Our data indicate a lower rate of co-prescription with controlled drugs than reported by other studies. Gingras et al., found that a third of the patients were using opioids or benzodiazepines concurrently with gabapentinoids.[30] A study in the UK found that gabapentinoids were co-prescribed with opioids and benzodiazepines in 50% and 27% of the cases, respectively.[28] Co-prescribing benzodiazepines or opioids with gabapentinoids is a significant risk factor for misuse.[35] Gabapentinoids alone are associated with serious adverse effects including, suicidal intentions, accidental overdose, and risk of head or body injury especially when used for off-label indications.

Some countries have enacted regulations to control the increasing trend in the off–label use of gabapentinoids. For instance, in the UK, gabapentinoids have been reclassified as class C controlled substances, which prohibits prescription refills without meeting with the prescriber.[12] Therefore, the patient must request a monthly prescription from the treating physician and obtain his medication within 28 days of the prescription date, and only a 30-day supply per prescription is permitted. Similar or more stringent regulations may be required to curb the overuse of gabapentiniods in our setting and others.

Our study had a few limitations. First, the generalisability of our findings may be limited because this study was conducted at a single tertiary care hospital; therefore, it may be difficult to apply our findings to other hospitals across the country or the region. Second, data were collected in a retrospective manner; as a result, incomplete or missing information or insufficient documentation may have affected the conclusions. Third, we were unable to evaluate the level and outcome of misuse and/or abuse in our cohort.

CONCLUSIONS

This is the first study to describe the gabapentinoids' usage pattern in Oman and possibly the region. Both drugs have a high proportion of off-label indications, including co-prescription with controlled substances. There is a need to re-evaluate the guidelines, policies, and protocols that govern the use of gabapentinoids. There is also a need for larger sample size studies in various hospital settings to assess the extent of drug misuse and/or abuse.

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None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: MZ, AH; Data curation: AB; Formal analysis: AB; Methodology: MZ, AB, AH, IR; Supervision: MZ; Writing – original draft: MZ, AB; Writing –review & editing: MZ, AH, IR

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