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Prevalence and indication of gabapentin and pregabalin prescriptions among adults in King Abdulaziz Hospital in Makkah AL-Mukarramah, KSA

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Gabapentin and pregabalin prescribing have increased substantially over the recent years. Some evidence supports that gabapentin and pregabalin use in non-neuropathic pain disorders indicates they are less effective than several other licensed non-opioid analgesics. On the other hand, other studies have shown that those drugs are to be beneficial in the treatment of non-neuropathic pain and improves the analgesic efficacy of opioids both at rest and in movement, reduces analgesic consumption and opioid-related adverse effects. Therefore, it is essential to evaluate the rate of their prescriptions as well as monitoring and checking any severe side effects. The study is aimed at identifying the rate and the indications of gabapentin and pregabalin prescriptions at King Abdul-Aziz (Alzaher) Hospital-Makkah. A cross-sectional study was conducted from medical records of in-patients and outpatients clinics from January, 2018 through January, 2019. Data analysis was performed using SPSS and Prism 5.0 softwares. A total of 1197 prescriptions were reviewed. Pregabalin prescriptions rate were higher than gabapentin specifically in outpatients clinics (*P*<0.05). Females showed higher rates of using both gabapentin and pregabalin than males (*P*<0.05). In general there was a high rate of gabapentin and pregabalin prescriptions. Further studies need to be done to evaluate the most serious side effects and to control the safety of these prescriptions as well as preventing their misuse.

Key words: Gabapentin, Pregabalin,Indications, Off label.

INTRODUCTION

Gabapentin and its uses

Gabapentin (brand names include Neurontin and Horizant) is an anti-epileptic and an anticonvulsant drug

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(Cheng and Chiou, 2006). It works by affecting the chemicals and nerves inside the body that can cause seizures and some types of pain. Gabapentin has a chemical structure that is derived from the addition of a cyclohexyl group to the backbone of gamma-aminobutyric acid (GABA). Gabapentin has no activity at GABAA or GABAB receptors of GABA uptake carriers of the brain, also Gabapentin can interact with a high-affinity binding site in brain membranes, which has recently been identified as an auxiliary subunit of voltage-sensitive Ca^{2+} channels. However, the functional mechanisms of gabapentin is unclear and remains under study. Gabapentin crosses several lipid membrane barriers via system L amino acid transporters (Han et al., 2016).

Gabapentin has the ability to prevent pain responses in several animal models of hyperalgesia also it can show efficacy *in-vitro* and *in-vivo* by preventing neuronal death with models of the neurodegenerative disease amyotrophic lateral sclerosis (ALS) (Cheng and Chiou, 2006). It can be found in the form of capsule: 100 mg, 300 mg, 400 mg or in the form of tablet: 300 mg, 600 mg and 800 mg. The label uses of gabapentin are fibromyalgia, nerve pain (neuralgia), pain, peripheral neuropathy, numbness and tingling with pins and needles. Major side effects of gabapentin include dizziness, drowsiness, unsteadiness, memory loss, lack of coordination, difficulty speaking, viral infections, tremors, double vision, fever, unusual eye movements and jerky movements (Han et al., 2016). For the rare but serious possible side effects include suicidality, depression, allergic reaction, severe skin reaction and/or swelling and muscle tissue breakdown (Han et al., 2016).

According to researchers, individuals have reported that abusing gabapentin will produce euphoric effects which are similar to the effects produced by using cannabis and these effects are increasing in sociability, calmness and relaxation (Han et al., 2016). The essential inspiration for abusing gabapentin incorporates amusement, self-damage and self-drug. The abuse of gabapentin can be perilous for a few reasons. At the point when an individual begins on gabapentin by a human services endorse, the prescriber should screen that individual for any unfriendly impacts. Gabapentin has short half-life approximately about 5 to 7 h and the withdrawal symptoms may occur within 1 to 2 days after. The possible signs and symptoms of gabapentin withdrawal include irritability, sweating, nausea, anxiety, confusion, insomnia, increased heart rate, pain and seizures.

Pregabalin and its uses

Pregabalin marketed under the brand name Lyrica is a lipophilic gamma-amino-butyric acid (GABA) analog (Baidya et al., 2011), which have anticonvulsant, anxiolytic and sleep-modulating properties. It works by binding to the α2-δ subunit of presynaptic, voltage-dependent calcium channels which they are widely distributed throughout the central nervous system and peripheral nervous system (Baidya et al., 2011). Pregabalin absorption takes one hour and the bioavailability is 90%. When the dose increases, the absorption increases resulting in linear kinetics. The elimination half-life is 5.5 to 6.7 h independent of dose and repeated administration. It is not expose to hepatic metabolism and is not bound to plasma proteins. Around 98% of the absorbed dose is excreted unchanged in urine. Pregabalin elimination depends on creatinine clearance (CLcr) and it is recommended to reduce half the dose for patients with CLcr < 60 ml/min. Pregabalin is available in tablets dosage form with different doses as 50, 75, 100, 150, 200, 225 and 300 mg. Daily dose can be between 50 to 600 mg/day. Several studies declared that adverse events observed when Pregabalin was taken in overdose range from 800 mg/day to 11,500 mg as a single dose (Baidya et al., 2011). The major label use of pregabalin consist of neuropathic pain, incisional injury, and inflammatory injury and anxiety disorder.

Pregabalin is associated with transient mild to moderate adverse effects which are dose dependent. Less common adverse effects are dry mouth, peripheral edema, blurred vision, weight gain, and inability to concentrate. Pregabalin in acute postoperative pain is used because of the anxiolytic effect and its ability to prevent opioid tolerance (Morrison et al., 2017). Moreover, Pregabalin is considered one of the drugs that can cause dependence on or addiction to, even if the patient is taking it exactly as prescribed; the reason is it produces a relaxed, calm and euphoric sensation. So, when you suddenly stop the drug after chronic use there is potential to develop withdrawal symptoms including difficulty sleeping, nausea, headache and diarrhea (Morrison et al., 2017).

Off-label use

Off-label use, as defined by Health Canada, is the use of a marketed health product outside indications included in the approved product labelling. Off-label use of medications is a common practice in medicine; it is neither restricted to highly specific clinical situations nor to single countries (Boos, 2003). Challenged by diseases without effective treatments or the failure of standard therapies, physicians may try new drug approaches that have some theoretical basis (Gazarian et al., 2006). Off-label drug use does not imply improper or illegal use, and it can provide opportunities to capitalize on a drug's potential effectiveness. However, there are also potentially negative effects of off-label use, which include adverse reactions, liability for pharmaceutical

Table 1. Rate of gabapentin and pregabalin prescriptions in both in-patients and outpatients clinics.

Parameter	Gabapentin			Pregabalin		
	In-pateints	Out pateints	Total	In-pateints	Out pateints	Total
Total number of prescriptions	40±6	287±21	327±25	**114±34***	**756±45***	**870±66***
Total number of discharged prescriptions	0	19±13	19±13	0	39±23	39±23

*(P<0.05) pregabalin (in-patient, outpatient and total) vs. gabapentin (in-patient, outpatient and total).

manufacturers and health care practitioners, lack of patient reimbursement for medications purchased for off-label uses and concerns with respect to the illegal promotion, advertising and marketing of off-label uses by the manufacturer (Gazarian et al., 2006). As Haw and Stubbs state, "The use of a medication off label represents an area of potentially increased risk, since the national body that licenses drugs for medicinal use… has not examined the risks or benefits of using the drug in these circumstances" (p. 402) (Haw and Stubbs, 2005). Off-label prescribing and use also have the potential to be ineffective, resulting in wasteful medication use and possibly putting patients at risk.

The off-label uses of Gabapentin include restless legs syndrome, insomnia, diabetic neuropathy, hot flashes-cancer related, amyotrophic lateral sclerosis, bipolar disorder, attention deficit disorder, periodic limb movement disorders of sleep, premenstrual syndrome, migraine headache, drug, and alcohol withdrawal seizures (Wiffen et al., 2017) (Peckham et al., 2017). While the off-label uses of Pregabaline can be for cough, chronic refractory, anxiety disorder, postoperative pain, pruritus, neuropathic or malignancy related, uremic, social anxiety disorder, and vasomotor symptoms associated with menopause (Morrison et al., 2017).

Aim

The aim of this study was to identify the rate of prescription of Gabapentin and Pregabalin and the rate of prescription in male and female adults. In addition, is identifying the indications for those prescriptions and their percentages.

METHODS

Study design

A cross-sectional study was conducted from medical records of in-patients and outpatients clinics from January, 2018 through January, 2019.

Study setting

The study was conducted at King Abdul-Aziz (Alzaher) Hospital – Makkah.

Sample size

A total of 1747 prescriptions, 550 total of unaccessible prescriptions and a total of 1197 accessible prescriptions, of which 870 and 327 Pregabalin and Gabapentin prescriptions, respectively.

Data collection

Data was collected from medical case records.

Inclusion criteria

Male and female adult ranged from 30 to 55 years old patients under treatment with gabapentin and or/pregabalin.

Exclusion criteria

This include children, old age, refill prescription and other types of pain medications.

Data analysis

Data analysis was performed using SPSS and Prism 5.0 software. Values were expressed as means ± SD unless otherwise indicated. General linear models were used in the analysis. Repeated measures analysis of variance (Two- way ANOVA) was used in case of indications percentages. t-test with a Bonferroni correction for multiple comparisons was used as a post hoc test. All the tests were two-tailed with the significance level set at $P<0.05$.

Ethics

Ethical approval was obtained from Umm Al-Qura University Institutional Review Board (IRB) commity UQU- COP-EA-#143914.

RESULTS

Rate of gabapentin and pregabalin prescriptions in both in-patients and outpatients clinics/ departments

Table 1 demonstrates the rate of gabapentin and pregabalin prescriptions in both in-patients and outpatients clinics/departments; it appeared that pregabalin prescriptions rate were higher than gabapentin specifically in outpatients clinics (t-test $P<0.05$). It was a total of 327 and 870 for gabapentin and pregabalin

Table 2. Percentage of gabapentin and pregabalin dispensing in each department.

Gabapentin		Pregabalin	
Department	**Percentage**	**Department**	**Percentage**
Urology	0.45	Urology	0.37
Rheumatology	11.16	Rheumatology	3.56
Respiratory	1.34	Respiratory	0.75
Radiology	0.22	Radiology	0.09
Psychiatry	0.22	Psychiatry	0.28
Physical therapy	0.22	Physical therapy	0.37
Orthopedic surgery	1.12	Orthopedic surgery	10.58
Opthalmology	0.22	Opthalmology	0.28
Neurosurgery	32.81	Operation rooms	0.19
Neurology	26.79	Neurosurgery	28.18
Nephrology	0.45	Neurology	20.69
Internal medicine	4.24	Nephrology	1.12
General surgery	1.56	Internal medicine	15.45
General practitioner	0.22	Infectious diseases	0.37
ENT surgery	0.45	General surgery	1.69
Endocrinology	1.12	General practitioner	0.37
Emergency	2.90	Gastroentrology	1.69
Dermatology	1.79	ENT Surgery	0.37
Dentist	0.67	Endocrinology	3.75
Cardiology	10.04	Emergency	2.34
		Dermatology	2.43
		Dentist	0.66
		Cardiology	5.99

prescriptions, respectively.

Rate of gabapentin and pregabalin dispensing in each department

Table 2 demonstrates the percentages of gabapentin and pregabalin dispensing in each department. Gabapentin was prescribed at high percentage in the following clinics: Neurosergury, neurology and rheumatology with 32.81, 26.79 and 11.16%, respectively. Pregabalin was also prescribed at high rates at neurosurgery and neurology clinics with 28.18 and 20.69%, respectively. In addition, pregabalin was also prescribed at high rates in Internal medicine clinics with 15.45%.

Female and male rate of prescriptions

Females showed higher rates (~60%) of using both gabapentin and pregabalin than males, moreover there was a higher significant use of gabapentin over pregabalin in females by ~15% (t-test, $P<0.05$; Figure 1).

Percentages of each indication

Table 3 demonstrates the percentages of each indication for gabapentin and pregabalin prescriptions. In general a significant interaction was shown between gabapentin and pregabalin number of prescriptions and each indication, two-way Anova, $F(1, 13) = 9.518$, $P<0.05$.

CNS disrdors such as cord compressions, carpal tunnel syndrome and epilepsy were among the highest percentages of prescriptions of 27.83 and 22.76% for gabapentin and pregabalin, respectively. Next was bone disorders such as congenital deformaties of the spine and knee constitutions with 24.46 and 27.24% for gabapentin and pregabalin, respectively. However, there was a very large number of prescriptions without any indications written on it with 17.43 and 12.53% for gabapentin and pregabalin, respectively.

DISCUSSION

The main aim of this study was to investigate the rate of

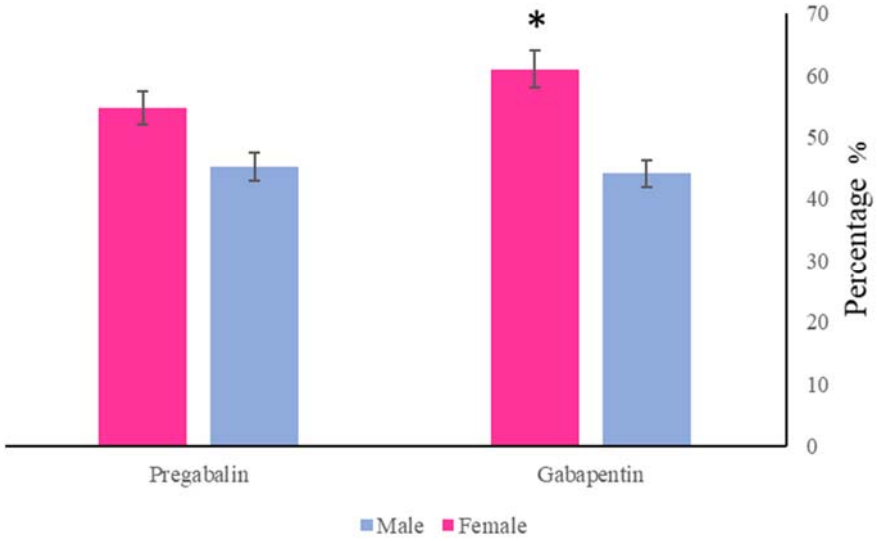

Figure 1. Bar-chart representing males and females percentages of using gabapentin and pregabalin (n=1197; Males=479, Females=712). * *P*< 0.05 gabapentin in females vs. pregabalin in females.

Table 3. Percentages of each indication for gabapentin and pregabalin prescriptions.

Indication	Gabapentin (%)	Pregabalin (%)
GIT disorders	1.22	1.61
Infection and inflammations	2.14	4.94
CNS disorders	27.83	22.76
Kidney disorders	0.92	1.26
Bone disorders	24.46	27.24
Cardiac disease	8.87	7.59
Psychiatric disorders	0.61	0.92
Trauma	0.31	0.69
Ocular disorders	0.61	0.11
Respiratory disease	0.61	1.26
Endocrine diseases	7.95	12.99
Skin disorders	4.89	4.02
Miscellaneous	2.14	2.07
No indication written	17.43	12.53

prescription of gabapentin and pregabalin notwithstanding the rate of their use in male and female grown-ups. Besides, the indications for those drugs and their rates were identifyed. A cross-sectional investigation was led; information were collected from restorative medical records from the in-patients and out-patients clinics and/or departments picking a period from January 2018 until January 2019. The investigation secured both male and female grown-up patients somewhere in the range of 30 and 55 years old under treatment with gabapentin as well as pregabalin.A study in North America and parts of Europe showed that nearly more than half of the patients newly prescribed pregabalin and gabapentin for neuropathic pain were adults (Moore et al., 2014). This elucidates the importance of better understanding of the prevalence and indications of pregabalin and gabapentin in those group of the population. After every single prescriptions was screened, the non-accesiable were around 550 prescriptions, while the accessible were around 1197 prescriptions that were chosen relying on the inclusion/exclusion criteria. Via looking through the literature, it was found that this is the first study that

assess the prevelance rate and indications of gabapentin and pregabalin prescriptions in Makkah Almukarramah, Saudi Arabia.

Results in this study demonstrated that in both in-patients and outpatients pregabalin prescriptions rate were higher than gabapentin specifically in outpatients clinics. Moreover, the rate of prescriptions at the out patients clinics were significantly higher than the in-patients.

The results also demonstrated the percentage of gabapentin and pregabalin dispensing in each department; It was found that gabapentin was highly prescribed as the most in neurosurgery. Additionally, it was found that females showed higher rates of using both gabapentin and pregabalin than males. To be more precise, there was higher significant use of gabapentin over pregabalin in females by ~15%. A study of retrospective criteria demonstrated that females also used gabapentin more frequently than males, this might be due to the nature of their indications such as after breast cancer surgery and sciatica pain (Fleet et al., 2018; Grice and Mertens, 2008).

It also demonstrated the percentages of each indication for gabapentin and pregabalin prescriptions. The most significant interaction between gabapentin and pregabalin number of prescriptions and each indication were the CNS and bone disorders. However, there was a very large number of prescriptions without any indications written on it. This might indicate a missuse or off-label prescription matter that should be investigated thouroghly in a future study. A scope of ongoing reports have stressed the capability of gabapentin and pregabalin abuse in chosen populaces. Pregabalin was recognized in 12.1% (n = 15) of pee tests from sedative dependent subjects going to a German habit facility. None of these patients were experiencing any of the signs for pregabalin endorsing, with most having confirmed that they had obtained pregabalin illegally while being very much aware that the particle was excluded in the standard medication checking framework (Grosshans et al., 2013). One of the restrictions in this investigation that we could not most likely know any conceivable symptoms of those medications in the examination populace, along these lines we were not ready to survey this issue. Another constraint of the investigation was that it did not locate some other sedatives or opiates that were recommended with gabapentin or pregablalin; in this manner, the impact of gabapentin and pregabalin in diminishing the utilization of different sedatives/ painkillers or not could not be surveyed.

It is intriguing to take note of the fact that gabapentin and pregabalin has been endorsed in Canada and the USA since 2005, and endorsement by the European Commission to treat summed up uneasiness issue was gotten in 2006 (Canadian Agency for Drugs and Technologies in Health (CADTH), 2012). However, the discussion with respect to mishandle and reliance did not show up in the medicinal writing before 2010 (Filipetto et al., 2010). Essentially, staying physician endorsed drugs with abuse potential (for example benzodiazepines; z-hypnotics) were considered 'safe' for a long time before their addictive risk levels were identified (Filipetto et al., 2010). This might be a result of pre-advertising clinical preliminaries commonly including the organization of deliberately controlled, every day helpful measurements. Besides, it is a notable shortcoming of these preliminaries that subjects with compulsion issue are rejected (Schwan et al., 2010). As an outcome, the genuine capability of abuse of the file atom will be all the more appropriately refreshing just when countless, who will include powerless people, are presented to the medication. Therefore, a superior appraisal/clarification of gabapentin and pregabalin abuse potential dimensions is without a doubt of intrigue. Truth be told, interestingly with maltreatment obligation information, gabapentin and pregabalin may conceivably speak to a significant resource in the pharmacological collection of habit prescription (Schwan et al., 2010) . Since these drugs are generally endorsed drugs, wellbeing experts ought to be very much aware of both the potential dangers for their abuse and the related cessation side effects. Doctors considering endorsing gabapentin and pregabalin for neurological/mental or pain scatters should cautiously assess a conceivable past history of medication misuse. Moreover, they ought to have the capacity to immediately recognize indications of pregabalin/gabapentin abuse, while giving help with decreasing the prescription (Filipetto et al., 2010). Further exact examinations with gabapentin and pregabalin ought to be empowered, concentrating on a superior appraisal of their addictive obligation levels over a scope of doses and in people with a past substance abuse history.

Conclusion

A high rate of gabapentin and pregabalin prescriptions has been seen in general. Further studies need to be done to evaluate the most serious side effects and to control the safety of these prescriptions as well as preventing their misuse.

Recommendations

One of the vital bearing of this examination is to guarantee the wellbeing of patient from the unsafe unfavorable impacts that may happen from utilizing gabapentin and pregabalin; the checking procedure is favored likewise to help in decreasing the endorsing of gabapentin and pregabalin as could reasonably be expected or to locate an elective analgesics with less hazard to conquer any conceivable extreme antagonistic impacts. Gabapentin and pregabalin both have the

capability of being manhandled; numerous systems ought to be considered for this; independently persistent instructive intercessions about the right use, portion, term, will be useful to control the abuse. To make new rules for gabapentin and pregabalin use and organization that will be useful and can be actualized inside medical clinics.

Limitations

Limitations of this study include:

1. Not all prescription were clear with the precise diagnosis.
2. Some errors were detected in entries at the pharmacy, especially quantities of issued medicines and some double entries.
3. Inability to identify any side effects or other medications used by the study populations from the medical records.

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