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Review

Tremendous health benefits and clinical aspects of *Smilax china*

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A lot of species of *Smilax* known as Baqia in China are used in folk medicine for various purposes. *Smilax china* L., is a small vine that grows in the southern parts of China, known as Jin Gang Ten, which has a long history of indigenous use in China. *S. china* consists of fat, saponins, glucosides, gum, starch, flavonoids, tannins, and alkaloids. *S. china* has been used in traditional Chinese medicine because it has effective components such as triterpenoid saponins, flavones, stilbenes, and organic acids. Roots are the most common used part; stems and rhizome can be used also in the form of powder or paste, raw or cooked. The most important health benefits of *S. china* are energy tonic, impotency and seminal disorders, chronic arthritis and secondary and tertiary syphilis, schizophrenia and epilepsy, pemphigus and skin diseases, osteoarthritis, leucorrhea or white discharge, relieving joints numbness, diabetes and excretory system. The obtained findings strongly suggest potential of *S. china* as an additive in pharmaceutical industries.

Key words: Health benefits, *Smilax china*, pharmaceutical industries, traditional Chinese medicine.

INTRODUCTION

The use of traditional Chinese herbs and fruits for the treatment and management of diseases is common in developing countries and it is improving in developed countries (Soleymani and Shahrajabian, 2012; Ge et al., 2018; Shahrajabian et al., 2018; Shahrajabian et al., 2019a,b,c,d). In recent years, pharmacokinetic and metabolic studies of traditional Chinese medicine have attracted extensive attention and promoted in many regions (Ogbaji et al., 2018; Soleymani and Shahrajabian, 2018). The genus *Smilax* (Liliaceae family) comprises about 300 species of climbing flowering shrub (Xie et al., 2018). Some of the *Smilax* plant distributed in Asia area includes Taiwan, China, and Japan (Huang, 2000). China cultivates this drug in large amount; hence, it is usually recognized as China root. The most important popular common names of the plants are China root, Chinese smilax and Bambook Briar Root. Many species of *Smilax* are known as Baqia in China and are used in folk medicine for various purposes (Ao, 2013). Shu et al. (2006) reported that *Smilax china* L., is a small vine that grows in the southern parts of China, known as Jin Gang Ten, which has a long history of indigenous use in China. Yang et al. (2008) found that the rhizome of *S. china* has been used in traditional Chinese medicine because it has effective components such as triterpenoid saponins, flavones, stilbenes and organic acids. Local

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names of *S. china* L. in different languages are shown in Table 1.

### CHEMICAL CONSTITUTIONS

*S. china* consists of fat, saponins, glucosides, gum, starch, flavonoids, tannins and alkaloids (Saravanakumar et al., 2014). Feng et al. (2003) showed that 5 phenyl compounds were isolated from the roots of *S. china* and they are dihydrokaempferol (1), 3,5,4′-trihydroxystilbene (2), 3,5,2′,4′-tetrahydroxystilbene (3), dihydrokaempferol 3-O-α-L-rhamnoside (engeletin, 4), and quercetin 4-O-β-D-glucoside (5). Shao et al. (2009) found that seven flavonoids and four stilbenes were isolated and identified as dihydrokaempferol-5-O-β-D-glucoside (I), engeletin (II), isoengeletin (III), dihydroquercetin-3-O-glycoside (IV), 3, 5, 7, 3′, 5′-pentahydroxy-flavanonol (V), astilbin (VI), quercetin-3′-O-glycoside (VII), piceid (VIII), scirpusin A (IX), resveratrol (X), and oxyresveratrol (XI). Results of phytochemical tests of *S. china* are shown in Table 2. Names of flavones and isoflavones isolated from *S. china* are shown in Table 2.
L. are shown in Table 3. Shao et al. (2007) reported that the six major active constituents in S. china are (1) Taxifolin-3-O-glycoside; (2) piceid; (3) oxyresveratrol; (4) engeletin; (5) resveratrol; (6) scirpusin A. Structural compounds 1 to 6 identified from S. china are as shown in Figure 1.

### HEALTH BENEFITS

*S. china* L. known as Jin Gang Ten, has been widely used as a traditional herbal medicine for the treatment of gout, rheumatoid arthritis and other diseases for a long time in China (Chen et al., 2011). Shu et al. (2004) confirmed that the tuber of *S. china* has anti-inflammatory, anticancer, and anticoagulation activities. In Chinese medicine, it has been extensively used for clinical treatment of syphilis, acute bacillary dysentery acute, chronic nephritis and antitumor (Chen et al., 2002). The rhizomes of *S. china* is commonly used as herbal materials in traditional Chinese medicine (Liang et al., 2016). Park et al. (2014) concluded that *S. china* methanol extract (SCME) has active compounds which have anti-obesity activities. Vijayalakshmi et al. (2013) reported that the ethyl acetate fraction of *S. china* rhizome showed maximum antipsoriatic activity. Chen et al. (2011) concluded that *S. china* L. exhibits anti-hyperuricemic and nephroprotective activity in hyperuricemic animals. Jeong et al. (2013) reported that *S. china* has antimicrobial, antimutagenic, antioxidant, anti-inflammatory, anti-cancer and neuroprotective effects. Shim (2012) also recognized *S. china* has a good source of natural antioxidant. Raju et al. (2012) also showed that *S. china* is an anti-diabetic plant which is responsible for the hypoglycemic activities. Bhati et al. (2011) reported that the hydroalcoholic and aqueous fractions exhibited anti-diabetic activity in rats with alloxan-induced diabetes. Seo et al. (2012) indicated that *S. china* L. possesses antioxidant and antimicrobial substances, and suggested that the ethanol extract can be applied into food and cosmetic industry. Wu et al. (2010) showed that polyphenols are the active components of *S. china* L. responsible for the anti-breast tumor cell activities. Saraswathi and Nithya (2010) suggested that the hypoglycemic and hypolipidemic property of *S. china* could be useful for the treatment of diabetes. Saraswathi and Nithya (2010) also claimed that *S. china* extracts have antioxidant activity which can be used to treat various diseases. Shu et al. (2006) stated that ethyl acetate extract of *S. china* possesses remarkable anti-inflammatory effects on acute inflammation, and also displays anti-inflammatory effects on the chronic inflammation at a certain extent. Pan et al. (2014) concluded that water extraction from *S. china* (WESC) suppressed fat accumulation and decreased the weight gain in mice, which was mainly due to increase of the activity of fat oxidation enzyme in liver, promotion of the fatty acid β-oxidation. Lee et al. (2016) suggested that the extract from *S. china* L. has great potential as a cosmetic ingredient with whitening effects. Vijayalakshmi et al. (2012) have found the flavonoid quercetin in *S. china* and they have stated that it is promising for further investigations to prove its anti-psoriatic activity. Cong et al. (2016) noted that those patients who received Azithromycin therapy added with *S. china* capsules concurrently could significantly improve levels of lymphocyte subsets, cytokines and hemorheology index. Yang et al. (2019) stated that *S. china* L. ethanol extract (SCLE) could lead to a decrease in body weight gain and fat mass by inhibiting the lipid synthesis and promoting lipolysis and β-oxidation in high-fat diet (HFD) fed mice. Pharmacological studies have also suggested that *S. china* has a neuroprotective effect (Ban et al., 2006). Lee et al. (2018) demonstrated the potent therapeutic efficacy of *S. china* L., and its potential use as a cost-effective natural alternative medicine against type 2 diabetes and its complications. Nho et al. (2015) reported that *S. china*...
Figure 1. Structural compounds 1-6 identified from *S. china*. (1) Taxifolin-3-O-glycoside; (2) piceid; (3) oxeysveratrol; (4) engeletin; (5) resveratrol; (6) scirpusin A (Shao et al., 2007).

Table 4. The most important traditional uses and benefits of China root.

<table>
<thead>
<tr>
<th>Uses and Benefits</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root is alternative, anti-scrophulatic, carminative, depurative, diaphoretic, diuretic and tonic.</td>
<td>It is useful when taken internally in the treatment of old syphilitic cases and it also used for certain skin diseases, including psoriasis, rheumatoid, arthritis, gout, enteritis, urinary tract infections, skin ulcers, etc.</td>
</tr>
<tr>
<td>Root is alternative, anti-scrophulatic, carminative, depurative, diaphoretic, diuretic and tonic.</td>
<td>Large doses can cause nausea and vomiting, which is appreciated in weakened and depraved conditions due to a poisoned state of the blood.</td>
</tr>
<tr>
<td>Smilax is helpful in improving muscle mass and body strength.</td>
<td>Smilax is helpful in improving muscle mass and body strength.</td>
</tr>
<tr>
<td>Smilax is helpful in improving muscle mass and body strength.</td>
<td>It is used as a tonic for male sexual energy.</td>
</tr>
<tr>
<td>Decoction of roots and rhizomes used as depurative in cases of herpetism and syphilis.</td>
<td>Smilax has a special property as it acts against the problems caused due to malnourishment of Dhatus such as poor immunity and weakness.</td>
</tr>
<tr>
<td>It is Sudorific and demulcent, used in rheumatism.</td>
<td>Decoction of roots and rhizomes used as depurative in cases of herpetism and syphilis.</td>
</tr>
<tr>
<td>It is used for various skin diseases.</td>
<td>It is used for various skin diseases.</td>
</tr>
<tr>
<td>It is used as a depurative, diaphoretic, stimulant, alterative, antisyphilitic and aphrodisiac</td>
<td>It is used as a depurative, diaphoretic, stimulant, alterative, antisyphilitic and aphrodisiac</td>
</tr>
<tr>
<td>It is used as alterative in old syphilitic cases and in chronic rheumatism.</td>
<td>It is used as alterative in old syphilitic cases and in chronic rheumatism.</td>
</tr>
<tr>
<td>In TCM, used as diuretic and for treatment of rheumatic arthritic conditions; also used for detoxification, treatment of gout, tumors and lumbago.</td>
<td>It is used for syphilis, skin disease, epilepsy, insanity, flatulence, dyspepsia, constipation, fever, neuralgia, rheumatism, gout and general debility in Ayurveda, Siddha and Unani medical system.</td>
</tr>
<tr>
<td>It is used as a remedy for inflammatory disease and ischuria.</td>
<td>It is used as a remedy for inflammatory disease and ischuria.</td>
</tr>
<tr>
<td>Rhizome is made into a paste and applied to painful swellings.</td>
<td>Rhizome is made into a paste and applied to painful swellings.</td>
</tr>
<tr>
<td>It has also been supported in the treatment of leprosy, scrofula and many skin infections developing into ulcers.</td>
<td>It has also been supported in the treatment of leprosy, scrofula and many skin infections developing into ulcers.</td>
</tr>
<tr>
<td>Roots have been used to treat abscesses, pyoderma and burns.</td>
<td>Roots have been used to treat abscesses, pyoderma and burns.</td>
</tr>
<tr>
<td>It was one of the drugs used in the treatment of acute appendicitis, taeniasis and constipation.</td>
<td>It was one of the drugs used in the treatment of acute appendicitis, taeniasis and constipation.</td>
</tr>
<tr>
<td>Roots have been used to treat cases of paralysis and sciatica.</td>
<td>Roots have been used to treat cases of paralysis and sciatica.</td>
</tr>
<tr>
<td>It is used to treat urinary tract infection, stone and ulcers of the bladder and even chyluria by the physicians.</td>
<td>It is used to treat urinary tract infection, stone and ulcers of the bladder and even chyluria by the physicians.</td>
</tr>
<tr>
<td>It is also used to treat fever and other inflammatory conditions associated with fever like acute lymphadenitis.</td>
<td>It is also used to treat fever and other inflammatory conditions associated with fever like acute lymphadenitis.</td>
</tr>
<tr>
<td>It helps in relieving strangury and also seminal weakness.</td>
<td>It helps in relieving strangury and also seminal weakness.</td>
</tr>
</tbody>
</table>

L. extract (SCLE) exerts an anti-metastatic effect on human breast cancer cells. The most important traditional uses and benefits of *S. china* are shown in Table 4. The most important health benefits of China root are shown in
CONCLUSION

S. china L. known as China root has been used for thousand years in numerous tribal and folk medicine. The plant is native to China, Korea, Taiwan, Japan, Philippines, Vietnam, Thailand, Myanmar and Assam. S. china consists of fat, saponins, glucosides, gum, starch, flavonoids, tannins and alkaloids. The rhizomes are bitter, acrid, thermogenic, anodyne, anti-inflammatory, digestive, laxative, depurative, diuretic, febrifuge and tonic. It is used in dyspepsia, flatulence, colic, constipation, helminthiasis, skin diseases, leprosy and psoriasis, syphilis, strangury, seminal weakness, general debility, detoxifies organs, cleanses blood, aids absorption and kills bacteria; it is also used for fever, epilepsy, insanity, neuralgia and stimulates digestion, increases urination, protects liver and promotes perspiration. In Chinese medicinal science, it has been used for clinical treatment of syphilis, acute bacillary dysentery acute, chronic nephritis and antitumor. On the basis of scientific literatures, S. china L. demonstrates important and promising health benefits. In general, treatment with natural and traditional medicine, especially S. china L. is recommended.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Effect of the anticancer drug tamoxifen on chronic toxoplasmosis in experimentally infected rats


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Toxoplasma gondii is an opportunistic parasite that can cause severe disorders in infants and pregnant women and can also be lethal in immunologically compromised individuals. During unfit host immune conditions, and as a consequence to latent stage opportunity, the protozoan stimulates serious infection, and signifies higher morbidity and mortality including humans with Acquired Immuno-Deficiency Syndrome (AIDS) or those receiving corticosteroids and cancer chemotherapy. Tamoxifen drug (TAM) is a selective estrogen receptor modulator (SERM), which is commonly used for treatment of breast cancer; it has a known immunomodulatory effects on the patient, especially if administered for a long time as happens in cases of post breast cancer surgery and anti-recurrence prophylactic measures where women might persist to take TAM for years. The research question here was: Can TAM reactivates latent toxoplasmosis? To assess the possible stressful effect of TAM, rats were experimentally infected by T. gondii (RH strain). Three months later, they were treated by oral administration of TAM (10 mg/kg body weight/day) for 7, 14, 21 and 28 days. Tamoxifen effect on toxoplasmosis dynamics was estimated by counting Toxoplasma brain cysts and serological detection of anti-parasitic IgM and IgG all through the experiment time. The results showed an initial insignificant decrease in parasitic burden in groups treated for one week followed by a significant increase in groups treated for 14, 21 and 28 days. There was also a significant decrease in IgM titers in groups treated for one and two weeks while there was a significant increase in IgM titers in groups treated for three and four weeks. There was a significant increase in IgG titers in groups treated for 14 and 21 days and a borderline significant increase in the 4th week while there was non-significant increase in 4th week.

Key words: Toxoplasmosis, tamoxifen, breast cancer, serological, Toxoplasma brain cysts, immunomodulatory.

INTRODUCTION

Toxoplasma gondii (T. gondii) is the causal agent of toxoplasmosis and one-third of the world population had...
been affected by this parasite (El-On and Peiser, 2003). In immune suppressed individuals, such as those undergoing chemotherapy, organ transplantation or in AIDS patients, reactivation of a latent T. gondii infection is often fatal. T. gondii has been identified as an important opportunistic infection in HIV/AIDS patients and a major contributor to death of AIDS patients in the developing world (Carruthers and Suzuki, 2007). Host afflection was confirmed a sequel to reactivation of primary infection (Saadatnia and Golkar, 2012). Breast cancer is the most common malignancy in women around the world. Information on the incidence and mortality due to breast cancer is essential for planning preventive health measures (Ghoncheh et al., 2016). Treatment with TAM lowers the risk of breast cancer recurrence and also lowers the risk of death from breast cancer (Early Breast Cancer Trialists' Collaborative Group, 2011). Since both toxoplasmosis and breast cancer are widely distributed globally, the research question was: Could tamoxifen treatment lead to reactivation of latent primary toxoplasmosis? For that purpose, we treated toxoplasmosis experimentally infected rats with TAM for different periods and observed the possible stressful effects of it on Toxoplasma parasitosis.

MATERIALS AND METHODS

Study site

This study was conducted in National Research Center; NRC (Cairo, Giza).

Ethical considerations

The study was approved by the Parasitology Department Research Committee and the Ethical Committee at the Faculty of Medicine, Benha University.

Parasites

Toxoplasma gondii (RH strain) was obtained from Zoonotic Diseases Department, National Research Center, Egypt. Tachyzoites of T. gondii (RH) strain maintained through serial intra-peritoneal (i.p.) passage were used for experimental infection. Tachyzoites were collected from mouse peritoneal cavity 72 h post infection (p.i.), the parasites were counted and adjusted to 10⁶/ ml in saline. Each 1 ml solution was inoculated subcutaneously into each experimental rat.

Drugs

Tamoxifen (nolvadex) (Sigma-Aldrich) 10 mg tablets was orally administered to the rats at a dose of 10 mg/kg body weight daily (Perumal et al., 2005), via oral gavage 90 days post infection for 1, 2, 3 and 4 weeks. Tablets were dissolved in sunflower oil (Sigma-Aldrich) and the dose was adjusted for each rat according to its weight.

Animals, infection and treatment schedule

To test the efficacy of tamoxifen in a chronic model of experimental toxoplasmosis, a total of 45 laboratory-bred male rats were used (10 weeks old, weighing ~250 g). Animals were housed and maintained in a suitable rearing environment with free access to food and water throughout the experiment. Infected rats were divided into four groups consisting of 10 to 11 rats each group (7 infected and treated + 3-4 rats served as positive control; infected non treated) in addition to 3 healthy non infected- non treated; negative control rats. The first group was treated by tamoxifen for 7 days, the second group treated for 14 days, the third one treated for 21 and fourth group treated for 28 days. At the end of each group treatment time, rats were sacrificed, their brains were dissected and examined for immediate direct parasitological assessment and blood samples were collected individually, sera were separated and kept at -20°C for later serological evaluation.

Evaluation of tamoxifen efficacy

Parasitological assessment

To prepare the brain suspension, rats were sacrificed, brains were removed and prepared in a tissue homogenizer (Wheaton USA) with 1 ml saline each. For cyst enumeration, 0.1 ml of the brain suspension was placed on a slide. The number of Toxoplasma cysts was counted in ten high power fields (HPF) and then the mean number was determined for each rat followed by calculation of the mean numbers of cysts in each infected group (Djakovic and Milenkovic, 2001).

Serological assay

Serum samples were serologically assayed by ELISA to detect IgM & IgG titer according to procedures described by Lind et al. (1997).

Statistical analysis

Gathered data were tabulated and analyzed using SPSS statistical software (IBM Corp., Armonk, NY, USA). Data were expressed as mean ±SD. Analysis of variance between groups was done using t test. P value<0.05 was considered statistically significant.

RESULTS

The results showed that there was a decrease in average brain parasitic load (ABPL) in TAM infected and treated (IT) group for one week as compared to the infected untreated (IU) control group (3.4%), however the difference was statistically non-significant (p = 0.448). Inversely, in the other IT groups which were treated for 14, 21 and 28 days, there were a statistically significant (p = 0.0001 - 0.0045) increases in ABPL (by 11.4, 30.3 and 48.7%, respectively) as shown in Table 1. In the serological study, there was a statistically significant decrease (p = 0.0001 - 0.027) in Anti Toxoplasma IgM titers in IT groups treated for 7 and 14 days, inversely, in IT groups treated for 21 and 28 days, a statistically significant increase (p = 0.0001 - 0.0012) was found in anti-Toxoplasma IgM titers as shown in Table 2. Concerning anti Toxoplasma IgG titers, throughout the
**DISCUSSION**

*T. gondii* is an obligate intracellular, parasitic protozoan. It is the etiologic agent for toxoplasmosis. About 30 to 50% of the world population is infected with the parasite, and it is the most prevalent infection among humans (Tenter et al., 2000; Flegr et al., 2014). Cluster of differentiation (CD4+) and (CD8+) T cells are highly activated during infection and are essential for adaptive immunity. As such, patients with defects in T cell-mediated immune responses (for example, patients with AIDS) are at risk for reactivation of latent *T. gondii* infections. CD4+ and CD8+ T cells act synergistically to prevent cyst reactivation during chronic latent *T. gondii* infection. CD8+ T cells mediate protective immunity against toxoplasmosis primarily through the generation of interferon-gamma (IFN-γ). Interleukin-12 (IL-12) drives the generation of terminally differentiated CD8+ effector T cells (Aliberti, 2005). CD4+ T cells are critical for avoiding reactivation of latent toxoplasmosis, as the emergence of severe toxoplasmosis is concomitant with the decline in T cell numbers in patients infected with HIV (Luft et al., 1984; Israelski and Remington, 1988) and in mouse models, the lack of CD4+ T cells is associated with increased susceptibility of reactivation during the chronic stage of infection (Johnson and Sayles, 2002). CD8+ T cell responses to *T. gondii* are influenced by good functioning provided by CD4+ T cells (Lutjen et al., 2006). CD4+ T cells are necessary for the maintenance of CD8+ T cell effector functions during the chronic stage of infection, and this help must be provided during the acute stage of infection (Lutjen et al., 2006). Tamoxifen (TAM) is a broadly known anti-estrogen, which has been used in adjuvant treatment of early stage, estrogen-sensitive breast cancer for over 20 years, especially for women who still have significant ovarian estrogenic activity which could not be controlled by aromatase inhibitors. Five years of adjuvant tamoxifen safely reduced 15-year risks of breast cancer recurrence and death (Behjati1 and Frank, 2009; Early Breast Cancer Trialists’ Collaborative Group, 2011). It has also immunomodulatory effects. Tamoxifen is capable of inducing a shift from cellular (T-helper 1) to humoral (T-helper 2) immunity. Interestingly, the immune modulatory effects of tamoxifen appear to be independent of the estrogen-receptor and may be mediated through the multi-drug resistance gene product (Behjati1 and Frank, 2009). Robinson et al. (1993) studied the effects of tamoxifen on immunity in patients with bilateral breast cancer who were in remission and had completed radiotherapy and chemotherapy at least one year prior to the study. They observed that the relative proportion and absolute number of CD4+ lymphocytes was reduced in tamoxifen treated patients, compared to untreated breast cancer patients and to healthy controls. Moreover, *in vitro* proliferation of lymphocytes derived from tamoxifen treated patients was decreased. Since CD4+ cells have the main rule in immunity against *T. gondii* whether on their own or by promotion of CD8+ cells as mentioned above, so theoretically, letting down CD4+ cells number or activity - as recorded before for TAM - can impair host immunity against toxoplasmosis. A community where both

### Table 1. Average brain parasite load (ABPL) of Tamoxifen treated rats as compared with untreated rat at different time points.

<table>
<thead>
<tr>
<th>DPI / DPT</th>
<th>Group/average brain parasite load (ABPL/10 mg/brain)</th>
<th>p value</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (IPL)</td>
<td>26553.67±1031.253</td>
<td>-</td>
<td>0.79</td>
</tr>
<tr>
<td>107(7DPT)</td>
<td>24206±1024.24</td>
<td>-</td>
<td>0.045</td>
</tr>
<tr>
<td>110(14DPT)</td>
<td>21141.25±1151.39</td>
<td>+15587.05</td>
<td>13.36</td>
</tr>
<tr>
<td>111(21DPT)</td>
<td>19836.75±1239.87</td>
<td>+606.39</td>
<td>8.23</td>
</tr>
<tr>
<td>118(28DPT)</td>
<td>16335.67±875.22</td>
<td>-</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ABPL: Average brain parasite load; IPL: Initial parasite load; IU: Infected untreated; IT: Infected treated; DPT: Day post treatment; DPI: Day post infection; ADG: Average difference between treated and untreated groups.

Experiment duration, the antibody generally increased starting from the first week and continued increasing till the fourth week, however those rises in IgG titers were statistically significant (p = 0.0062 - 0.0315) in groups treated for 14 and 21 days, borderline significant (p = 0.0579) in animals treated for 1 week and insignificant (p = 0.188) in groups treated for 28 days as shown in Table 3.
Table 2. Optical density (ODs) of anti-toxoplasma IgM ELISA titers in Tamoxifen treated rats as compared with control groups.

<table>
<thead>
<tr>
<th>Result</th>
<th>Uninfected control ODs</th>
<th>Infected control ODs</th>
<th>1 week ODs</th>
<th>2 weeks ODs</th>
<th>3 weeks ODs</th>
<th>4 weeks ODs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 DPI</td>
<td>97 DPI</td>
<td>7 DPT</td>
<td>104 DPI</td>
<td>14 DPT</td>
<td>111 DPI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.179</td>
<td>0.678</td>
<td>0.623</td>
<td>0.535</td>
<td>0.524</td>
<td>0.363</td>
</tr>
<tr>
<td></td>
<td>0.151</td>
<td>0.708</td>
<td>0.564</td>
<td>0.496</td>
<td>0.502</td>
<td>0.389</td>
</tr>
<tr>
<td></td>
<td>0.209</td>
<td>0.734</td>
<td>0.617</td>
<td>0.521</td>
<td>0.521</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.611</td>
<td>0.521</td>
<td>0.354</td>
<td>0.293</td>
<td>0.439</td>
<td>0.583</td>
</tr>
<tr>
<td></td>
<td>0.515</td>
<td>0.403</td>
<td>0.354</td>
<td>0.293</td>
<td>0.439</td>
<td>0.583</td>
</tr>
<tr>
<td></td>
<td>0.489</td>
<td>0.342</td>
<td>0.354</td>
<td>0.293</td>
<td>0.439</td>
<td>0.583</td>
</tr>
<tr>
<td></td>
<td>0.541</td>
<td>0.406</td>
<td>0.354</td>
<td>0.293</td>
<td>0.439</td>
<td>0.583</td>
</tr>
</tbody>
</table>

**Mean OD**

<table>
<thead>
<tr>
<th>Uninfected control ODs</th>
<th>Infected control ODs</th>
<th>1 week ODs</th>
<th>2 weeks ODs</th>
<th>3 weeks ODs</th>
<th>4 weeks ODs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.179±0.029</td>
<td>0.601±0.032</td>
<td>0.529±0.04</td>
<td>0.521±0.015</td>
<td>0.382±0.028</td>
<td>0.317±0.036</td>
</tr>
</tbody>
</table>

**P-value between uninfected control and other groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>1 week ODs</th>
<th>2 weeks ODs</th>
<th>3 weeks ODs</th>
<th>4 weeks ODs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 DPI</td>
<td>97 DPI</td>
<td>7 DPT</td>
<td>104 DPI</td>
</tr>
<tr>
<td></td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>t=22.63</td>
<td>t=16.77</td>
<td>t=13.36</td>
<td>t=20.53</td>
</tr>
<tr>
<td></td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.0012</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>t=5.31</td>
<td>t=8.037</td>
<td>t=3.48</td>
<td>t=11.87</td>
</tr>
</tbody>
</table>

**P-value between each treated and untreated groups at the same time point**

<table>
<thead>
<tr>
<th>Group</th>
<th>1 week ODs</th>
<th>2 weeks ODs</th>
<th>3 weeks ODs</th>
<th>4 weeks ODs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 DPI</td>
<td>97 DPI</td>
<td>7 DPT</td>
<td>104 DPI</td>
</tr>
<tr>
<td></td>
<td>0.027*</td>
<td>0.0001*</td>
<td>0.0012</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>t=2.68</td>
<td>t=8.82</td>
<td>t=4.62</td>
<td>t=9.11</td>
</tr>
</tbody>
</table>

Toxoplasmosis and breast cancer are commonly recorded was the targeted one by this research, the assumption here was that TAM can lead to reactivation of latent toxoplasmosis through its immune modulatory effect mentioned above, consequently lead to unrecognizable exacerbated T. parasitosis with its possible serious sequelae on patients who are already devastated by the primary oncogenic condition. In this study, parasitologically, it was observed that the average brain parasitic load (ABPL) in infected treated (IT) rat group after one week decreased but the difference was statistically non-significant (3.4%). Inversely, there was a statistically significant increase in (ABPL) in other (IT) rat groups treated for 14, 21 and 28 days by 11.4, 30.3 and 48.7.1%, respectively. In the same line were the results of serological study of anti-Toxoplasma IgM antibodies; there was a significant decrease in Anti Toxoplasma IgM optical density in (IT) rat groups treated for 7 and 14 days followed by a significant increase in (IT) rat groups treated for 21 and 28 days. Assessing Anti Toxoplasma IgG antibodies showed that they generally increased throughout the experimental period with no initial decrease as happened with ABPL & IgM titers, which may be explained by the fact that IgG antibodies persist for a longer period after the primary infection in the infected host than IgM, so the general rise of IgG titers as compared to IgM may be attributed to the persisting IgG antibodies with the primary infection plus those generated as a result of infection reactivation. The initial decrease in both ABPL and anti-Toxoplasma IgM titers could be explained by the lethal effect of TAM on Toxoplasma parasites observed earlier by Dittmar et al. (2016) who explained that by the fact that estrogen was previously shown to increase the numbers of Toxoplasma tissue cysts in the brains of parasite-infected mice. Since TAM is the best-characterized antiestrogen inhibitor, it has anti Toxoplasma effects (Pung and Luster,
Table 3. Optical density (ODs) of Anti Toxoplasma IgG ELISA titers in Tamoxifen treated rats as compared with control groups.

<table>
<thead>
<tr>
<th>Result</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uninfected control ODs</td>
</tr>
<tr>
<td></td>
<td>97 DPI</td>
</tr>
<tr>
<td>Uninfected control ODs</td>
<td>0.227</td>
</tr>
<tr>
<td>Infected control ODs</td>
<td>0.154</td>
</tr>
<tr>
<td></td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>1.365</td>
</tr>
<tr>
<td></td>
<td>1.362</td>
</tr>
<tr>
<td>Mean OD</td>
<td>0.189±0.036</td>
</tr>
<tr>
<td>P-value between uninfected control and other groups</td>
<td>0.0001∗</td>
</tr>
<tr>
<td></td>
<td>t=40.34</td>
</tr>
<tr>
<td>P-value between each treated and untreated groups at the same time point</td>
<td>0.0579?</td>
</tr>
<tr>
<td></td>
<td>t = 2.211</td>
</tr>
</tbody>
</table>

Dittmar et al. (2016) also indicated that TAM inhibited Toxoplasma replication via a mechanism independent of its ability to antagonize estrogen receptor (ER) signaling even though they found that Toxoplasma activates ER-dependent transcription. In addition, they showed that tamoxifen reduced the overall number of parasite vacuoles and also induced the accumulation of LC3-green fluorescent protein (GFP) on the parasitophorous vacuole membrane (PVM). These data point to a mechanism by which tamoxifen kills Toxoplasma by inducing xenophagy. Xenophagy is now a well-recognized mechanism used by IFN-γ and CD40⁺ to control Toxoplasma replication (Choi et al., 2014; Andrade et al., 2006). However, with continuing TAM administration to rats for another two weeks, it was observed that ABPL, IgM and IgG titers were vividly increased denoting that TAM induced a concrete reactivation of latent toxoplasmosis in subjected rats as proven comparing their ABPLs, IgM, IgG titers with those belonging to the control groups. It was assumed that with continuation of TAM treatment, its immune modulatory effects mediated through shifting from TH1 to TH2 cells and decreasing CD4 numbers as reported previously (Rotstein et al., 1988; Robinson et al., 1993; Behjati1 and Frank, 2009), contradicted and predominated its anti toxoplasmic effects reported before by Dittmar et al. (2016) yielding a flare up of infection as estimated by both parasitological and serological parameters. This study concluded that TAM treatment in chronically infected mice with T. gondii protozoon parasite resulted in initial control of infection then flare up and exacerbation of infection. Thus more studies was recommended on wider scale and for longer periods for assessment of the cost/benefit and medical rationale of screening patients of breast cancer on adjuvant TAM treatment for Toxoplasma infection before the start of and during the course of treatment so as to detect early any incoming reactivation of chronic infection by observation of the rising titers of anti-Toxoplasma IgM and IgG to guard against the fatal risk and complication of.
toxoplasmosis in such immunocompromised patients.

There was a significant decrease in anti-Toxoplasma IgG optical density in (IT) group treated for 7, 14 and 21 days, and there was rising in anti-Toxoplasma IgG optical density in groups treated for 28 days but with no significant difference between (IU) and (IT) groups. These results confirmed the previous findings of ABPL and anti-toxoplasma IgM titre (Dittmar et al., 2016). The initial decrease of ABPL, IgM and IgG titers, might be due to the anti-Toxoplasma effects of tamoxifen reported previously by Dittmar et al. (2016) who explained that by the fact that estrogen was previously shown to increase numbers of Toxoplasma tissue cysts in the brains of parasite-infected mice. Since TAM is the best-characterized antiestrogen inhibitor, it has anti Toxoplasma effects (Pung and Luster, 1986). Dittmar et al. (2016) also indicated that TAM inhibited Toxoplasma replication via a mechanism independent of its ability to antagonize estrogen receptor (ER) signaling even though they found that Toxoplasma activates ER-dependent transcription. In addition, they showed that tamoxifen reduced the overall number of parasite vacuoles and also induced the accumulation of LC3-green fluorescent protein (GFP) on the parasitophorous vacuole membrane (PVM). Together, these data point to a mechanism by which tamoxifen kills Toxoplasma by inducing xenophagy. Xenophagy is now a well-recognized mechanism used by IFN-γ and CD40+ to control Toxoplasma replication (Choi et al., 2014; Andrade et al., 2006). However, with continuing TAM administration to rats for another two weeks, it was observed that ABPL, IgM and IgG titers were vividly increased denoting that TAM induced a concrete reactivation of latent toxoplasmosis in subjected rats as proven by comparing their ABPLs, IgM and IgG titers with those belonging to the control groups. It was assumed that with continuation of TAM treatment, its immune modulatory effects mediated through shifting from TH1 to TH2 cells and decreasing CD4 numbers as reported before (Rotstein et al., 1988; Robinson et al., 1993; Behjati and Frank, 2009), contradicted and predominated its anti toxoplastic effects yielding a flare up of infection as estimated by both parasitological and serological parameters. This study concluded that TAM treatment in chronically infected mice with T. gondii protozoon parasite resulted in initial control of infection then flare up and exacerbation of infection. Thus it was recommended that screening of Toxoplasma infection in patients of breast cancer on adjuvant TAM treatment before the start of and during the course of treatment so as to early detect any incoming reactivation of chronic infection by rising titer of anti-Toxoplasma IgM and IgG to guard against the fatal risk and complication of toxoplasmosis in such immunocompromised patients. More studies on TAM and toxoplasmosis in humans should be done.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES


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 GABA A or GABA B 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 Ca2+ 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-butryic 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
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 Pregabalin 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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In-pateints</td>
<td>Out pateints</td>
</tr>
<tr>
<td>Total number of prescriptions</td>
<td>40±6</td>
<td>287±21</td>
</tr>
<tr>
<td>Total number of discharged prescriptions</td>
<td>0</td>
<td>19±13</td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th>Department</th>
<th>Gabapentin Percentage</th>
<th>Pregabalin Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urology</td>
<td>0.45</td>
<td>0.37</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>11.16</td>
<td>3.56</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.34</td>
<td>0.75</td>
</tr>
<tr>
<td>Radiology</td>
<td>0.22</td>
<td>0.09</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>0.22</td>
<td>0.28</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>0.22</td>
<td>0.37</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>1.12</td>
<td>10.58</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>0.22</td>
<td>0.28</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>32.81</td>
<td>28.18</td>
</tr>
<tr>
<td>Neurology</td>
<td>26.79</td>
<td>20.69</td>
</tr>
<tr>
<td>Nephrology</td>
<td>0.45</td>
<td>1.12</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>4.24</td>
<td>15.45</td>
</tr>
<tr>
<td>General surgery</td>
<td>1.56</td>
<td>1.69</td>
</tr>
<tr>
<td>General practitioner</td>
<td>0.22</td>
<td>0.37</td>
</tr>
<tr>
<td>ENT surgery</td>
<td>0.45</td>
<td>General surgery</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>1.12</td>
<td>3.75</td>
</tr>
<tr>
<td>Emergency</td>
<td>2.90</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Dermatology</td>
<td>1.79</td>
<td>ENT Surgery</td>
</tr>
<tr>
<td>Dentist</td>
<td>0.67</td>
<td>2.43</td>
</tr>
<tr>
<td>Cardiology</td>
<td>10.04</td>
<td>5.99</td>
</tr>
</tbody>
</table>

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: Neurosurgery, 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 disorders 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 deformities 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
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 identified. 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-accessible 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

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

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

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

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

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 thoroughly 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 and gabapentin 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 and gabapentin abuse in choosing a superior appraisal of their addictive 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.

REFERENCES


