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Targeted Monitoring of Adverse Drug Reactions Following Pregabalin and Nortriptyline Prescription Against Neuropathic Pain

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Abstract: Neuropathic pain is associated with lesions or illness affecting the somatosensory nervous system (periphery or centrally). Clinically speaking, neuropathic pain is characterized by a pain that comes on suddenly, lasts for a long time, or shoots, and by pain responses that are amplified in response to noxious or non-noxious stimuli. The present study was designed to monitor various incidences of adverse drug reactions (ADRs) associated with pregabalin (75 mg), and nortriptyline (10 mg) treatment of neuropathic pain either individual use or in combined form. The study enrolled 75 patients in three groups (each containing 25 patients) suffering from neuropathic pain. The patients in different groups were treated with pregabalin (75 mg), nortriptyline (10 mg) and pregabalin + nortriptyline combination (75 mg + 10 mg) for 120 days and monitored for ADRs. Dryness of mouth, dizziness and sedation were the most common ADRs reported in 75 patients. The other ADRs include tingling sensation, weakness, constipation, skin rashes, irritability and dizziness, etc. However, the patients treated with nortriptyline and pregabalin combination reported fewer ADRs as compared to when used individually in the management of neuropathic pain.

Keywords: Neuropathic pain; Pregabalin; Nortriptyline; Adverse drug reactions; Pain; Monitoring; Clinical study.

1. Introduction

Clinical practice guidelines (CPGs), defined as "statements that include recommendations intended to optimize patient care that is informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options", have been anticipated to enable more reliable, efficient, and effective medical care, which would ultimately enhance health outcomes (Graham et al., 2011; Sabharwal et al., 2014). Over the past few decades, numerous organisations from throughout the world have released CPGs on related subjects, yet it has been discovered that their quality varies greatly (Ward and Grieco, 1996; Kis et al., 2010). Using the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument, we conducted a systematic assessment of the CPGs that are currently available for treating neuropathic pain. In addition, we also evaluated the consistency of the CPG recommendations.

Neuropathic pain is characterized by a somatosensory lesion or other related disorders which include a wide range of diverse heterogeneous situations (Jensen et al., 2010). Millions of people have neuropathic pain globally, and 7-8 percent of the general population may be affected by it (Bouhassira et al., 2008; Gilron et al., 2015). Generally, neuropathic pain is severe, chronic, and resistant to almost all over-the-counter analgesics. Therefore, the treatment of neuropathic pain is always challenging. To improve the management of neuropathic pain, the European Federation of Neurological Societies (EFNS) (Cruccu et al., 2010; Attal et al., 2010; Cruccu et al., 2007), the Canadian Pain Society Special Interest Group on Neuropathic Pain (NePSIG) (Moulin et al., 2007; Mailis and Taenzer, 2012; Moulin et al., 2014), the Assessment Committee of the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP) (Dworkin et al., 2007; Haanpää et al., 2011; Dworkin et al., 2013), the National Institute for Health and Care Excellence (Centre for

Clinical Practice at NICE (UK), 2013), as well as an expert panel of the Middle East region (Bohlega et al., 2010), Latin American (Acevedo et al., 2009), and South Africa (Chetty et al., 2012), have developed the CPG for the management of neuropathic pain.

2. Methodology

A total of 75 patients (18-70 years) of healthy weight between 40-80 kg, suffering from neuropathic pain were designated for the study. The designated patients were divided into three groups, each containing 25 patients. The duration of the study was four months and the observations during the study were recorded and analysed. Multiple visits were performed during the research work to collect the drug treatment data used for the management of neuropathic pain.

2.1. Criterion for inclusion

The criterion for the inclusion of the experimental volunteers is given below:

- Age between 18-70 years, body weight between 40-80 kg and cooperative.
- Signed informed consent and anticipated compliance.
- For the past four weeks, there has been no new or increasing neuropathic pain treatment.
- Compressive nerve states are linked to neuropathic pain (including failed surgery).
- Pain DETECT score of at least 13 and four-week mean pain intensity of at least 6/10. In addition, a pain DETECT pattern indicates that the underlying neuropathic pain is persistently present.
- Referring to the physician's consent to monitor the patient after the trial is over and provide the best pain management options.
- Where appropriate, a negative pregnancy test within seven days of each treatment session.
- Men and women who are or may become parents must take effective contraception for the duration of the study and 30 days following the final administration of study medication.

2.2. Criterion for exclusion

The criterion for the exclusion of the experimental volunteers is given below:

- Age should not be less than 18 years or should not be greater than 70 years.
- The central nervous system is the place where neuropathic pain begins.
- Ascending distal small fibre peripheral neuropathy.
- A different type of pain state could make it difficult to assess the investigated neuropathic pain condition.
- The investigator believes that any underlying medical or psychiatric illness, clinical problem, or laboratory finding may have an impact on the goals of the study.
- Diabetes that is uncontrolled or unstable.
- Severe cerebrovascular illness in the six months before enrollment.
- Active and persistent conditions of the eyes, skin, or newly discovered stomach ulcers that may interfere with the study treatment.
- Red means, tick bites, or a history of allergies to any of the research therapy components.
- women who are expecting or breastfeeding.
- Involvement in a different clinical trial within the previous 90 days.
- Use of any experimental substance within 90 days of the study drug's first day.
- Legal incapacity, restricted legal competence, a history of drug or alcohol addiction, or any other circumstance that, in the view of the investigator, prevents the person from participating.

2.3. Criterion for withdrawal

During the study, if serious conditions develop, this requires urgent treatment; such subjects will be withdrawn from the study.

2.4. Experimental protocols

2.4.1. Group 1: Pregabalin treated group: The patients received 75 mg pregabalin twice daily, which was not exceeding 300mg twice a day, for 120 days.

2.4.2. Group 2: Nortriptyline treated group: The patients received a 10 mg starting dose of nortriptyline at night, which was then increased to 25 mg after 3-7 days, for 120 days.

2.4.3. Group 3: Nortriptyline + pregabalin treated group: The patients received a combination of nortriptyline (10 mg) and pregabalin (75 mg) twice or three times a day, for 120 days.

2.5. Data collection

Data on adverse drug reactions (ADRs) of different drugs will be collected by screening the patients individually. For capturing the data of the suspected ADR, a case record form has been designed. ADRs detected during the study will be reported using the standard ADR reporting form from CDSCO. The form allows data to be organized in four sections given below:

1. Patient information
2. Suspected adverse reaction details
3. Suspected medication
4. Reporter details

3. Results and Discussion

3.1. Demographic details

Group 1 (pregabalin-treated group) consisted of 12 (48%) females and 13 (52%) males with a mean age of 52.35 years. Group 2 (nortriptyline-treated group) consisted of 15 (60%) females and 10 (40%) males with a mean age of 44.37 years. Group 3 (nortriptyline + pregabalin treated group) consisted of 14 (56%) females and 11 (44%) males with a mean age of 44.37 years. The demographic details of each group of patients who suffered and reported ADR monitoring centres are represented in Figure 1.

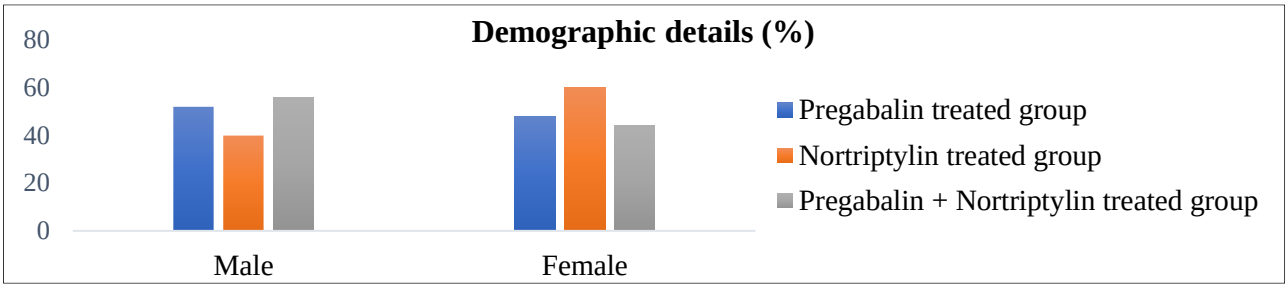

Figure 1. Demographic details of the pregabalin-treated group, nortriptyline-treated group, and pregabalin + nortriptyline-treated group.

3.2. Primary illness diagnosed by the registered medical practitioner

There were 5 major types or categories of illnesses for which drugs were prescribed to patients. The most important single disease in which the maximum number of ADRs were reported in each group was type 2 diabetes mellitus. The break-up of primary illnesses along with the treatment which led to ADRs are represented in Figure 2.

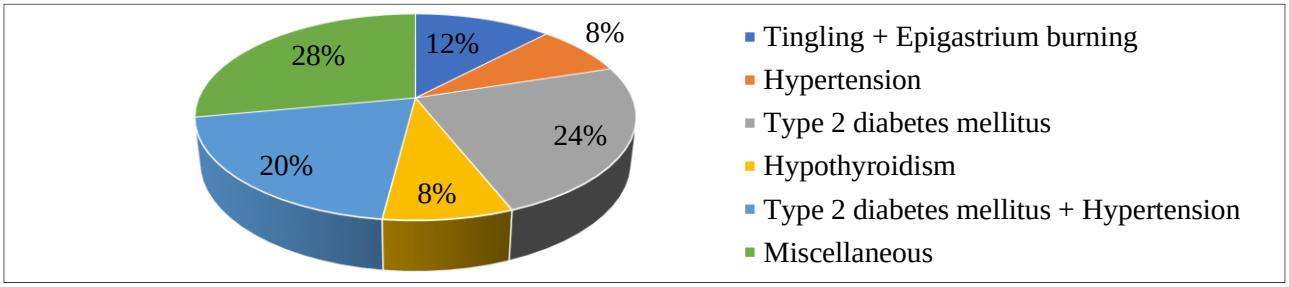

Figure 2. Primary illness of patients in which ADRs were reported.

3.3. Adverse drug reactions

Group 1 (pregabalin-treated group) reported a total of 62 ADRs to the ADR monitoring centre. Out of these the most common ADRs found in the maximum number of patients were dryness of mouth, dizziness, sedation, etc., as depicted in Figure 3.

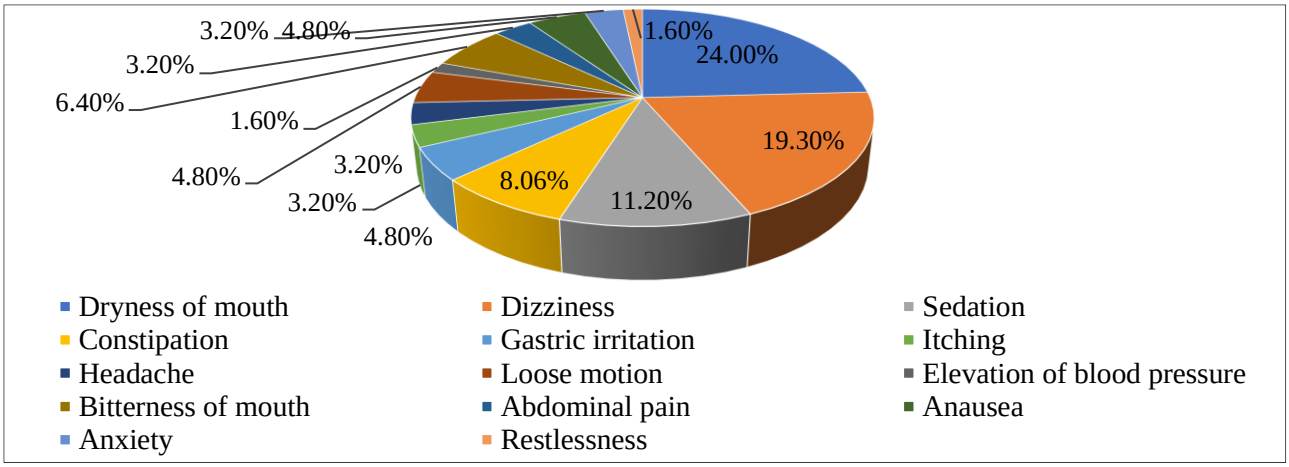

Figure 3. Description of reported ADRs in Group 1.

Group 2 (nortriptyline-treated group) reported a total of 98 ADRs to the ADR monitoring centre. Out of these the most common ADRs found in the maximum number of patients were dryness of mouth, dizziness, sedation, etc., as depicted in Figure 4.

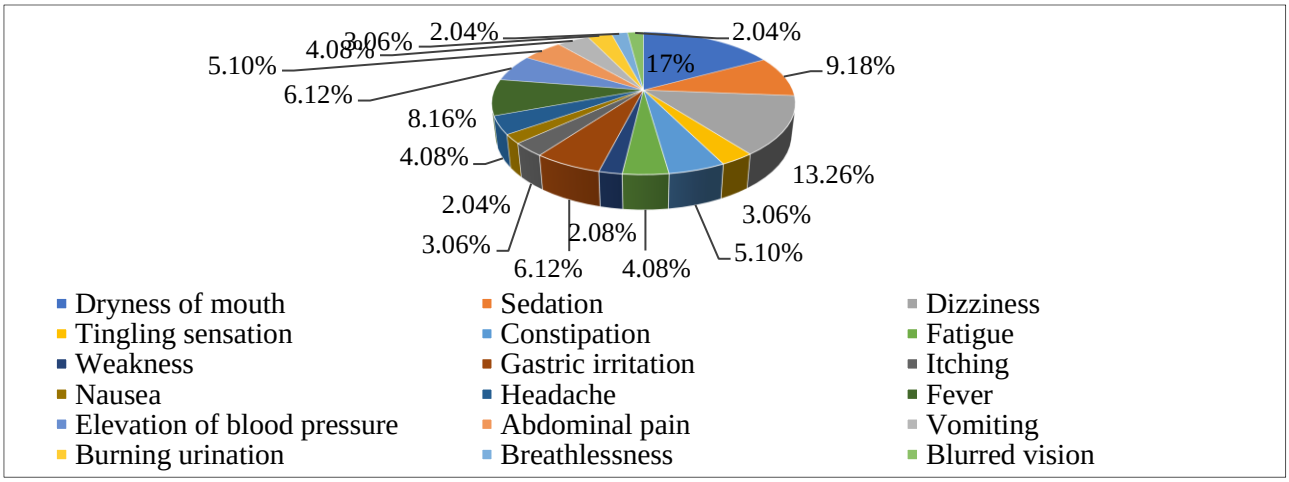

Figure 4. Description of reported ADRs in Group 2.

Group 3 (nortriptyline + pregabalin treated group) reported a total of 42 ADRs to the ADR monitoring centre. Out of these the most common ADRs found in the maximum no. of patients were dizziness, skin rashes, sweating, etc. as depicted in Figure 5.

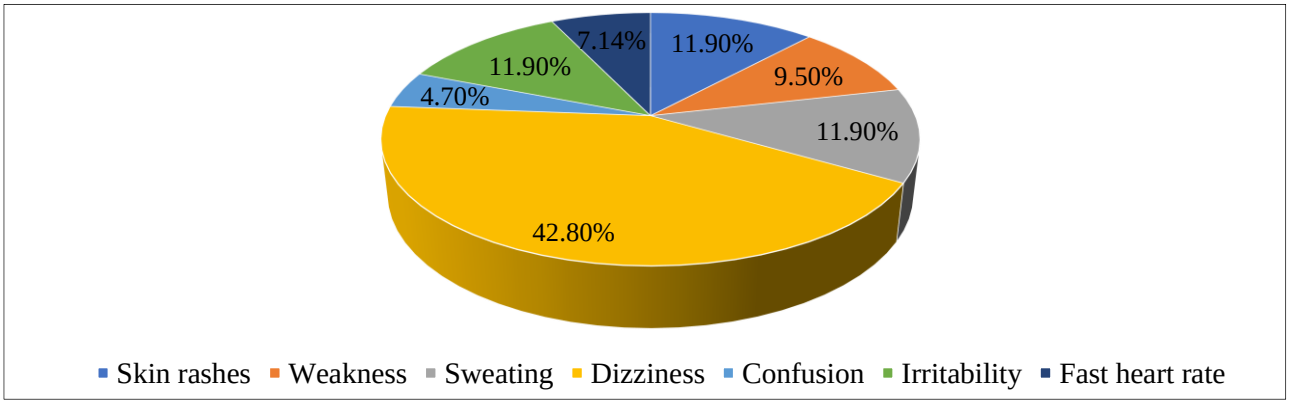

Figure 5. Description of reported ADRs in Group 3.

3.4. The severity of reported ADRs

The severity of reported ADRs is depicted in Figure 6. Out of 62 reported ADRs of group 1 (pregabalin-treated group) 1 (1.61%) was severe, 45 (72.58%) were mild, and 16 (25.80%) were moderate. Out of 98 reported ADRs of group 2 (nortriptyline-treated group) 4 (4.08%) were severe, 59 (60.20%) were mild, and 35 (35.71%) were moderate. Out of 42 reported ADRs of group 3 (nortriptyline + pregabalin treated group) 1 (2.38%) was severe, 30 (71.42%) were mild and 11 (26.19%) were moderate.

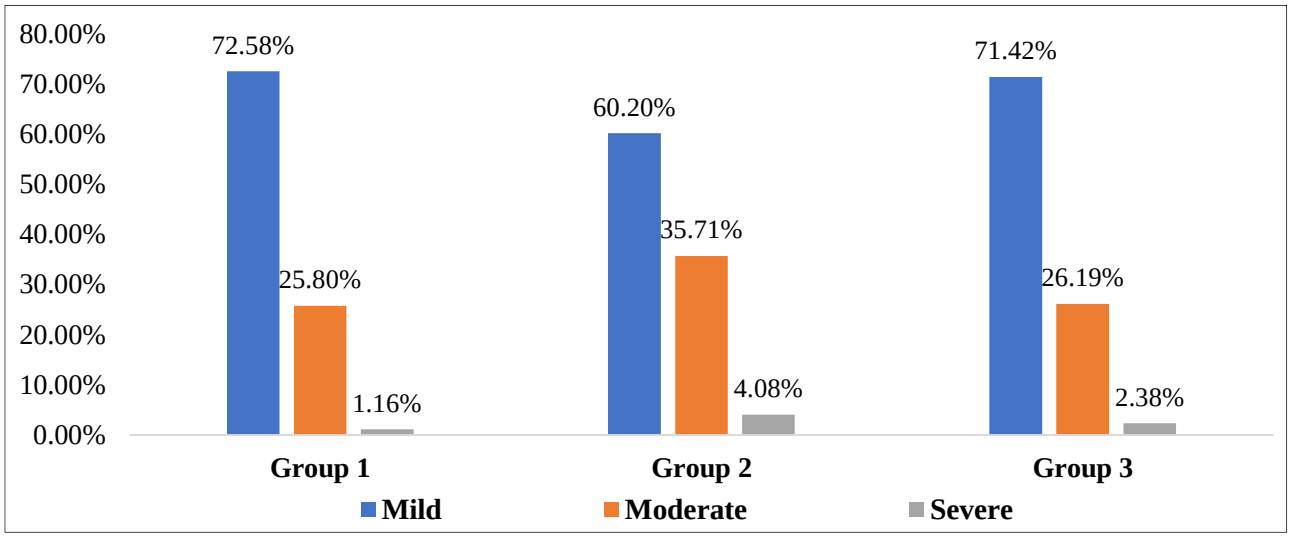

Figure 6. The severity of reported ADRs in Groups 1, 2 and 3.

3.5. Progression of ADRs

The progression of ADR was considered and these progressions of ADRs were divided into 4 categories: 1 (increased), 2 (decreased), 3 (running) and 4 (stopped). Most of the ADRs of group 1 (pregabalin-treated group) and group 2 (nortriptyline-treated group) came under category 1 (increased). However, most of the ADRs group 3 (nortriptyline + pregabalin treated group) came under category 2 (decreased). The progressions of ADRs in each group are represented in Figure 7.

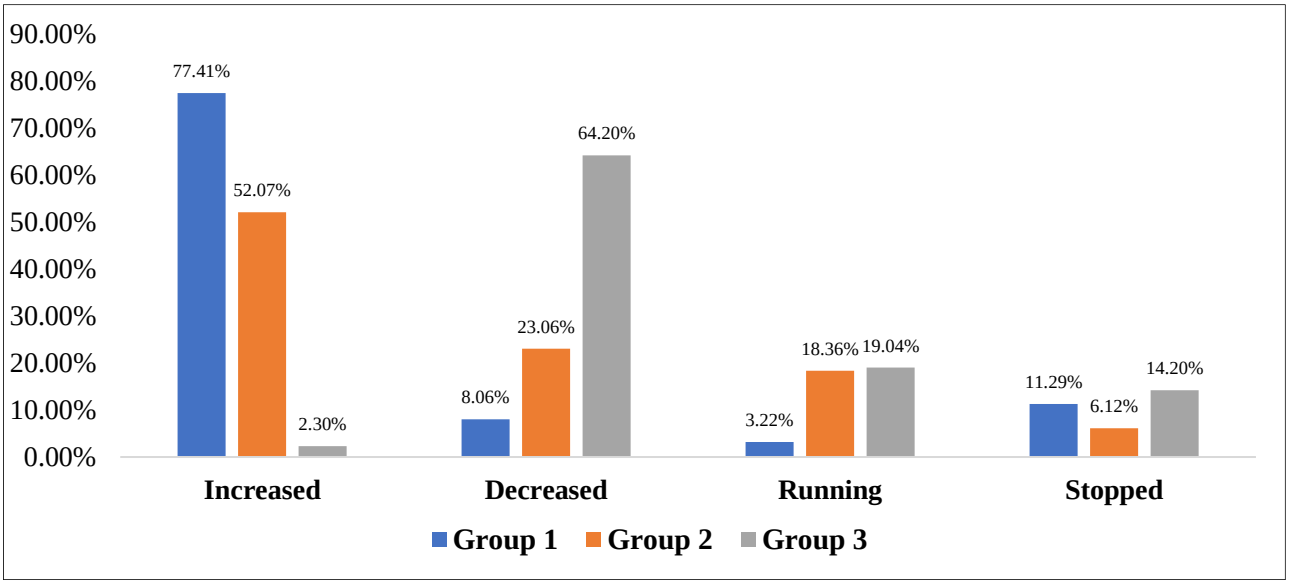

Figure 9: Progression of reported suspected ADRs in pregabalin-treated group

4. Conclusions

Out of 75 patients suffering from neuropathic pain, 34 (45.33%) were male and 41 (54.66%) were female. The pregabalin-treated group (25 patients) showed a total number of 62 ADRs out of which the most common were found to be dryness of mouth, dizziness and sedation. The severity of these ADRs was reported to be severe

(1.61%), mild (72.58%) and moderate (25.80%). Furthermore, the nortriptyline-treated group (25 patients) showed a total number of 98 ADRs out of which the most common ADRs were found to be the same, i.e., dryness of mouth, dizziness and sedation. The severity of these ADRs was reported to be severe (4.08%), mild (60.20%) and moderate (35.71%). However, the pregabalin and nortriptyline combination-treated group (25 patients) showed a total number of 42 ADRs out of which the most common were found to be dizziness, skin rashes and sweating. The severity of these ADRs was reported to be severe (2.38%), mild (71.42%) and moderate (26.19%). By using the WHO scale causality assessment of ADRs was found under the probable range, and some ADRs were possible.

Conflicts of Interest

The authors declare no conflict of interest.

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