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Original article

A study on comparative efficacy and cost effectiveness of Pregabalin and Duloxetine used in diabetic neuropathic pain

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ABSTRACT

Aim: The study was designed for comparing the efficacy and cost effectiveness of Pregabalin and Duloxetine used in Diabetic Neuropathic Pain.
Methods: The prospective interventional 6 month study was conducted in a diabetic clinic of a 500 bedded tertiary care hospital in South India. The subjects having diagnosed with diabetic neuropathy and not treated with Pregabalin and Duloxetine or any other drugs of its class were selected. The data were collected using NPS and Neuro QoL questionnaires. The cost of both drugs used in the study was calculated as the mean of the price of 3 leading common brands of those drugs. The comparative efficacy was calculated by comparing the mean difference produced by both drugs in NPS and QoL scores. The cost effectiveness were calculated by ICER ratio.
Results: The results have shown a significant improvement in the mean difference of NPS and Neuro QoL scores of both Pregabalin ($p = <0.001$) and Duloxetine ($p = <0.001$) before and after the therapy, the Duloxetine dominates over Pregabalin in both. The mean cost of Pregabalin for 3 months therapy was found to be INR 668.7 and that for Duloxetine was INR 756. Duloxetine showed a better effect but more expensive. ICER ratio was calculated and found that a cost of INR 61.47 per extra QoL gained by Duloxetine.
Conclusion: The study have revealed that, both drugs are found to be effective.On conducting cost effective analysis, a significant better improvement in QoL of patients was obtained by Duloxetine with comparatively mild increase in the price.

1. Introduction

Diabetes has emerged as a major healthcare problem in India. The Diabetes Atlas published by the International Diabetes Federation (IDF), have revealed that an estimate of 40 million peoples with diabetes live in India.The number of diabetes patients are predicted to rise in India, China and USA by 2030 [1]. The prevalence of gestational diabetes mellitus also found to be increased in past twenty years [2]. Neuropathy is a common condition associated with diabetes, affecting 60–70% of diabetic patients. Diabetic neuropathies are nerve disorders which can be classified as peripheral, autonomic, proximal, and focal.

Diabetic peripheral neuropathy (DPN) is one of the main complications associated with diabetics. It is a heterogeneous group of disorders that can affect neuronal function throughout the body and approximately 16–26% of all diabetic patients can develop this condition [3]. The pain associated with diabetic peripheral neuropathy may be due to the failure of endogenous analgesic mechanisms in the descending spinal pathways which control pain transmission to the brain [4]. According to the International Association for the Study of Pain, DPN is defined as "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes." DPN is described as a burning, tingling, prickling, aching, sharp pain characterized by symptoms that are symmetric and distal, often worsening at night and sometimes associated with allodynia, hyperalgesia, and paresthesia [5]. Simple numeric rating scales are available to assess the frequency and severity of pain [6]. Some of the scales used for this include, visual analog scale or the numerical rating scale, such as 11-point Likert scale in which 0 indicates no pain and 10 indicates worst pain. These scales can then be used for monitoring the response to treatment in clinical practice or in research context. The validated scales and questionnaires used in

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clinical practice include, The modified Brief Pain Inventory Short Form (BPI-MSF) [7] recently used as the primary end point in pharmacological treatment trials for painful Distal Symmetrical Polyneuropathy (DSPN), The neuropathic pain symptom inventory [8], used in evaluating the different symptoms and dimensions of neuropathic pain, The neuropathic pain questionnaire [9]. The quality of life (QoL) can be assessed by generic instruments which allow cross comparison with other chronic medical conditions. The usage of validated neuropathy-specific measures of QoL, such as Neuro-QoL [10], are reliable for capturing the key dimensions of patient's experience of DSPN. The Neuro-QoL is a valid tool for studying the impact of neuropathy and foot ulceration in QoL.

Several pharmacological treatments are proved, for managing painful DPN, Duloxetine and Pregabalin are commonly used for treating neuropathic pain in diabetes and are approved both by the Food and Drugs Administration (FDA) of the U.S. and the European Medicines Agency.The European Federation of Neurological Societies proposed that first-line treatment might comprise of TCAs, SNRIs, Gabapentin, or Pregabalin [11]. The National Institute for Health and Care Excellence in UK has given the guidelines for managing neuropathic pain in non-specialist settings. The guidelines has proposed that Duloxetine should be the first-line treatment with Amitriptyline as an alternative, and Pregabalin as a second-line treatment for painful DSPN [12]. The American Academy of Neurology recently have recommended, Pregabalin as the most effective drug therapy and should be offered for relief of painful DSPN [13], whereas venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids, and capsaicin are used for treatment of painful DSPN [14]. This recommendations were primarily based on the achievements made in clinical trial completion. Finally, the International Consensus Panel on Diabetic Neuropathy recommended TCAs, duloxetine, pregabalin, and gabapentin can be used as first-line agents after having careful review of all the available literature regarding the pharmacological treatment of painful DSPN [2], the final drug of choice are based on particular patient's demographic profile and comorbidities. Pregabalin is a chemical analogue of the neurotransmitter Gamma Amino Butyric Acid (GABA) present in mammals. Pregabalin is inactive at GABA receptors and does not appear to mimic GABA physiologically. Pregabalin binds with $\alpha 2\delta$ subunit of pre synaptic, voltage dependent calcium channels [15] which probably contributes to its anticonvulsant properties, since these activities correlates with a decrease in calcium channel function. The Pregabalin was developed as an antiepileptic drug but has been reported to have clinical efficacy as an analgesic for neuropathic pain and fibromyalgia and as an anxiolytic in patients with generalized anxiety disorder. Dizziness, somnolence, facial edema, peripheral edema and weight gain are the most common adverse effects reported in the Pregabalin group [16].

The Duloxetine initiate the pharmacological response by reuptake inhibition of both serotonin and nor epinephrine in the central nervous system, there by increases the activity of these neurotransmitters and subsequently reduces the perception for pain by modulating the pain signals [17,18]. Side effects with Duloxetine are generally mild for the SNRI class which includes nausea, dizziness, somnolence, fatigue, sweating, dry mouth, constipation, and diarrhoea. The Duloxetine is a good choice for DPNP treatment in patients with coexisting depression, anxiety, fibromyalgia, or chronic musculoskeletal pain.

The role of new intervention in clinical practice can be determined by assessing its clinical effectiveness. But the new interventions may provide only a modest advantage over existing treatment, usually at higher cost. In the case of pharmaceutical interventions, Pharmacoeconomics attempts to measure the added benefit of one intervention is worth the added cost of that intervention. Pharmacoeconomics has been defined as the description and analysis of the costs of drug therapy to health care systems and society. The analysis will help to measure and compare the costs and consequences of pharmaceutical products and services. A cost-effectiveness analysis (CEA) will measure the costs in currency and expressed the outcomes in natural health units. Results of cost-effectiveness analyses are usually presented as incremental cost-effectiveness ratios (ICERs),which are calculated by dividing the difference in costs by the difference in health benefits [19]. The cost-effectiveness analysis (CEA) ratio is applied as a practical tool for decision making than Cost Benefit Analysis, since it involves the comparison of the costs of achieving a particular non-monetary objectives; such as life saved, health improvement, or quality of life. CEA ratios can be applied when the costs are expressed in money and the benefits are in specific health outcomes. Benefits can be expressed in any unit of measure (asthma free days, hospitalizations, etc.) but can only be reliable and meaningful when the output units are consistent across projects or models. The goal of applying CEA is to allow for comparison of a variety of interventions in terms of non-monetary (health) gains at a given cost, keeping the comparators in the same terms or units of measure. In practice, once the common measure of the outcomes are established, the different entities are compared, and common cost are determined as a means for assigning relative effectiveness to different modes of treatment or intervention. Cost-effectiveness analyses are often visualized on a cost-effectiveness plane consisting of four-quadrants. Outcomes plotted in Quadrant I are more effective and more expensive. The Quadrant II is more effective and less expensive, whereas Quadrant III is less effective and less expensive. The Quadrant IV is less effective and more expensive [20]. The Cost Effectiveness Ratio (CER) is the mathematical representation of these analysis. The CER consists of the change in societal costs (e.g., resources, money) placed in the numerator and the change in health (e.g., disability or functionality, shortened or prolonged life) in the denominator.

ICER = (cost in Rs of A − cost in Rs of B)/(effect of A − effect of B)

In the current study we have tried to compare the different class of drugs which are used for the same condition of DPNP, affecting a large percentage of patients and significantly increase the costs of medical care. As a result cost-effectiveness analysis of Duloxetine and Pregabalin were conducted.

2. Materials and methods

The study was conducted in the diabetic clinic attached to a 500 bedded tertiary care hospital for 6 months. Detailed literature review was done and protocol was prepared. The protocol was presented and Ethical clearance was obtained from the Institutional Ethics Committee. Patients were selected based on well-defined inclusion and exclusion criteria. The Patients enrolled in diabetic clinic who diagnosed with diabetic neuropathic pain and not on Pregabalin or Duloxetine or any other drugs of their class were included in the study. The Patients less than 18 years old, Pregnant women, Patients who have intolerance towards Pregabalin and Duloxetine, Mentally retarded and physically handicapped patients were excluded. The sources of data includes the Patients case records, laboratory investigation reports,the study specific documents such as Neuro-Qol form, Neuropathic Pain scale and direct interview.

A pilot study was conducted. Based on the data obtained from pilot study, sample population was calculated (Machin et al., 1997) [21].

Formula: −m (size per group) = $2c/\delta^2 + 1$, where $\delta = |\mu_1 - \mu_2|/\sigma$

C = power of the study (90%)

μ_1, μ_2 = means of the two treatment groups

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