QUALITY OF LIFE OF PATIENTS WITH PERIPHERAL DIABETIC NEUROPATHY PAIN AND THE ANALGESIC EFFECT AND SAFETY OF GABAPENTIN-CARBAMAZEPINE COMBINATION IN AN ANIMAL MODEL AND ITS FORMULATION

BY

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ABSTRACT

Background: Peripheral Diabetic Neuropathy (PDN) is a late manifestation of uncontrolled Diabetes Mellitus (DM). PDN has a wide variety of clinical manifestations, at somatic, autonomic and central nervous system levels and can significantly modify the quality of life. Peripheral Diabetic Neuropathy Pain (PDNP) is a result of injury to the peripheral nervous system. PDNP is often chronic, and if inadequately managed, patients often experience anxiety and depression. Despite the evaluation of many pharmacologic and nonpharmacological therapies, there are few drugs approved by Food and Drug Administration (FDA) as a treatment of PDNP. **Objectives:** There are three main scopes of objectives include epidemiology study of PDNP, evaluate the effectiveness and safety of gabapentin (GBP) and carbamazepine (CBZ) combination therapy in an animal model, as well as to develop and formulate a suitable pharmaceutical dosage form of GBP and CBZ combination. **Methodology:** To evaluate the quality of life (QoL) of PDNP patients, the study adopted a cross-sectional design, and the Douleur Neuropathy 4 (DN4) and Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaires were used for data collection. In addition, to explore the factors influencing the severity of pain in patients suffering from PDNP, the Short-Form McGill Pain Questionnaire (MPQ) was applied. In the animal study, PDN was produced in rats by a single intraperitoneal injection of streptozotocin (STZ) at 60 mg/kg. CBZ, GBP, and their combination were orally administered at varying doses comparable to their therapeutic doses in humans. Nociceptive responses in the diabetic rats were assessed using hot plate test. The safety of concurrent use of two medications was explored after one month of treatment at moderate therapeutic doses calculated by using drug load formula in an animal model. The formulation of a fixed dose combination of GBP and CBZ was done by a standard method of capsule preparation. **Results:** The results of this study indicated that individuals with diabetes and PDNP have a low QoL, particularly, with regard to "freedom to eat", "freedom to drink", "physical health", "family life", and "living condition". Certain ADDQoL domain scores are adversely impacted by factors such as female sex, younger age, lack of employment, marriage, good financial position, diabetes duration, and insulin-based treatment. The majority of PDNP patients experienced mild pain, and the severity of pain may be affected by ethnicity and the long duration of diabetes. The combination of GBP and CBZ in the hot-plate test at doses equivalent to human therapeutic doses (GBP 90 mg + CBZ 20 mg) of the two drugs was more efficacious than GBP and CBZ given separately. Concurrent administration of GBP and CBZ at moderate therapeutic doses appeared safe and may be reasonable with fewer adverse effects compared with high doses of single drug or combination. Finally, a fixed dose combination of CBZ and GBP capsule has been easily formulated by the standard method. **Conclusion:** PDNP is a serious problem and need more attention regarding the health care and management. Combination therapy of GBP and CBZ at moderate dose can be used to control the pain with few side effects and easily can be formulated in a fixed pharmaceutical dosage form.

خلاصة البحث

خلفية البحث: الاعتلال العصبي السكري المحيطي هو مظهر متأخر لمرض السكري غير المتحكم فيه. يحتوي الاعتلال العصبي السكري المحيطي على مجموعة واسعة من المظاهر السريرية ، على مستويات الجهاز العصبي الجسدي ، اللاإرادي والجهاز العصبي المركزي ويمكن أن يغير بشكل كبير من جودة الحياة. **اهداف البحث:** هناك ثلاثة مجالات رئيسية للأهداف تشمل دراسة علم الأوبئة لألم ألاعتلال العصبي المحيطي السكري ، وتقييم فعالية وسلامة علاج الجابابنتين والكاربامازبين في نموذج حيواني ، وكذلك تطوير وصياغة جرعة صيدلانية واحدة تحتوي على الجابابنتين والكاربامازيبين. **منهجية البحث:** لتقييم نوعية الحياة لمرضى ألم ألاعتلال العصبي المحيطي السكري ، اعتمدت الدراسة على تصميم مستعرض ، واستخدمت استبيانات (DN4) و (ADDQoL) لجمع البيانات . بالإضافة إلى ذلك ، لاستكشاف العوامل التي تؤثر على شدة الألم في المرضى الذين يعانون من ألم ألاعتلال العصبي المحيطي السكري ، تم تطبيق نموذج استبيان ماكغيل للالم (MPQ). في دراسة الحيوان ، تم إستحداث ألم ألاعتلال العصبي المحيطي في الفئران عن طريق حقنها داخل الصفاق بمادة الستربتوزوتوسين 60 ملغم /كغم. تم تقييم استجابات مسبب للألم في الفئران المصابة بداء السكري باستخدام اختبار الصفيحة الساخنة. وقد تم دراسة سلامة إستخام العلاجين في آن واحد بعد شهر واحد من العلاج بجرعات علاجية معتدلة. وقد تم إستخدام الطرق القياسية في تحضير المركب الذي يجمع الجابابنتين والكاربامازيبين في صيغة صيدلانية واحدة .**النتائج:** أشارت نتائج هذه الدراسة إلى أن الأشخاص المصابين بألم ألاعتلال العصبي المحيطي السكري لديهم نوعية الحياة منخفضة. تتأثر بعض نتائج نطاق ADDQoL بشكل سلبي بعوامل مثل الجنس الأنثوي ، والعمر الأصغر ، ونقص العمالة ، والزواج ، والوضع المالي الجيد ، ومدة السكر ، والعلاج القائم على الأنسولين. يعاني معظم مرضى ألم ألاعتلال العصبي المحيطي السكري من ألم خفيف ، وقد تتأثر شدة الألم بسبب العرق وطول مدة مرض السكري. كان الجمع بين الجابابنتين والكاربامازيبين في اختبار الصفيحة الساخنة بجرعات مكافئة للجرعات العلاجية البشرية من العقارين أكثر فعالية من العلاج المعطى بشكل منفصل. ومن جهه اخرى , كان إستخدام الجابابنتين والكاربامازيبين في جرع متوسطة آمن وباعراض جانبية بسيطه مقارنة مع الجرعات العالية الكبيرة. وأخيرًا ،تمكنا من تحضير مركب دوائي واحد على شكل كبسول يحتوي على الجابابنتين والكاربامازيبين بطريقة سهلة وفقًا للطرق القياسية. **الاستنتاج:** ان ألم ألاعتلال العصبي المحيطي السكري مشكلة خطيرة وتحتاج إلى مزيد من الاهتمام فيما يتعلق بالرعاية الصحية والإدارة. يمكن استخدام العلاج المركب من الجابابنتين و الكاربامازيبين بجرعة متوسطة للسيطرة على الألم.

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

ADDQoL	Audit of Diabetes-Dependent Quality of Life
AED	Antiepileptic Drug
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
APIs	Active Pharmaceutical Ingredients
AST	Aspartate Transaminase
CBZ	Carbamazepine
DM	Diabetes Mellitus
DN	Diabetic neuropathy
DN4	Douleur Neuropathy 4
ED	Effective dose
FDA	Food and Drug Administration
FDCs	Fixed-dose combinations
GBP	Gabapentin
HTAA	Hospital Tengku Ampuan Afzan
HTD	Human Therapeutic Dose
ICF	Information Consent Form
IDF	International Diabetes Federation
K_m	Michaelis constant
kPa	Pascal (unit)
MOPD	Medical Outpatient Department
PDN	Peripheral Diabetic Neuropathy
PDNP	Peripheral Diabetic Neuropathy Pain
QoL	Quality of Life
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Diabetes Mellitus (DM) is a metabolic disease or group of diseases of unknown cause resulting from an alteration in the availability and use of the insulin and abnormalities in the endocrine system that may involved other hormones such as thyroid hormone and the body's ability to use insulin. DM has been known for centuries, and although research has elucidated many of the mysteries and resulted in the design of lifesaving treatments, the cause and the prevention of DM has remained elusive (Diana & Richard, 2008).

DM is one of the diseases with greater impact on public health, not only because of its high prevalence, but, above all, by the consequences of the chronic complications arising from this disease (Isla, 2012). According to the 8th edition of Diabetes Atlas, International Diabetes Federation (IDF) has reported that about 425 million adults have DM worldwide in 2017 (Atlas, 2017). IDF also estimates that there will be 693 million people living with DM by 2045, an increase of over 50% compared with the 2017 figure if no action was taken (Atlas, 2017).

Diabetic Neuropathy (DN) is a multifactor complication of diabetes, which occurs at an earlier point in the progression of the disease. Although it remains uncertain what exactly causes DN, a range of pathological conditions are likely involved, as in other diabetes complications (Shaikh & Somani, 2010).

Peripheral Diabetic Neuropathy (PDN) is a late manifestation of uncontrolled DM (Baron et al., 2017). PDN has a wide variety of clinical manifestations, at somatic, autonomic and central nervous system levels and can significantly modify the quality of life (Cohen & Mao, 2014). Neuropathic pain is a result of injury to the peripheral or central nervous system. Peripheral Diabetic Neuropathy Pain (PDNP) is often chronic, and if inadequately managed, patients often experience anxiety and depression (Vinik & Casellini, 2013). In the United States and Europe, PDNP is estimated to occur in up to one-third of all patients with diabetes (Malik et al., 2017). Although diabetes is an increasing problem in Asia, studies estimating the prevalence of PDNP are scarce (Malik et al., 2017). Some previous studies have reported the prevalence of PDNP and the rates show considerable variation, from as low as 26% up to 47% (Barrett et al., 2007).

1.2 STATEMENT OF THE PROBLEM

PDN is a serious complication of diabetes and, affecting a high percentage of patients with diabetes. It is one of the leading causes of morbidity and increased mortality. The main clinical indicators are painful neuropathic symptoms and insensitivity, which enhances the risk of injuries, burns and foot ulceration. In the course of recent years, a few recommendations have been proposed for the pharmacotherapy of neuropathic pain, particularly painful diabetic neuropathies. Many pharmacological therapies have been tested, and high-quality clinical trials have been done to find the suitable treatment for PDNP. Despite the evaluation of many pharmacologic and nonpharmacological therapies, there are few drugs approved by Food and Drug Administration (FDA) as a treatment of PDNP. In addition, according to estimates the most therapies for DPNP

result in a 50% reduction in pain, but this level of improvement is often disappointing to patients.

Knowledge about the quality of life of individuals suffering from PDNP is lacking, even though this aspect is clearly highly important. In addition, the prevalence, intensity and associated factors of pain in patients suffering from PDNP is a very crucial issue but there is insufficient information despite the high associated comorbidities.

Combination therapy might be useful for patients complaining of severe pain, but there is a paucity of studies, and further research is required. Combining therapy with different mechanisms of action is very common in the treatment of many medical disorders, especially if there is no interaction between the drugs. Future research must be established to find effective drug combinations without significant adverse effects to produce a new drug specifically to manage PDNP. The fixed-dose combination is accepted because of simplified treatment regimens, superior clinical effectiveness, and better patient adherence and economical. The combination of gabapentin and carbamazepine in one dosage form is not available on the market yet.

1.3 RESEARCH OBJECTIVES

In this study, there are three main scopes of objectives that include epidemiology study of PDNP, animal study, as well as drug development.

The specific objectives of this study can be outlined as follows:

1- To evaluate the quality of life in diabetic patients suffering from PDNP.

2- Determining the factors influencing the severity of pain in patients suffering from PDNP.

3- To investigate the effectiveness of gabapentin (GBP) and carbamazepine (CBZ) combination therapy at moderated doses in the management of peripheral diabetic neuropathy pain in rat model.

4- To evaluate the safety of concurrently administering moderate therapeutic doses of GBP and CBZ on the histopathological features and biochemical parameters of kidney and liver in rat.

5- To develop and formulate a suitable dosage form of GBP and CBZ combination.

1.4 RESEARCH QUESTIONS

1- Is there any relationship between PDNP and quality of life?

2- Is there any factor that influences the severity of pain in patients suffering from PDNP?

3- Is the combination of the moderate doses of GBP and CBZ be more effective than single drug treatment in animal model of PDNP?

4- Is the combination of moderate doses of GBP and CBZ safe in animal study?

5- Is it possible to formulate a pharmaceutical dosage form of two drugs (GBP & CBZ)?

1.5 RESEARCH HYPOTHESES

Pain and its severity in the diabetic patient suffering from PDNP may affect the quality of life. The combination therapy of moderate doses of GBP & CBZ is more effective and safer than the single drug treatment as well as can be formulated in one pharmaceutical dosage form.

1.6 SIGNIFICANCE OF THE STUDY

As mentioned in the problem statement, until today, there are few drugs approved by FDA as a treatment of PDNP. Combination therapy might be useful for patients complaining of severe pain in diabetic patients suffering from PDNP. This study is the first one to evaluate the effectiveness and safety of the concurrent use of GBP and CBZ as well as the first research to formulate the two drugs in one pharmaceutical dosage form. In addition, the obtained results from the epidemiology study may help the healthcare practitioners in formulating effective approaches and strategies for enhancing the quality of life and reduce the severity of pain in patients suffering from PDNP.

1.7 DEFINITIONS OF TERMS

Diabetes Mellitus (DM)

It is a metabolic disease or group of diseases of unknown cause resulting from an alteration in the availability and use of insulin (Diana & Richard, 2008).

Diabetic Complications

It is a consequence of long-term diabetes which include nephropathy, retinopathy and neuropathy (D'silva, Lin, Staecker, Whitney, & Kluding, 2016).

Diabetic Neuropathy (DN)

It is regarded as a common complication of DM, and there are many types but without any standard universal classification (Vinik & Casellini, 2013).

Peripheral Diabetic Neuropathy (PDN)

The most widely recognised type of neuropathy that is diagnosed in patients with Diabetes Mellitus attributed to chronic hyperglycaemia and is defined as the presence of peripheral nerve dysfunction in diabetics after exclusion of other causes (Rai, Mishra, Chandra, Saxena, & Mangal, 2016).

Peripheral Diabetic Neuropathy Pain (PDNP)

Peripheral Diabetic Neuropathy Pain (PDNP) is a chronic or severe pain due to nerve damage (Vinik & Casellini, 2013).

Gabapentin (GBP)

It is a drug approved by the FDA as an anticonvulsant for the adjunctive treatment of partial seizures with/without secondary generalisation and as a treatment of neuropathy (Mack, 2003).

Carbamazepine (CBZ)

It is a first-generation anticonvulsant drug used for many types of epilepsy and neuropathic pain (Lim, Chia, Kang, & Yap, 2016).

Synergism Effect

An effect arising between two or more agents, entities, factors, or substances that produce an effect greater than the sum of their individual effects. Synergistic drug combinations could provide an effective strategy to overcome drug resistance (Chen et al., 2016).

Analgesic Effect

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia or relief from pain. Analgesic drugs act in various ways on the peripheral and central nervous systems (Chen, Ren, Chen, Wang, Zhang, & Yan, 2016).

Quality Of Life (QoL)

It is the general well-being of individuals and societies, outlining negative and positive features of life. It observes life satisfaction, including everything from physical health, family, education, employment, wealth, religious beliefs, finance and the environment (Stahl-Pehe et al., 2017).

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

It was documented that despite the existence of research surrounding Diabetes Mellitus (DM) the root causes still remain unknown; this is against a backdrop of great advancement in the management of the disease and the daily use of life saving treatments (Guthrie & Guthrie, 2008). The lack of understanding of the root causes mean at present, there's no sound way of preventing it from advancing further. This metabolic disease (or wider collection of diseases), relates specifically to problems within the endocrine system and the body's inability to produce the correct levels of insulin, resulting in a change in the production of this and other associated hormones.

According to Ng, Ton & Kadir (2016), the Malaysian population has witnessed a steady increase in the numbers of over 30 year olds suffering with DM in recent years. Numbers have steadily risen from 8.3% of the population in 1996 to 14.9% in 2006. This increasing trend has since continued to rise with 20.8% of the population being diagnosed in 2011. According to Noor Hasimah, Nurhanani & Ramli (2010), this trend has been attributed to four known contributory factors which include poor diet, lack of exercise, an increasingly ageing population and population growth itself. The numbers registered in the National Diabetes Registry between 2009 and 2012 also reflect this; a total of 657,839 patients were listed during this time.

Vinik & Casellini noted that despite there being the acknowledgement of the existence of Diabetic Neuropathy (DN), there is currently no standardised classification behind the diagnosis of the condition (Vinik & Casellini, 2013). It is universally accepted that there is a 'loss of the peripheral nerve function', (Dejgaard & Hilsted, 2007) as a 'direct result of prolonged periods of hyperglycemia'. It's also been noted that through 'morphological damage' there is also more permanent damage to the nervous and peripheral nervous systems, but this is as far as the understanding goes. According to (Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011), the majority of diabetes sufferers will develop Peripheral Diabetic Neuropathy (PDN) and for these patients, the chance of having an amputation as a result as around 15%.

According to Tesfaye & Selvarajah (2012), Peripheral Diabetic Neuropathy Pain (PDNP) is the most widely acknowledged and accepted condition associated directly with diabetes; this painful condition can also prove to be incredibly debilitating. According to Vinik & Casellini (2013), if it's not managed correctly, it can result in patients suffering with longer term depression and anxiety. This sentiment was reiterated by Finnerup et al. (2015) who also noted that the pain has a significant impact on the patient's overall quality of life, not to mention, the financial costs for both the individual personally and for the wider society as a whole.

Veves & Malik (2008) also highlighted the gaps in epidemiological knowledge, when they said that 'not a great deal is understood about the condition in comparison to some of the more widely acknowledged complications such as renal, retinal and cardiovascular disease'. Veves and Malik, also highlighted that peripheral nerves might well be damaged as a result of 'various pathological processes'; however they didn't elaborate on this. Despite the apparent lack of information surrounding the condition, there are some medicines readily available which do work at reducing the painful

symptoms, they don't however, address the underlying causes. This was highlighted by Veves, Backonja & Malik (2008) when they said that despite these therapies being useful for pain reduction; they do not 'prevent the further advancement of the disease itself'. Further to this, Edwards, Vincent, Cheng, & Feldman (2008) argued for a concerted effort to introduce specific therapies for this condition due to its 'physical, psychological and economic implications'.

2.2 EPIDEMIOLOGY AND PREVALENCE

Boulton & Vileikyte (2011) highlighted that the present epidemiology surrounding PDN is poor; this is due in part to how the sample patients are selected and the diagnostic techniques which have been utilised. Other undermining factors include the asymptomatic nature of the condition itself and the wider populous that may or may not be aware that they have the condition.

There is scant factual information on the subject of PDN and what is known is inadequate, even though the condition is highly prevalent in the general populace. What we do know however is that as a person ages, the chances of PDNP manifesting itself increases. Edwards et al. (2008) highlighted that there is also a difference in how different diabetic patients are affected; those with Type 1 Diabetes Mellitus (T1DM) are less likely to be affected than those with Type 2 Diabetes Mellitus (T2DM).

A study undertaken by Azidah, Hasniza & Lili Husniati (2014) in Malaysia showed that over 51% of elderly diabetic patients, showed signs of the disease. This demographic is also more likely to show signs of PDN meaning that they are effectively at greater risk of contracting PDNP associated complications as a result. Early detection of the disease is essential if we are to avoid later secondary complications. This was reinforced by Hanewinckel, Van Oijen, Ikram & Van Doorn (2016) who after several