

**INTERVENTION STRATEGIES USED BY DOCTORS FOR THE MANAGEMENT OF
DIABETIC NEUROPATHIC PATIENTS IN UNIVERSITY OF ABUJA TEACHING
HOSPITAL**

BY

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MARCH, 2017

DECLARATION

I hereby declare that this work is the product of my own research efforts; undertaken under the supervision of Prof. Oyerinde, O. O. and that it has not been presented and will not be presented elsewhere for the award of a degree or certificate. All sources have been duly acknowledged.

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CERTIFICATION

This is to certify that the research work for this dissertation and the subsequent preparation of the dissertation by Abubakar Sadiq, Hajara (SPS/12/MHE/00034) was carried out under my supervision.

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DEDICATION

This work is dedicated to my late brother, Alh Alhassan Bello Gololo, May Jannatul Firdaus be your final abode, ameen.

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ABSTRACT

This study was carried out to investigate the intervention strategies used for managing diabetic neuropathic patients in University of Abuja Teaching Hospital (UATH). To achieve the purpose of the study, two research questions were raised; one major hypothesis and four sub-hypotheses were formulated. Descriptive design of survey type was used for the study. The population of the study comprised 145 subjects who were exclusively diabetic patients with neuropathic pain at the Teaching Hospital, from January 2015 to May 2016. A researcher developed questionnaire which was designed in line with the four points modified Likert scale was used as instrument for data collection. It was validated and subjected to a test-retest reliability method that yielded a reliability index of 0.78. Frequency counts and percentages were used to analyze the demographic variables while Chi-square and ANOVA were used to test the hypotheses of the study at 0.05 level of significance. The data from 122 respondents who duly completed and returned the questionnaire forms were analyzed and reported. The findings of the study showed that doctors in UATH significantly ($p = 0.0001 > 0.05$) adopt the use of drugs, diet, exercise and combined therapy as interventions in the management of DPN. The result also revealed that dieting and exercise were to a lesser extent adopted and recommended by the doctors in UATH. The implication of the study is that diabetic neuropathic patients are not strongly aware that they can control and reduce neuropathy through exercise and dieting to a large extent without reliance on drugs as the only therapy. Based on the findings of the study, it was therefore recommended, that hospitals should be encouraged to engage the services of qualified exercise scientist, physiotherapists and nutritionists/dieticians among others in the management of neuropathic pain among patients.

CHAPTER ONE

INTRODUCTION

1.0 Background of the Study

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, stroke, kidney failure, foot ulcers and damage to the eyes (Njolstad, Sagen, Bjorkhaug, Odili, Shehadeh, Bakry, Sarici, Alpay, Molnes, Molven, Sovik & Matschinsky, 2003).

Diabetes mellitus is a chronic metabolic disorder related to insulin deficiency and can involve many organs. Peripheral diabetic neuropathy (PDN), a significant microvascular complication of diabetes, is characterized by the prickling, tingling, burning, electric shock like, freezing pain with allodynia and hyperalgesia in the legs, feet, and hands affecting 21percent of diabetic patients (Apfel, Asbury, Bril, Burns, Campbell, Chalk, & Dyck, 2001; Abbot, Malik, van Ross, Kulkarni, & Boulton, 2011). It is estimated that half of the diabetic patients develop neuropathy and the prevalence of PDN ranges from 10 to 20 % in diabetic patients and from 40 to 50% in those with diabetic neuropathy (Veves, Backonja & Malik, 2008). PDN, even though common and often severe, is frequently unreported (12.5 %) and more frequently untreated (39.3 %) (Daousi, MacFarlane, Woodward, Nurmikko, Bundred & Benbow, 2004).

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. According to Veves,*et al.*, (2008), there are three main types of diabetes mellitus

- Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.
- Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.

One of the many complications of diabetes mellitus is diabetic peripheral neuropathy. It is estimated that 60% to 70% of individuals with diabetes have mild to severe forms of nervous system damage (Centers for Disease Control & Prevention, 2007). A simple definition of Diabetic peripheral neuropathy (DPN) is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes (Boulton, Vilnik & Arezzo, 2005).

Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage have no symptoms. Others may have symptoms such as pain, tingling, or numbness loss of

feeling in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs (Veves, *et al.*, 2008).

About 60 to 70 percent of people with diabetes have some form of neuropathy. People with diabetes can develop nerve problems at any time, but risk rises with age and longer duration of diabetes. The highest rates of neuropathy are among people who have had diabetes for at least 25 years. Diabetic neuropathies also appear to be more common in people who have problems controlling their blood glucose, also called blood sugar, as well as those with high levels of blood fat and blood pressure and those who are overweight (Veves, *et al.*, 2008).

Patients with DN experience reduced mobility in physical activity, and lack of enjoyment of life, fatigue, limitations in social activities, diabetic foot infections, sleep impairment, anxiety, and depression (Schmader, 2002 & Gore, Brandenburg, Dukes, Hoffman, Tai, & Stacey, 2005).

Intervention is the systematic process of assessment and planning employed to remediate or prevent a social, educational, or developmental problem. It is an attempt through one or more ways to seek professional help in conditions of ill health, traumatic events, addictions or crisis (Intervention Techniques and Models, 2016). During management, interventions and treatments, some patients find some relief from this nerve damage or neuropathy by keeping blood sugars as closely controlled as possible, getting regular exercise and keeping their weight under control. Using non-narcotic pain relievers consistently throughout the day rather than waiting until nighttime when symptoms can become more severe also seems to help if pain is the major symptom. Similarly, clinicians have also found that certain antidepressants may be helpful and can take the edge off the pain of neuropathy when applied as interventions (Boulton, Kempner, Ametov & Ziegler, 2013).

1.1 Statement of the Problem

More than 220 million people worldwide have diabetes in 2004. WHO projects that diabetes deaths will double between 2005 and 2030. Almost half of diabetes deaths occur in people under the age of 70 years. Almost 80% of diabetes deaths occur in low and middle-income countries. The prevalence in Nigeria varies from 0.65-11.0percent, it is well established that good glycemic control intervention in diabetic patients lead to reduced morbidity and mortality. With the incidence of diabetes in the African population on the rise, the incidence of late diabetic complications is also expected to increase correspondingly. This will eventually pose major health care and economic problems (Nwosu, 2000).

Clearly these statistics demonstrate a need for interventions that can reduce the risk of morbidity and mortality associated with diabetic neuropathy and its complications. While, many interventions have been shown to impact the natural progression of the disease, no single intervention has been able to eliminate the risk of nerve complications in these populations (CDC, 2007).

There is no clear evidence-based guidance about treatment selection of analgesic agents for painful diabetic neuropathy. Stepwise approach and algorithms may be used, but comparative effectiveness of treatments to control pain in patients with diabetic neuropathy is unclear and there is little or no evidence of relative superiority across the different drug classes or the individual agents.

Several studies carried out by the Diabetes Complications and Control Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS) in 1993 and 1999 respectively and their follow-up studies in 2008, found that adequate management of diabetes improves the outcome in terms of morbidity, mortality, and quality of life. For this reason, it is necessary to follow recommended

international and national guidelines in managing diabetic neuropathic patients. These include glycemic targets, systolic and diastolic blood pressure targets, control of body mass index (BMI), lipid levels, self-management, and behavioral targets. It has also been documented that diabetes education is critical for ensuring the attainment of targets in patients undertreatment. Countries like the United States of America and South Africa have studied the status of diabetic neuropathic control in their populations. Some Nigerian studies covered only sections of the population.

Nationwide data are desirable for the Nigerian diabetic neuropathic population and are presently scarce. Being one of its kind in Nigeria, this study aims at evaluating the status of diabetic neuropathic care (quality of DM control, management practices, and interventions present for late complications of DM) in University of Abuja Teaching Hospital, where high standard of care is offered to persons suffering from diabetes and its different complications where those who are at risk can be empowered to prevent the disease. Due to the high standard of care offered by the teaching hospital, the Rotary International choose it as a center for their Endocrine and Diabetology center proposed as Rehabilitation And Provision of Diabetes Centre, University of Abuja Teaching Specialist Hospital. The study was guided by the following research questions.

- What are the interventions used by Doctors for managing diabetic neuropathic patients in University of Abuja Teaching Hospital (UATH)?
- Are there differences in the intervention strategies used by Doctors in the management for diabetic neuropathic patients in UATH?

1.2 Hypotheses

Major hypothesis

There are no significant differences in intervention strategies used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Sub-hypothesis

- There is no significant difference in the use of drugs treatment as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.
- There is no significant difference in the use of dietary control as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.
- There is no significant difference in the use of exercise therapy as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.
- There is no significant difference in the use of combined treatment as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

1.3 Purpose of the Study

The main purpose of the study was to evaluate the different intervention strategies that are used by Doctors in the management of diabetic neuropathy of diabetic patients attending University of Abuja Teaching hospital, with the intent of ascertaining intervention(s) that will lead to an eventual improvement of Diabetic Peripheral Neuropathic management among patients and possible reduction in the disease incidence.

1.4 Significance of the Study

The results of this research will help to enlighten the health institutions about the more effective care and ways to manage patients battling with diabetic neuropathy.

To the community, the study outcomes will help the community members to be aware of the factors that help in the management of the complications of diabetes and the importance of managing the condition by applying the available intervention(s).

To the government, the result of the study will serve as advocacy to people in authority to carry out enlightenment campaigns to diabetic patients, especially those in the rural areas to see the benefits and importance of utilization of health facilities in the management and control of diabetic neuropathic pains.

To future researchers, the study outcome will help contribute to knowledge about diabetic neuropathy and the different interventions used in its management.

It is hoped that data obtained will be an invaluable resource for diabetes advocacy, program evaluation, planning resource allocation, and improving diabetes services across Nigeria with an eventual improvement in diabetic neuropathic outcome and a reduction in the disease incidence.

1.5 Delimitation of the Study

This study covered all diabetic patients attending University of Abuja Teaching Hospital, Gwagwalada. Subjects included consisted of adult patients predominantly with DPN. The study is

further confined to drugs treatment, dietary control, exercise therapy and combined therapy as interventions used in management of DPN.

1.8Operational Definition of Terms

- **Diabetic Neurophatic Patients**are those diabetic patients suffering from freezing, numb-like sensations, prickling pain in the toes, legs, feet and handin University of Abuja Teaching Hospital.
- **Neuropathic pain** is a complex, chronic pain state that is usually accompanied by tissue injury among diabetic patients in University of Abuja Teaching Hospital.
- **Intervention Strategies Used**or planned procedures such as drugs, exercise, dieting surgery or a combination of two or more of these strategies used in the control and management of diabetic neuropathy

CHAPTER TWO

REVIEW OF RELATED LITERATURE

2.0 Introduction

Literature related to the topic of this research were reviewed based on the following headings:

- Diabetes
- Health implications of diabetes
- Diabetic neuropathy
- Different diabetic neuropathic interventions and Contemporary studies
- Health implications/complications of Diabetic Neuropathy
- Summary

2.1 Diabetes

Diabetes is a serious complex condition which can affect the entire body. Diabetes requires daily self care and if complications develop, diabetes can have a significant impact on quality of life and can reduce life expectancy. While there is currently no cure for diabetes, one can live an enjoyable life by learning about the condition and effectively managing it (WHO, 2011).

Types of Diabetes

There are different types of diabetes; all types are complex and serious. The three main types of diabetes are type 1, type 2 and gestational diabetes.

2.1.1 Type 1 diabetes

Previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that produce the hormone insulin that regulates blood glucose. To survive, people with type 1 diabetes must have insulin delivered by injection or a pump. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. In adults, type 1 diabetes account for approximately 5% of all diagnosed cases of diabetes. Risk factors for type 1 diabetes may be autoimmune, genetic, or environmental. There is no known way to prevent type 1 diabetes. Several clinical trials for preventing type 1 diabetes are currently in progress or are being planned (Raju & Raju, 2010).

Epidemiology and Etiology of type 1 diabetes

Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide (American Diabetes Association, 2001). Although type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood (Blood, Hayes & Gamble, 1975). The incidence of type 1 diabetes is rising. Across Europe, the average annual increase in the incidence in children under 15 years is 3.4percent (EURODIAB ACE study Group, 2000), with the steepest rise in those under 5 years old (Karvonen, Pitkaniemi, & Toumilehto, 1999). Type 1 diabetes is the result of an autoimmune reaction to proteins of the islets cells of the pancreas (Holt, 2004). There is a strong association between IDDM and other endocrine autoimmunity (for example, Addison disease) and an increased incidence of autoimmune diseases are seen in family members of IDDM patients. The three types of autoantibodies as presented by Raju and Raju (2010) are:

i) Islet cell cytoplasmic antibodies (ICCA): The primary antibodies found in 90percent of type 1 diabetics are against islet cell cytoplasmic proteins. The presence of ICCA is a highly accurate predictor of future development of IDDM.

ii) Islet cell surface antibodies (ICSA): Autoantibodies directed against islets cell surface antigens (ICSA) have also been described in as many as 80percent of type 1 diabetics. Some patients with type 2 diabetes have been identified, which are ICSA positive.

iii). Specific antigenic targets of islet cells: Antibodies to glutamic acid decarboxylase (GAD) have been identified in over 80percent of patients newly diagnosed with IDDM. Anti GAD antibodies decline over time in type 1 diabetics. The presence of anti GAD antibodies is a strong predictor of the future development of IDDM in high risk populations. Anti insulin antibodies (IAAs) have been identified in IDDM patients and in relatives at risk to developing IDDM. These IAAs are detectable even before the onset of insulin therapy in type 1 diabetics. IAA is detectable in around 40percent of young children with IDDM.

Pathophysiology of type 1 diabetes

The autoimmune destruction of pancreatic β -cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, the function of pancreatic α -cells is also abnormal and there is excessive secretion of glucagons in IDDM patients. Normally, hyperglycemia leads to reduced glucagons secretion, however, in patients with IDDM, glucagons secretion is not suppressed by hyperglycemia (Raju & Raju, 2010). The resultant inappropriately elevated glucagons levels exacerbate the metabolic defects due to insulin deficiency. The most pronounced example of this metabolic disruption is that patients with IDDM rapidly develop diabetic ketoacidosis in the absence of insulin administration. Although insulin deficiency is the primary defect in IDDM, there is also a defect in the administration of insulin. There are multiple biochemical mechanisms that account for impairment of tissue's response to insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle (Raju & Raju, 2010). This

impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue. Raju and Raju (2010) explained that the major metabolic derangements, which result from insulin deficiency in IDDM are impaired glucose, lipid and protein metabolism.

2.1.2 Type 2 diabetes

Previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce it. Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or other Pacific Islanders are at particularly high risk for type 2 diabetes and its complications. Type 2 diabetes in children and adolescents, although still rare, is being diagnosed more frequently among American Indians, African Americans, Hispanic/Latino Americans, and Asians/Pacific Islanders (Raju & Raju, 2010).

Epidemiology and Etiology of type 2 diabetes

Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus (Gonzalez, Johansson, Wallander & Rodriguez, 2009). The rise in prevalence is predicted to be much greater in developing than in developed countries (69 versus 20%) (Shaw, Sicree & Zimmet, 2010). In developing countries, people aged 40 to 60 years (that is, working age) are affected most, compared with those older than 60 years in developed countries (Shaw *et al.*, 2010). This increase in type 2 diabetes is inextricably linked to changes towards a Western

lifestyle (high diet with reduced physical activity) in developing countries and the rise in prevalence of overweight and obesity (Chan, Malik, Jia, Kadowaki, Yajnik, Yoon & Hu, 2009; Colagiuri, 2010). There are approximately 1.4 million people with diagnosed type 2 diabetes in the UK (Bennett, Dodd, Flately, Freeth & Boiling, 1995). The incidence of diabetes increases with age, with most cases being diagnosed after the age of 40 years. This equates to a lifetime risk of developing diabetes of 1 in 10 (Neil, Gatlin, Mather, Thompson, Thorogood, Fowler, Hiel & Mnn, 1987). Type 2 diabetes is a heterogenous disorder caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging (Kaku, 2010). It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents (Holt, 2004).

Type 2 diabetes is the common form of idiopathic diabetes and is characterized by a lack of the need for insulin to prevent ketoacidosis. It is not an autoimmune disorder and the susceptible genes that predispose to NIDDM have not been identified in most patients. This could be due to the heterogeneity of the genes responsible for the susceptibility to NIDDM.

Pathophysiology of type 2 diabetes

Individuals with NIDDM have detectable levels of circulating insulin, unlike patients with IDDM (Raju & Raju, 2010). On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups:

- i) Those with normal glucose tolerance.
- ii) Chemical diabetes (called impaired glucose tolerance).
- iii) Diabetes with minimal fasting hyperglycemia (fasting plasma glucose less than 140 mg/dl).
- iv) Diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl).

The individuals with impaired glucose tolerance have hyperglycemia inspite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average NIDDM patients (Holt, 2004). Insulin resistance is the primary cause of NIDDM, however some researchers contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM (Raju & Raju, 2010). Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes (Raju & Raju, 2010). Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferators-

activated receptor g (PPARg). PPARg is also a transcription factor and when activated, binds to another transcription factor known as the retinoid x receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPARg is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPARg is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells (Raju & Raju, 2010).

Gestational diabetes

Gestational diabetes develops in some women when they are pregnant. Most of the time, this type of diabetes goes away after the baby is born. However, if you've had gestational diabetes, you have a greater chance of developing type 2 diabetes later in life. Sometimes diabetes diagnosed during pregnancy is actually type 2 diabetes (CDC, 2015).

2.2 Health Implications of Diabetes

Elevated blood sugar is a common effect of uncontrolled diabetes and over time, can damage the heart, blood vessels, eyes, kidneys, and nerves. Some health complications from diabetes include:

- Diabetic retinopathy is a significant cause of blindness, and occurs as a result of longterm accumulated damage to the small blood vessels in the retina. After 15 years of diabetes about 10percent of patients develop severe visual impairment.
- Diabetic neuropathy is damage to the nerves as a result of diabetes, and affects up to 50percent of people with diabetes. Common symptoms are tingling, pain, numbness, or weakness in the feet and hands.

- Combined with reduced blood flow, neuropathy in the feet increases the chance of foot ulcers and eventual limb amputation.
- Diabetes is among the leading causes of kidney failure; 10-20percent of people with diabetes die of kidney failure.
- Diabetes increases the risk of heart disease and stroke; 50percent of people with diabetes die of cardiovascular disease (primarily heart disease and stroke) (WHO, 2008).

2.3 Diabetic Neuropathy

Neuropathic pain is caused by damage to nerves in the central or peripheral nervous system. Damage can be due a number of mechanisms including trauma or surgery, diabetes mellitus, chemotherapy, radiotherapy, ischaemia, infection or malignancy. Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage have no symptoms, while others according to Daousi,*et al.*, (2004), show symptoms that may include:

- numbness, tingling, or pain in the toes, feet, legs, hands, arms, and fingers
- wasting of the muscles of the feet or hands
- indigestion, nausea, or vomiting
- diarrhea or constipation
- dizziness or faintness due to a drop in blood pressure after standing or sitting up
- problems with urination
- erectile dysfunction in men or vaginal dryness in women
- weakness

Daousi,*et al.*, (2004), further explained that there are symptoms that are not due to neuropathy, but which often accompany it, including weight loss and depression and that about 60 to 70 percent of people with diabetes have some form of neuropathy. People with diabetes can develop nerve problems at any time, but risk rises with age and longer duration of diabetes. The highest rates of neuropathy are among people who have had diabetes for at least 25 years. Diabetic neuropathies also appear to be more common in people who have problems controlling their blood glucose, also called blood sugar, as well as those with high levels of blood fat and blood pressure and those who are overweight.

Diabetic neuropathy can be classified as peripheral, autonomic, proximal, or focal. Each affects different parts of the body in various ways.

- Peripheral neuropathy, the most common type of diabetic neuropathy, causes pain or loss of feeling in the toes, feet, legs, hands, and arms.
- Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerves that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. Autonomic neuropathy can also cause hypoglycemia unawareness, a condition in which people no longer experience the warning symptoms of low blood glucose levels.
- Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs.

- Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. Any nerve in the body can be affected (Daousi,*et al.*, 2004).

2.3.1 Causes of Diabetic Neuropathy

The causes are probably different for different types of diabetic neuropathy. Generally, nerve damage is likely due to a combination of factors:

- metabolic factors, such as high blood glucose, long duration of diabetes, abnormal blood fat levels, and possibly low levels of insulin
- neurovascular factors, causing to damage to the blood vessels that carry oxygen and nutrients to nerves
- autoimmune factors that cause inflammation in nerves
- mechanical injury to nerves, such as carpal tunnel syndrome
- inherited traits that increase susceptibility to nerve disease
- lifestyle factors, such as smoking or alcohol use (Daousi,*et al.*, 2004).

2.3.2 Pathophysiology of Diabetic Neuropathy

The development of neuropathy in affected patients has been shown in animal and invitro models to be a result of hyperglycemia induced metabolic abnormalities. One of the more commonly described mechanisms of action is the polyol pathway. In the development of neuropathy, the hyperglycemic state leads to an increase in action of the enzymes aldose reductase and sorbitol dehydrogenase. This results in the conversion of intracellular glucose to sorbitol and fructose. The accumulation of these sugar

products results in a decrease in the synthesis of nerve cell myoinositol, required for normal neuron conduction. Additionally, the chemical conversion of glucose results in a depletion of nicotinamide adenine dinucleotide phosphate stores, which are necessary for the detoxification of reactive oxygen species and for the synthesis of the vasodilator nitric oxide. There is a resultant increase in oxidative stress on the nerve cell and an increase in vasoconstriction leading to ischemia, which will promote nerve cell injury and death. Shy et al., (2003) also described hyperglycemia and oxidative stress to contribute to the abnormal glycation of nerve cell proteins and the inappropriate activation of protein kinase C, resulting in further nerve dysfunction and ischemia. Neuropathy in diabetic patients is manifested in the motor, autonomic, and sensory components of the nervous system.

Neuropathy causes loss of protective sensation and loss of coordination of muscle groups in the foot and leg that lead to increased mechanical stresses during ambulation.

- Increase of plantar pressure plays a crucial role in the development of plantar ulcers in neuropathic diabetic patients. Elevated foot pressure is an important risk factor for foot complication. Many studies confirmed a high plantar pressure as a principal factor in the development and non-healing of plantar ulcers in diabetic patients (Daousi, et al., 2004).

2.3.3 Assessment and diagnosis

The diagnosis of PDN is primarily clinical, based on a history of neuropathic pain and confirmatory examination findings, establishing deficits associated with neuropathy.

Although one might argue that confirming neuropathy using tests which assess large fibre deficits (loss of sensation, monofilament exam, reflexes) are not relevant to painful symptoms which are driven principally by small fibre damage. Patients report intermittent or continuous symptoms of pain described as burning, stabbing, tingling, numb, hot, cold or itching in a distal-to-proximal ‘glove-and-stocking’ distribution, usually beginning in the feet. The pain is typically symmetrical and worsens at night. Abnormal sensory perception, such as reduced or heightened perception of hot, cold, touch or pin-prick sensation, or allodynia, may be present on examination (Callaghan, Cheng, Stables, Smith & Feldman, 2012).

Neuropathic pain scales have been devised to aid diagnosis and these may also provide insight into the severity of the patient’s symptoms (Papanas & Ziegler, 2011). The Michigan Neuropathy Screening Instrument (MNSI) and Neuropathy Disability Score (NDS) are designed to assess neuropathic impairment and can act as screening tools for DSPN (Feldman, Stevens, Thomas, Brown, Canal & Greene, 1994; Weintrob, Amitay, Lilos, Shalitin, Lazar & Josefsberg, 2007). The severity of pain in PDN can be assessed through pain scores such as the Brief Pain Inventory and the Neuropathic Pain Questionnaire (NPQ) (Cleeland & Ryan, 1994; Krause & Backonja, 2003). The NPQ can also be used to follow up patients along with the Neuropathic Pain Symptom Inventory, a 10-item questionnaire to quantify and evaluate symptoms of neuropathic pain (Kelly, Cook & Backonja, 2005). In addition, the quality of life can be assessed through neuropathy-specific quality of life scores such as the Neuro-QoL (Cella, Lai, Nowinski, Victorson, Peterman & Miller, 2012).

Due to the subjective nature of the symptoms reported by patients, these scales may not produce consistent results and may lack the sensitivity to track any objective changes in neuropathy status, partly because these scales assess pain status and are thus subjective, measuring largely positive symptoms (Dyck, Norell, Trischler, Schuette, Samigullin & Zeigler2007). In comparison, measures of the severity of neuropathy typically focus on negative signs and symptoms. Quantitative sensory testing (QST) has been used in clinical trials to measure progression of neuropathy. However, PDN is principally caused by small-nerve fibres, which are not assessed using the standard QST of vibration perception (Shy, Frohman. So, Arezzo, Cornblath & Guiliani 2003; Tavakoli, Mojaddidi, Fadaui & Malik, 2008). Recent guidance has clearly stipulated that QSTs should not be used as standalone tests for the diagnosis of neuropathic pain (Backonja, Attal, Baron, Bouhassira, Drangholt& Dyck 2013). Bakkers, Faber, Hoeijmakers, Lauria & Merkies (2014), further stated that, although skin biopsies which measure intraepidermal nerve fibre density have been used to diagnose and assess neuropathy, corneal confocal microscopy has been proposed as a reliable, noninvasive marker of neuropathy that may be used to objectively assess the condition.

2.4 Diabetic Neuropathic Interventions

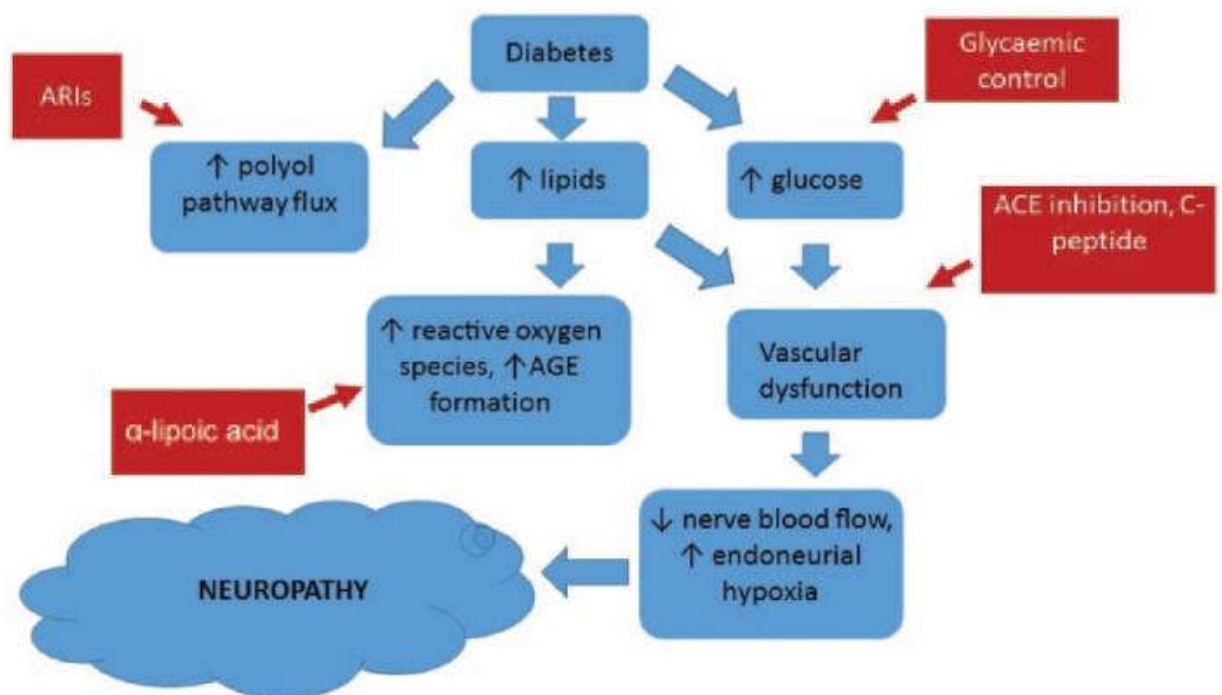
PDN represents an ongoing therapeutic challenge for patients and caregivers and it is thought that as many as 39percent of cases of PDN may be untreated (Daousi *et al.* 2004). Guidelines have been developed by professional organizations to provide a rational approach to the treatment of PDN (Spallone, 2012).

Upon the finding of peripheral neuropathy in a patient, other potential causes of neuropathy must be excluded. Once the diagnosis of PDN is established, there are two therapeutic approaches:

- Pathogenetic treatments targeting the underlying pathophysiological processes to prevent nerve fibre loss, and
- Symptomatic treatments aimed at alleviating the painful symptoms of PDN to normalize physical and psychological functioning (Saad, Ioannis , Uazman, & Rayaz, 2015).

Pathogenetic treatments

A number of pathogenetic treatments have been evaluated in PDN. A relationship between chronic hyperglycaemia and diabetic neuropathy has been established in several observational studies (Tesfaye, Stevens, Stephenson, Fuller, Plater & Ionescu-Tirgo viste,1996; Herman, Aubert, Engelgau, Thompson, Ali & Sous,1998; Oyibo, Prasad, Jackson, Jude&Boulton,2002). It is thought that prevention of diabetic neuropathy would also help arrest the development of PDN, although there are contradictory data on the association between hyperglycaemia and PDN (Sorensen, Molyneaux & Yue,2002; Chong & Hester, 2007).



KEY

ACE - Angiotensin-Converting Enzyme;

AGE - Advanced Glycation End Product;

ARI - Aldose-Reductase Inhibitor.

Figure 1. Integrating pathophysiology of diabetic neuropathy and the sites of action of pathogenetic drugs (Adopted from Tesfaye, *et al.*, 1996).

Glucose control

Data from the Diabetes Control and Complications Trial (DCCT) emphasized a role for intensive glucose control through insulin in both the primary and secondary prevention of PDN in patients with type 1 diabetes. The prevalence of DSPN remained lower in the

intensive insulin therapy group of the DCCT many years after the initial intervention in what has been termed a memory effect (The Diabetes Control and Complications Trial Research Group, 1993). Similarly, the Epidemiology of Diabetes Interventions and Complications study demonstrated a reduced incidence of neuropathy in patients with type 1 diabetes receiving intensive insulin therapy (Albers, Herman, Pop-Busui, Feldman, Martin & Cleary, 2010).

In patients with type 2 diabetes, the role of intensified glycaemic control in preventing and managing DSPN is less clear with studies offering contradictory conclusions. A recent meta-analysis of randomized control trials found no significant benefit of intensive glycaemic control in reducing the incidence of DSPN in patients with type 2 diabetes (Boussageon, Bejan, Angoulant, Saadatian-Elahi, Lafont, Bergeonneau & Kassai, 2011). This conclusion was supported by a Cochrane review which demonstrated no significant improvement in markers of neuropathy in patients with type 2 diabetes managed through intensive glycaemic control (Callaghan, Little, Feldman & Huges, 2012b). However, most studies conducted in patients with type 2 diabetes were not specifically designed to investigate the effect of intensive glycaemic control on DSPN and thus only incorporated a rudimentary assessment of neuropathy.

Pancreas transplant

The only known therapy to restore insulin secretion in response to feedback mechanisms in patients with diabetes is pancreas transplant. It has been suggested that the reversal of neuropathy takes around 10 years after transplantation (Fioretto, Steffes, Sutherland, Goetz & Maver, 1998). Neurophysiological examination at 3 months and 1 year in a

series with 26 patients noted improvements in action potential amplitude and conduction velocity following transplantation (Agudo, Valls-Sole, Recasens, Fabregat, Ricart & Esmatjes 2002). However, another study that followed up 61 patients with type 1 diabetes after pancreas transplantation found an improvement in motor and sensory function but nerve conduction velocity and autonomic function was unaffected at 10-year follow up (Kennedy, Navarro, Goetz, Sutherland & Najarian, 1990; Navarro, Sutherland & Kennedy, 1997). These findings were confirmed by a subsequent study. A study of 18 patients found no improvement in intraepidermal nerve fibre density (IENFD) on skin biopsy in 15 patients, with only 3 patients showing an increase in IENFD after kidney and pancreas transplantation. It has been suggested that in some patients DSPN may reach a nonreversible stage (Boucek, Havrdova, Voska, Lodererova, He & Saudek, 2008). However, any improvement in neuropathy depends entirely on the endpoint chosen to assess efficacy. Thus in another study reported by Mehra, Tavakoli, Kallinikos, Efron, Boulton & Augustine in 2007, whilst there was no change in electrophysiology, QST and IENFD, there was a significant corneal nerve regeneration in 15 patients, 6 months after transplantation.

The role of pancreas transplantation in the management of DSPN is limited by the availability of suitable organs, the complications of surgery and the consequences of long-term immunosuppression. Islet-cell transplantation is being considered as a less invasive option in patients with type 1 diabetes and marked improvements in neurophysiology have been reported in these patients, although skin biopsy results showed no improvement (Del Carro, Fiorina, Amadio, De Toni Franceschini, Petrelli & Menini, 2007).

α -Lipoic acid

An increased free-radical production along with defective antioxidant mechanisms can generate oxidative stress that has been linked to the development of DSPN (Vincent, Callaghan, Smith & Feldman, 2011). α -Lipoic acid (ALA) is an antioxidant that has been licensed to treat symptomatic DSPN in Germany (Chong & Hester, 2007). ALA has been found to be well tolerated, however it must be delivered intravenously for symptom relief. Indeed a meta-analysis of four placebo-controlled trials by Ziegler, Nowak, Kempler, Vargha & Low (2004) found a clinically meaningful improvement in the symptoms of DSPN after administration of 600 mg/day of ALA over 3 weeks. However, it should be noted that a placebo-controlled, randomized, double-blind trial reported no improvement in neuropathy after 4 years of treatment with ALA as assessed using neurophysiology, quantitative sensory testing and a composite neuropathy score. The results of this trial should be interpreted with caution as no worsening in neuropathy was reported in the placebo arm of the study, which may have important implications for study design (Dyck, et al. 2007).

Aldose reductase inhibitors

Aldose reductase is an important enzyme in the polyol pathway involved in the metabolism of blood glucose (Oates, 2002). Thus, aldose reductase inhibitors (ARIs) have been proposed to prevent DSPN. A number of ARIs have been tested but most have been found to have significant adverse effects and limited efficacy (Boulton, Kempler, Ametov & Ziegler, 2013). The ARI epalrestat has been found to improve patient-reported neuropathic symptoms with an acceptable safety profile, and a 3-year randomized trial

suggested a preventative role for DSPN with epalrestat (Goto, Hotta, Shigeta, Sakamoto & Kikkawa, 1995; Hotta, Akanuma, Kawamori, Oka, & Shichiri, 2006).

Benfotiamine

Benfotiamine, a fat-soluble analogue of thiamine/vitamin B1, has been shown in animal models to inhibit three different pathways involved in vascular damage in diabetes (Hammes, Du, Edelstein, Taguchi, Matsumura & Ju, 2003). In a phase III placebo-controlled trial involving 165 patients treated with benfotiamine for 6 weeks, improvement was seen in the primary outcome measure (Neuropathy Symptom Score) in the per-protocol arm compared with placebo, although no improvement was found in the intent-to-treat arm of the study. In contrast, another placebo-controlled study in a population with diabetes found no significant differences between the treatment and placebo arms in peripheral nerve function and soluble inflammatory markers. It should be noted, however, that DSPN was not evident in all of the patients at initial assessment (Stracke, Gause, Achenbach, Fedevlin & Bretzel, 2008).

Other Treatments

C-peptide, a 31-amino acid component of proinsulin, has been suggested to reverse the structural and functional changes due to diabetes in rats and humans. It does so by stimulating Na^+/K^+ ATPase and through activation of various transcription factors (Cotter, Ekberg, Wahren & Cameron, 2003; Kamiya, Zhang & Sima, 2004). C-peptide therapy in 139 human subjects in a double-blind, randomized, placebo-controlled trial

was found to improve sensory function in patients with type 1 diabetes and mild neuropathy (Cotter, et al., 2003).

In a placebo-controlled study, the angiotensin-converting enzyme (ACE) inhibitor trandolapril has been reported to improve the neurophysiological indices of neuropathy at 12 months, even in patients who are normotensive with mild diabetic neuropathy (Malik, Williamson, Abbott, Carrington, Iqbal & Schady, 1998). Furthermore, in a larger randomized trial (DEMAND study) the calcium channel blocker manidipine and ACE inhibitor delapril in combination, or Delapril on its own significantly reduced the progression of neuropathy compared with placebo. Hyperlipidaemia has been implicated in the pathogenesis of diabetic neuropathy and it has been suggested that adequate control of blood lipid levels through lipid-lowering agents may prevent or ameliorate the effects of DSPN (Fried, Forrest, Ellis, Chang, Silvers & Orchard, 2001). Additionally, HMG-coenzyme A reductase inhibitors (statins) have been suggested to have additional neuroprotective effects (Leiter, 2005). Elevated triglycerides have been shown to correlate with the loss of myelinated fibre density, independent of diabetes duration and glycaemic control (Wiggin, Sullivan, Pop-Busui, Amato, Sima & Feldman, 2009) and are also an independent risk factor for amputation in patients with diabetes (Callaghan, Feldman, Liu, Kerber, Pop-Busui & Moffet, 2011). An improvement in diet and exercise with an improvement in triglycerides has been shown to result in an increase in IENFD in subjects with IGT (Smith, Russell, Feldman, Goldstein, Peltier & Smith, 2006) and fenofibrate has been shown to significantly reduce amputations in the FIELD study (Malik, Tesfaye & Ziegler, 2013; Rajamani, Colman, Li, Best, Voysey & D'Emden, 2009).

Symptomatic treatment

The symptomatic management of neuropathic pain in diabetes remains a major management challenge for clinicians and a number of clinical guidelines have evolved to guide clinicians as to the most effective treatments for these patients. Safety and efficacy is usually compared for pain relief medication in PDN through numbers needed to treat (NNTs) or numbers needed to harm to achieve 30 or 50percent pain relief. The choice of first-line and second-line agents differs between guidelines due to intrinsic methodological differences in the criteria employed to define efficacy. However, most guidelines suggest usually using tricyclic agents (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) or γ -aminobutyric acid (GABA) analogues (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments (Spallone, 2012).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for short-term analgesia, primarily when the diagnosis is deemed not to be PDN. However, they have been found to be effective compared with placebo in an 18-patient placebo-controlled study, but their use has not been extensively evaluated, due to their potential to cause gastrointestinal haemorrhage or to exacerbate pre-existing renal dysfunction in diabetes (Cohen & Harris, 1987). TCAs, SNRIs and GABA analogues are commonly used for the treatment of PDN.

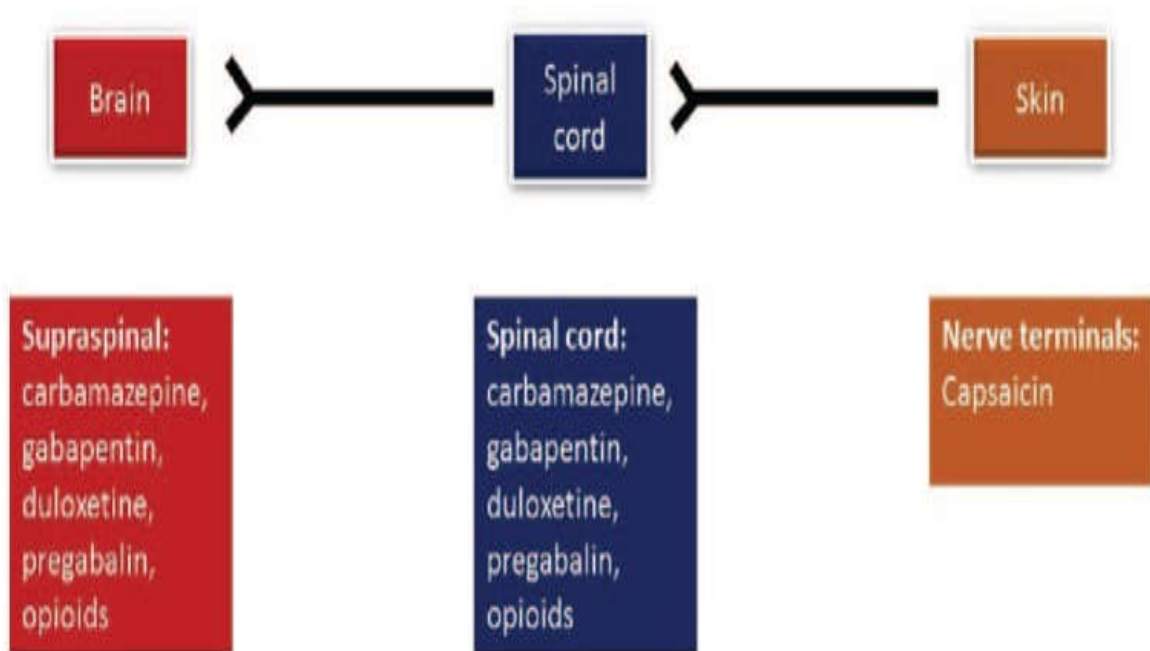


Fig. 2. Adopted from (Spallone, 2012)

The sites of action of current treatments for painful neuropathy.

Tricyclic agents

The TCAs have multimodal actions. These include blocking of serotonin and noradrenaline reuptake from synaptic clefts and varying degrees of anticholinergic receptor inhibition. Some agents, such as amitriptyline, have also been found to have a role in sodium channel blockade (Chong & Hester, 2007). Data on the efficacy of TCAs in the treatment of neuropathic pain are limited and studies usually do not accurately phenotype patients or apply accepted measures of pain relief.

Amitriptyline, desipramine and imipramine have been studied in PDN and have shown efficacy. In a crossover study of 29 patients, amitriptyline prescribed at an average dose of 90 mg daily was found to be superior to placebo in managing diabetic neuropathic

pain, even in patients without depression (Max, Lynch, Muir, Shoaf, Smoller & Dubner, 1992). A crossover study of desipramine in 20 subjects favoured active treatment over placebo (Max, Kishore-Kumar, Schafer, Meister, Gracely & Smoller, 1991). Additionally, three randomized controlled trials of imipramine have all favoured treatment over placebo for the management of PDN (Kvinesdal, Molin, Froland & Gram, 1984; Sindrup, Ejlersen, Froland, Sindrup, Brosen & Gram, 1989; Sindrup, Gram, Skjold, Froland & Beck-Nielsen, 1990). However, TCAs are associated with a high side-effect burden which may limit their use in patients with diabetes. In a meta-analysis of the efficacy and safety of six antidepressants and GABA analogues for the management of PDN, amitriptyline was found to be the least safe agent for this indication (Rudroju, Bansal, Talakokkula, Gudala, Hota & Bhansali, 2013). In clinical practice, the high doses used in the clinical trials are rarely used due to side effects and therefore lower doses are prescribed.

Serotonin–norepinephrine reuptake inhibitors

The SNRI duloxetine was the first drug to be approved for DPN by the US Food and Drug Administration in 2004 based on data from large randomized controlled trials (Tavakoli, et al., 2008). In the first placebo-controlled double-blind trial, patients treated with duloxetine at 60 mg and 120 mg reported significant improvement in average pain scores continuing throughout the study (Goldstein, Lu, Detke, Lee & Iyengar, 2005). These findings are supported by a recent Cochrane Collaboration review that analysed data from eight studies, including 2728 participants, and concluded that 60 mg and 120 mg daily doses of duloxetine were efficacious in the management of PDN, but lower

doses were not associated with improvement. Minor side effects were commonly present and occurred more frequently with higher doses but major side effects were rare (Lunn, Huges & Wiffen, 2014). Somnolence and constipation were reported in 20 and 14 percent of patients receiving 60 mg daily duloxetine (Goldstein, et al., 2005). In the UK, duloxetine has been found to be a cost-effective agent for PDN (Beard, McCrink, Le, Garcia-Cebrian, Monz & Malik, 2008) and was indeed endorsed by NICE (Clinical Guideline 173) in November 2013.

Venlafaxine is another SNRI that has been studied in patients with PDN. In one large placebo-controlled study, venlafaxine produced a greater symptomatic improvement in PDN compared with placebo. However, clinically important electrocardiogram changes were found in seven patients in the treatment arm. Venlafaxine only showed benefit in this study at doses exceeding 150 mg per day. Below this dose, venlafaxine only affects serotonergic transmission and does not act as an SNRI (Rowbotham, Goli, Kunz & Lei, 2004).

Carboxamides, GABA analogues and other historical anticonvulsants

Carbamazepine was among the first of the carboxamides to be studied for managing PDN and works by primarily blocking voltage-sensitive sodium channels to lower peripheral nerve excitability. Two small placebo-controlled studies have suggested that carbamazepine may be useful in controlling neuropathic pain (Rull, Quibrera, Gonzalez-Millan & Lozano Castaneda, 1969; Wilton, 1974). However, its adverse effects include bone marrow suppression and osteoporosis and thus it has been superseded by other agents (Chong & Hester, 2007).

Oxcarbazepine, a keto-analogue of carbamazepine, has also been studied in PDN. One multicentre trial reported a statistically significant reduction in its primary endpoint of pain score assessed through a visual analogue scale (VAS) (Dogra, Beydoun, Mazzola, Hopwood & Wan, 2005). However, two subsequent trials did not corroborate these findings and found no difference in VAS score from baseline measurements during these trials (Beydoun, Shaibani, Hopwood & Wan, 2006; Grosskopf, Mazzola, Wan & Hopwood, 2006).

Gabapentin mimics the actions of the neurotransmitter GABA, though its actions in relieving pain are thought to be due to inhibition of the $\alpha_2\delta$ unit of the calcium channel. It is now widely recommended in guidelines for the treatment of PDN (Spallone, 2012). In one placebo-controlled trial involving 165 patients, the NNT to achieve 50 percent pain relief was calculated to be 3.7 (Backonja, Beydoun, Edwards, Schwartz, Fonseca & Hes, 1998). A systematic review of 35 studies concluded that gabapentin was effective in managing neuropathic pain and a recent analysis of the efficacy of six agents for managing PDN found gabapentin to offer the most favourable balance between safety and efficacy (Mellegers, Furlan & Mailis, 2001; Rudroju, et al., 2013).

Pregabalin is a higher potency gabapentinoid with a similar mechanism of action to gabapentin. Four double-blind placebo-controlled trials have reported an improvement in pain scores following pregabalin therapy. A dose-dependent response in reduction of sleep interference and speed of onset of relief has been reported and a dose of 600 mg daily was associated with the greatest effect. However a number of side effects including mood disturbance, ankle oedema and sedation have been reported (Lesser, Sharma,

Lamoreaux & Poole, 2004; Rosenstock, Tuchman, Lamoreaux & Sharma, 2004; Richter, Portenoy, Sharma, Lamoreaux, Bockbrader & Knapp, 2005; Arezzo, Rosenstock, Lamoreaux & Pauer, 2008). Abrupt discontinuation of pregabalin can be associated with cerebral oedema and encephalopathy. It remains one of the few drugs licensed in both the USA and the UK for the treatment of PDN (Tavakoli, et al. 2008). A recent Spanish cost-comparative analysis of adding pregabalin or gabapentin therapy to patients with PDN who were community treated found that pregabalin therapy generated lower total healthcare costs compared with gabapentin (Sicras, Rejas, Navarro & Planas, 2013).

Another antiepileptic agent, lamotrigine, has been studied in patients with PDN. However, inconsistent results in pain relief have been reported, and a recent Cochrane review, which considered four trials of lamotrigine in PDN, did not find any convincing evidence for the use of lamotrigine in PDN (Eisenberg, Lurie, Braker, Daoud & Ishay, 2001; Wiffen, Derry & Moore, 2013).

Topiramate was shown in a large placebo-controlled trial to be efficacious in the symptomatic management of neuropathic pain in diabetes (Raskin, Donofrio, Rosenthal, Hewitt, Jordan & Xiang, 2004). This beneficial effect was maintained in the open-label extension of the study (Donofrio, Raskin, Rosenthal, Hewitt, Jordan & Xiang, 2005). However, three smaller studies found no significant change in pain relief in PDN with topiramate (Thienel, Neto, Schwabe, Vijapurkar and Topiramate Diabetic Neuropathic Pain Study Group, 2004).

N-methyl-D-aspartate receptor antagonist

N-methyl-D-aspartate receptor antagonists are generally used for the management of postoperative pain. Dextromethorphan has been found to be effective in alleviating the painful symptoms of diabetic neuropathy when used on its own or in combination with memantine (Sang, Booher, Gilron, Parada & Max, 2002). More recently, dextromethorphan coadministered with quinidine was found to be effective on all six pain rating scales used in a multicentre, double-blind, placebo-controlled trial that randomized 379 patients with DPN (Shaibani, Pope, Thisted & Hepner, 2012). These findings confirmed the results of a smaller open-label study (Thisted, Klaff, Schwartz, Wymer, Culligan & Gerard, 2006).

Recently, a randomized double-blind placebo-controlled trial investigated the role of a topical 5percent ketamine cream for the management of DPN and showed that it was no more effective than placebo for pain relief in these patients (Mahoney, Vardaxis, Moore, Hall, Haffner & Peterson, 2012).

Opioid analgesia

Although primarily a μ -opioid receptor agonist, tramadol has also been suggested to effect descending inhibitory pathways, modulating nociception (Chong & Hester, 2007). One multicentre, double-blind, placebo-controlled study reported that at an average dose of 200 mg per day, tramadol resulted in significant pain relief on a Likert scale and also improved social and physical functioning (Harati, Gooch, Swenson, Edelman, Greene & Raskin, 1998). However, adverse effects were reported at higher doses, including nausea

(23%), constipation (21%) and headache (17%) (Bril, England, Franklin, Backonja, Cohen and Del Toro, 2011). In 2012, tapentadol extended release (ER) was only the third drug to receive FDA approval for the treatment of neuropathic pain. Tapentadol ER was administered to 588 patients for a 3-week open-label phase, and subsequently, 395 patients with at least a one-point reduction in pain intensity were randomized 1:1 to receive placebo or the optimal fixed dose of tapentadol ER for a 12-week double-blind phase to show a highly significant reduction in pain intensity for those on active treatment (Schwartz, Etropolski, Shapiro, Okamoto, Lange and Haeussler, 2011). The mechanism of action is thought to be via opioid spinal-supraspinal synergy, as well as intrinsic spinally mediated μ -opioid receptor agonist-norepinephrine reuptake inhibitor effect (Christoph, Schroder, Tallarida, De Vry & Tzschentke, 2013). The other opioid that has been studied in PDN is oxycodone, which has higher bioavailability and potency compared with morphine and a reduced side-effect profile. One study involving 159 patients reported a reduction in pain intensity on VAS using 20 mg controlled release oxycodone (Gimbel, Richards & Portenoy, 2003). A placebo-controlled crossover study of 36 patients reported a reduction in daily pain scores in patients randomized to the oxycodone arm of the study (Watson, Moulin, Watt-Watson, Gordon & Eisenhoffer, 2003).

However, the use of opioids for the management of PDN remains controversial as most trials conducted have been small in both sample size and duration, and have not established risk–benefit ratios. Long-term adverse effects of opioid dependency and abuse, constipation, itching, and changes in immunological functioning and suppression of the pituitary axis may limit the use of opioid analgesics and increase costs associated

with monitoring use (Brennan, 2013). Additionally, the risk of aberrant opioid use should be evaluated prior to prescribing opioid through the use of a validated screening method, such as the Opioid Risk Tool or the Diagnosis, Intractability, Risk, Efficacy score (Moore, Jones, Browder, Daffron & Passik, 2009b).

Other treatments

Capsaicin is an alkaloid derived from red chilli peppers and topical application has been found to be effective in PDN (Zhang & Li Wan Po, 1994). The Capsaicin Study Group found significant improvements in pain relief and a decrease in pain intensity in a double-blind placebo-controlled trial of 277 patients (The Capsaicin Study Group, 1991). However, the demonstration of epidermal denervation in patients treated with capsaicin with impaired subsequent nerve regeneration in subjects with diabetes (Polydefkis, Hauer, Sheth, Sirdofsky, Griffin & McArthur, 2004) cautions the use of this therapy, especially in patients with established neuropathy.

A randomized, placebo-controlled trial demonstrated a nonsignificant trend towards reduction in foot pain in patients treated with a 0.1% topical clonidine gel compared with placebo (Campbell, Kipnes, Stouch, Brady, Kelly & Schmidt, 2012). However, this study reported a significant reduction in pain scores in patients with functional and possibly sensitized nociceptors (assessed through pain to topical capsaicin application) in the affected skin receiving topical clonidine therapy.

An isosorbide dinitrate spray has been found to reduce pain in diabetic neuropathy by 18% as evaluated through VAS in a short-term placebo-controlled trial. Some guidelines

suggest that its use should be considered in patients with PDN (Biril,et al., 2011; Spallone, 2012). Similarly, a small open-label, 3-week study of 56 patients with DPN showed that up to four 5percent lidocaine patches used for up to 18 h/day significantly improve pain and quality-of-life ratings, and allowed tapering of concomitant analgesic therapy (Barbano, Herrmann, Hart-Gouleau, Pennella-Vaughan, Lodewick & Dworkin, 2004).

It has been suggested that botulinum toxin type A may provide relief of neuropathic pain in diabetes through its modulatory effects on afferent sensory fibre firing. Indeed, a double-blind crossover trial of intradermal botulinum toxin type A in 18 patients with PDN demonstrated a significant reduction in pain and improvement in sleep quality (Yuan, Sheu, Yu, Chen, Tseng & Chang, 2009). Botulinum toxin type A may represent a novel approach to treatment in PDN but the results of this trial need to be verified in larger studies with longer periods of observation.

Nonpharmacological approaches

Patient education is considered essential to promote glycaemic control and help avoid the late complications of diabetic neuropathy (Biril, 2012). Some patients with PDN may not achieve adequate relief with conventional therapy or may suffer from adverse effects of the prescribed treatments (Biril,et al., 2011). Nonpharmacological approaches have been proposed for these patients.

Various forms of electrical stimulation have been used to manage pain in diabetic neuropathy, including transcutaneous electrical nerve stimulation, percutaneous electrical

nerve stimulation and frequency-modulated electromagnetic neural stimulation (Bril, et al., 2011). A recent review analysed eight studies that evaluated the use of electrical stimulation in PDN. Six of these studies found significant pain relief in patients treated with electrical stimulation compared with placebo or sham treatment, suggesting a likely role for treating diabetic neuropathic pain (Thakral, Kim, hbLafontaine, Menzies, Najafi & Lavery, 2013).

A single-blind placebo-controlled randomized trial to evaluate the use of acupuncture in PDN in 45 subjects recently reported an improvement in the outcome measures used to assess pain in the acupuncture arm relative to sham treatment (Garrow, Xing, Vere, Verrall, Wang & Jude, 2014). However, Chen and colleagues suggest that it is difficult to draw meaningful conclusions from acupuncture trials in diabetic neuropathy as trials often have flawed study design and avoid the use of the robust outcome measure of pain in diabetic neuropathy (Chen, Yang, Liu, Manheimer & Liu, 2013).

Dietary Supplementation interventions

Good nutrition can go a long way in helping both to prevent and manage neuropathy. Healthful eating plan is a mainstay of preventing nerve damage. By controlling carbohydrate intake, blood sugar is also controlled, which in turn, helps to limit or prevent nerve damage.

Plant-based dietary interventions typically improve glycemic control and other factors associated with type 2 diabetes and its complications. In a study of 99 type 2 diabetes

patients comparing a low-fat plant-based diet with a more conventional diet, in an analysis limited to participants making no medication changes, HbA1c (percent hemoglobin A1c) fell by 1.2 points in the plant-based group, compared with 0.4 points in the control group (Barnard, Cohen, Jenkins, Turner-McGrievy, Gloede & Jaster, 2006). Glycemic control appears to have a key role in the risk of complications (Yokoyama, Barnard, Levin and Watanabe, 2014). In intervention trials using plant-based diets, improvements in glycemic control (Barnard,*et al.*, 2006), blood lipid concentrations (Ferdowsian, Barnard, Hoover, Katcher, Levin& Sekikawa, 2014) have been consistently observed (Barnard,*et al.*, 2006; Yokoyama,*et al.*, 2014), and diet acceptability is similar to that of other therapeutic diets (Barnard, Scialli, Turner-McGrievy and Lanou, 2004).Two uncontrolled diet intervention studies showed promising results in individuals with diabetic neuropathy (Smith, Russell, Feldman, Goldstein, Peltier and Smith, 2006; Crane andSample,1994). In all the experiments, people following the plant based diet reported less pain and other neuropathy symptoms and improvements in cholesterol and quality of life compared to those that did not take the diet.

Herbs like *Azadirachta indica* (neem), *Gymnema sylvestre* (gumar/ sugar blocker), *trigonella foenum graecum* (fenugreek/hulba), *momordica charantia* (bitter lemon) and *moringa olifera* (zogale) are said to possess some hypoglycemic properties, which in turn relieves neuropathic pain to an extent.

Alcohol also worsens neuropathy symptoms, such as numbness and pain. Drinking too much alcohol may also make it harder to control blood sugar. It is therefore advisable to stay clear of alcohol.

Exercise intervention in management of diabetic neuropathy

Exercise contributes to improved glucose control. It has been found to slow or stop the progression of diabetic neuropathy among other benefits (Shalker & Stevens, 2011). Although current treatments for diabetic neuropathy have not been proven to reverse pathogenesis and progression and are thus aimed largely at pain control (Shalker & Stevens, 2011), it is still worthwhile to explore the benefits that exercise has to offer and promote exercise for patients as a viable therapeutic option.

Short and longterm benefits of Exercise Intervention

Lifestyle interventions, including exercise, are the first line in diabetes treatment. Acutely, exercise reduces blood glucose levels via uptake of glucose into active muscles. Exercise also stimulates glucose transporter type 4 (GLUT4) translocation enhancing glucose uptake into muscle cells and compensating for impaired insulin sensitivity associated with diabetes (Colberg, Albright & Blissmer, 2010). Although both aerobic and resistance exercise offer benefits to the patient with diabetes, a combination of the two may be more effective in controlling blood glucose. Exercise also enhances insulin action for 2 to 72 hours (Colberg, *et al.*, 2010).

In addition to short-term improvements in glucose control and insulin action, exercise over the long term reduces low density lipoprotein cholesterol levels and systolic blood pressure in diabetic patients; it also ameliorates symptoms of depression and improves health related quality of life (Colberg, *et al.*, 2010). Given its effects on blood glucose regulation and the role that tight glycemic control plays in preventing diabetic

neuropathy—exercise should be considered a mainstay of treatment for this complication of diabetes.

However, according to Colberg,*et al.*, (2010), exercise can also help patients manage symptoms after they have already begun. Research demonstrates that physical exercise, such as running on a treadmill for 30 to 60 minutes daily, is associated with an increase in heat shock protein 72. This protein is released in response to exercise and is associated with improved tolerance to stressors. It is believed that increased levels of this protein allow for better health of the nerves in the feet of patients with diabetic neuropathy.

Patients who performed a combination of aerobic and strength training exercise 3 or 4 days per week achieved significant reductions in pain and neuropathic symptoms after 10 weeks. Aerobic exercise included treadmill, stationary bike, or elliptical trainer for 30 to 50 minutes; strength training included weight machines targeting many different muscle groups for 10 to 20 repetitions per exercise. Further evidence of the response of peripheral nerves to exercise is provided by biopsy measurements of nerve fiber branching, which increased after a 10-week exercise program. This indicates that exercise induces physical changes to nerve structure as a means of altering disease progression and improving symptoms.

In a another study, patients who followed a 10-week program of aerobic and resistance exercise experienced significant decreases in pain and neuropathic symptoms and increases in cutaneous innervation; these results demonstrate that exercise can solve the very problems that may keep patients from exercising in the first place (Kluding, Pasnoor & Singh, 2012).

Aerobic exercise should be performed at least 3 days per week at a moderate to vigorous intensity corresponding to 40 to 60percent of maximum oxygen consumption; in most patients, brisk walking is adequate. Because exercise intensity is more highly correlated with blood glucose control than exercise volume, intensity should be emphasized when constructing an exercise program (Colberg,*et al.*, 2010). Aerobic exercise should be performed for at least 150 minutes spread throughout the week in bouts no shorter than 10 minutes at a time. Any form of aerobic exercise that involves large muscle groups and causes elevation in heart rate is recommended.

Resistance training should accompany aerobic training and should be performed at least 2 days per week at a moderate to vigorous intensity. A minimum of 5 to 10 exercises targeting major muscle groups should be performed in each session, with 3 or 4 sets of 10 to 15 repetitions performed per exercise (Colberg,*et al.*, 2010). Patients should work to progress to heavier weights over time.

Patients should also seek instruction and supervision by a qualified professional when beginning an exercise program. This is particularly important for patients with diabetic neuropathy, because they are at risk for falls. Flexibility training and other modes of exercise that promote balance training, such as yoga or tai chi, should also be undertaken to help reduce the risk of falls; however, this should not replace aerobic or resistance exercise but rather be done in conjunction with them (Colberg,*et al.*, 2010).

Future directions

It is evident from the broad range of drugs that have been evaluated in PDN that there is no consensus about a single most effective drug, and monotherapy rarely provides adequate pain relief. Additionally, most studies compare therapies against placebo or sham treatment and there is a need for comparative studies between different pharmacological agents. In a small study of 56 patients with DPN or postherpetic neuralgia (PHN) randomized in a 1:1:1 ratio to receive one of three sequences of daily oral gabapentin, nortriptyline, or their combination, the combination was more efficacious than either drug given alone. Therefore, it was recommended that a combination may be considered in patients who show a partial response to either drug given alone but who seek additional pain relief (Gilron, Bailey, Tu, Holden, Jackson & Houlden, 2009). Bansal and colleagues (2009) recently reported in a head-to-head study that pregabalin may be more efficacious than amitriptyline in patients with PDN. In a multicentre, double-blind, parallel-group study of 805 patients with DPN in the initial 8-week therapy 60 mg/day duloxetine was found to be superior to 300 mg/day pregabalin ($p < 0.001$) and subsequently a 50percent response rate for pain relief was shown in 52.1percent for combination and 39.3percent for high-dose monotherapy ($p = 0.068$) (Tesfaye, Wilhelm, Lledo, Schacht, Tolle & Bouhassira, 2013). Gilron and colleagues (2005) reported that a combination of morphine and gabapentin had superior efficacy in the treatment of neuropathic pain with a similar frequency of adverse effects compared with monotherapy with morphine or gabapentin at maximal tolerated doses. A number of target sites have been proposed for the treatment of PDN (Vincent, Callaghan, Smith & Feldman, 2011). Manipulation of the temperature-sensitive transient receptor potential

(TRP) channel on nociceptive neurons has been proposed as an attractive strategy in targeting the pain pathway, especially since TRPV1 desensitization by topical agonists such as capsaicin has been in use for PDN (Brederson, Kym & Szallasi, 2013).

Targeting growth factors involved in the pathogenesis of diabetic neuropathy remains an option for future pharmacological therapies. The therapeutic potential of vascular growth factors, particularly vascular endothelial growth factor (VEGF), is considerable, however there has been limited clinical translation in this area and indeed a recent clinical trial of VEGF was stopped due to futility (Verheyen, Peeraer, Lambrechts, Poesen, Carmeliet & Shibuya, 2013).

Mutations in the Nav1.7 sodium channel have been described in some patients with peripheral neuropathy (Galloway & Chattopadhyay, 2013). Nav1.7 antagonists are currently in development. Xenon402, a novel Nav1.7 blocker, was found to be effective in erythromelalgia and it has been suggested that Nav1.7 blockers may be useful in other types of neuropathic pain (McGowan, Hoyt, Li, Lyons & Abbadie, 2009; Goldberg, Price, Namdari, Cohen, Lamers & Winters, 2012).

Small molecule angiotensin II type 2 receptor (AT₂R) antagonists have also been proposed as analgesics for neuropathic pain (Smith, Wyse & Edwards, 2013). Most recently, a high-profile double-blind placebo-controlled trial demonstrated the efficacy of EMA401, a novel AT₂R antagonist, in the treatment of PHN and this drug remains in development as a therapeutic agent for neuropathic pain (Rice, Dworkin, McCarthy, Anand, Bountra & McCloud, 2014).

α -Conotoxins selective for GABA(B) receptor dependent inhibition of N-type Ca^{2+} channels have been shown to relieve allodynia in experimental models (Klimis, Adams, Callaghan, Nevin, Alewood & Vaughan, 2011) and of course ziconotide has been approved for severe refractory pain by the FDA since 2004, but the major limitation is the intrathecal mode of administration (Sanford, 2013).

2.5 Health Implications of Diabetic Neuropathy

According to Mayo Clinic, Diabetic neuropathy can cause a number of serious complications, including:

- **Loss of a limb.** Because nerve damage can cause a lack of feeling in your feet, cuts and sores may go unnoticed and eventually become severely infected or ulcerated, a condition in which the skin and soft tissues break down. The risk of infection is high because diabetes reduces blood flow to your feet. Infections that spread to the bone and cause tissue death (gangrene) may be impossible to treat and require amputation of a toe, foot or even the lower leg.
- **Charcot joint.** This occurs when a joint, usually in the foot, deteriorates because of nerve damage. Charcot joint is marked by loss of sensation, as well as swelling, instability and sometimes deformity in the joint itself.
- Early treatment can promote healing and prevent further damage.
- **Urinary tract infections and urinary incontinence.** Damage to the nerves that control your bladder can prevent it from emptying completely. This allows bacteria to multiply in your bladder and kidneys, leading to urinary tract

infections. Nerve damage can also affect your ability to feel when you need to urinate or to control the muscles that release urine.

- **Hypoglycemia unawareness.** Normally, when your blood sugar drops too low — below 70 milligrams per deciliter (mg/dL), or 3.9 millimoles per liter (mmol/L) — you develop symptoms such as shakiness, sweating and a fast heartbeat. Autonomic neuropathy can interfere with your ability to notice these symptoms.
- **Low blood pressure.** Damage to the nerves that control circulation can affect your body's ability to adjust blood pressure. This can cause a sharp drop in pressure when you stand after sitting (orthostatic hypotension), which may lead to dizziness and fainting.
- **Digestive problems.** Nerve damage in the digestive system can cause constipation or diarrhea or alternating bouts of constipation and diarrhea as well as nausea, vomiting, bloating and loss of appetite. It can also cause gastroparesis, a condition in which the stomach empties too slowly or not at all. This can interfere with digestion and cause nausea, vomiting and bloating, and severely affect blood sugar levels and nutrition.
- **Sexual dysfunction.** Autonomic neuropathy often damages the nerves that affect the sex organs, leading to erectile dysfunction in men and problems with lubrication and arousal in women.
- **Increased or decreased sweating.** When the sweat glands don't function normally, your body isn't able to regulate its temperature properly. A reduced or complete lack of perspiration (anhidrosis) can be life-threatening. Autonomic

neuropathy may also cause excessive sweating, particularly at night or while eating.

2.6 Summary

This chapter reviewed the different types of diabetes, their epidemiology and pathophysiology. Discussion found showed that there are two major types of diabetes, which are type 1 and type 2. Type 1 diabetes also called insulin-dependent or juvenile-onset diabetes develops when the pancreatic beta cells that produce the hormone insulin which regulates blood glucose are destroyed by the immune system. This usually affects children and young adults, and represents about 10 percent of all diabetes cases affecting approximately 20 million people worldwide. While type 2 diabetes also called non-insulin-dependent diabetes or adult-onset diabetes is a disorder in which the cells of the body do not respond to insulin properly, therefore the pancreas gradually loses its ability to produce insulin. Type 2 diabetes is usually associated with older age, obesity, family

history, impaired glucose metabolism and race. It is the most predominant form of diabetes and accounts for about 90-95 percent of all diabetes cases, and a rise in prevalence that is greater in developing than developed countries. Different health implications of diabetes such as retinopathy, nephropathy, heart diseases and neuropathy were found to occur among patients with especially neuropathy. Diabetic neuropathy was defined with its various classes, symptoms, and its pathophysiology. Diabetic neuropathic pain is caused by the damage to nerves in the central or peripheral nervous system which can be due to a number of mechanisms including trauma and presenting symptoms that may include numbness, tingling or pain in the limbs, wasting of the muscles, indigestion and weakness. Assessment and diagnosis of DPN were stated to include various diabetic neuropathic interventions like the pathogenic treatments targeting the underlying pathophysiological processes and symptomatic treatments aimed at alleviating the painful symptoms of PDN were also reviewed. Non pharmacological approaches like acupuncture, electrical stimulation, and dietary supplementation and exercise interventions were said to be in general practice. Future directions on other interventions were manipulation of the temperature-sensitive transient receptor potential (TRP) channel on nociceptive neurons targeting pain pathway, and targeting growth factors involved in the pathogenesis of diabetic neuropathy.

Drugs intervention strategy seems to carry the highest majority of the interventions, whereby diet and exercise is to a lesser extent used. The importance of exercise and dieting as sole intervention strategies goes a long way in the management of DPN, since it will reduce among others the side effects caused by these drugs.

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This study assessed the different Intervention Strategies used by doctors for the Management of Diabetic Neuropathy in University of Abuja Teaching Hospital. This chapter therefore explained the research design, population of the study, sample and sampling techniques, data collection instrument, validation and reliability of instrument, data collection, procedure and data analysis.

3.2 Research Design

This study used the descriptive survey design according to Fajemidagba (1995), descriptive survey design involves the collection of data for the purpose of describing an existing phenomenon. It is an exploration of and description in precise form, the characteristics of individuals, groups or phenomena in education. The design is suitable for this study because it analyzed precisely the different diabetic interventions employed in the management of diabetic neuropathy in diabetic patients in University of Abuja Teaching Hospital.

3.3 Population of the Study

The study populations were known diabetic neurophatics who were attending the diabetes clinic of University of Abuja Teaching Hospital (UATH) Gwagwalada, Abuja. This population was estimated to be 432 from January 2015 to May 2016 (University of Abuja Teaching Hospital Records). The hospital is one of the biggest tertiary hospital to which patients from every part of the FCT and some neighboring states are referred to for expert medical treatment.

3.4 Sample and Sampling Technique

A sample size of 145 was selected for the study. Sample size was obtained using 10% prevalence rate (Nwosu, 2000). Sample size was calculated using the formula $N = 4p(1 - P) / W^2$

Where N = total number of patients required

P = proportion of people assumed to have diabetic neuropathy, p = 10% (Nwosu, 2000)

W = required precisions level or probability level. For this study, W was taken to be

0.05(5%)

$N = 4P(1-P) = 4 \times 0.1(1-0.1) = 0.4 \times 0.9 = 0.36$

$W^2 = (0.05)^2 = 0.0025$

$0.36/0.0025 = 144$

The method of sampling used was purposive sampling technique for patients attending the diabetic clinic in the period of study at the teaching hospital. Those that have developed neuropathy were selected, and the hospital records were used in selecting the sample for the study.

3.5 Data Collection Instrument

The researcher used one instrument for collection of all data necessary for the research. The instrument is a questionnaire on different diabetic intervention strategies applied by doctors in the management of diabetic neuropathy. This questionnaire was designed by the researcher to consist of structural items that elicit information from respondents on the different diabetic interventions used in the management of diabetic neuropathy. The questionnaire comprised four sections A, B, C and D. Section A focused on

demographic data of the respondents, Section B on physical activities as an intervention, Section C on dietary intervention, Section D comprise items on drug treatment and Section E on combined therapy for neuropathic pain.

A modified four-point Likert scale of “Strongly Agree” (4 points), “Agree” (3 points), “Disagree” (2 points), and “Strongly Disagree” (1 point), responses were used for items on the questionnaire.

3.6 Validity of the Instrument

To determine the content validity of the instrument, five (5) copies of the questionnaire forms were given to five Lecturers in the Department of Physical and Health Education, Bayero University, Kano. Their corrections, advice, suggestions and criticisms were incorporated into the final draft of the questionnaire to the satisfaction of the researcher’s supervisor.

3.7 Reliability of the Instrument

To ascertain the reliability of the instrument, a test-re-test method of two weeks interval was carried out. Twenty (20) copies of the questionnaire were administered using test-re-test method on the respondents from Aminu Kano Teaching Hospital, Kano, which is not part of the area of study. The questionnaires were administered to patients with DPN, after a period of two weeks; the same copies of the questionnaires were readministered to the same subjects. The two results were analyzed using the Pearson’s Product Moment Correlation Co-efficient Statistics, and a reliability index of 0.78 was obtained, indicating that the instrument was 78% reliable which was good for this study.

3.8 Procedure for Data Collection

A letter of introduction was obtained by the researcher from Head of Department, Physical and Health Education Bayero University, Kano, to the office of the Chief Medical Director, University of Abuja Teaching Hospital and an application form was filled for ethical considerations. The consent of the clients was sought and the confidentiality of the information pledged so as to secure full co-operation and acceptance in the Teaching Hospital and with the target audience.

The instrument was administered by the researcher with the help of four research assistants from the Teaching Hospital. The questionnaire was administered as the respondents attend the clinic, during their clinical appointments for a period of two weeks.

3.9 Data Analysis

Descriptive statistical analyses of frequencies and percentage were used to summarize the demographic data of the respondents. All remaining analysis was done using Chi-square with SPSS (Version 20) at 0.05 level of significance.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.0 Introduction

The study investigated the different Intervention Strategies used by doctors for the Management of Diabetic Neuropathic Patients in University of Abuja Teaching Hospital. Out of 145 questionnaire forms distributed and administered, only 122 were duly completed and returned for the analysis. Hence, the data analysis was based on responses of 122 (84.7%) respondents whose questionnaire forms were correctly completed and returned.

The results are presented and discussed in this chapter according to the research questions raised and hypotheses stated in chapter one.

4.1 Results

The results of the study are presented in tables as indicated below. The demographic variables considered in this section include gender, age and educational qualification of the respondents. A total of 122 questionnaire forms duly completed and returned were used for analyses. Table 4.1.1 shows the demographic characteristics of the subjects involved in the study.

Table 4.1.1: Information on Demographic Characteristics of the Respondents

Variable	Classification	Frequency	Percentage (%)
Gender	Male	44	36.07
	Female	78	63.93
Age	15-19 yrs	3	2.5
	20-30 yrs	3	2.5
	30 yrs and above	116	95
Educational Qualific	Below Primary	22	18
	Primary	32	26.2
	Secondary	14	11.5
	Tertiary	54	44.3
TOTAL		122	100

As shown in Table 4.1.1; a total of 122 respondents (who duly completed and returned their questionnaire forms) participated in the study. Based on gender of the respondents 44 (36.07%) were males while females were 68 (63.93%). This reveals that more females attend the clinic than the males or because diabetic neuropathy is more prevalent among the females than the males. Based on age, 3 (2.5%) were between the age range of 15-

19years and 20-30 years respectively while 116 (95%) were aged 30 years and above. This shows that majority of the respondents were aged 30 years and above while the other age groups were the least, this may be as a result of the prevalence of diabetic neuropathy being more among this age group (30 years and above) . On educational qualification, 22 (18%) had below primary school level, 32 (26.2%) had primary school education, 14 (11.5%) had secondary school education and 54 (44.3%) had tertiary education. This indicates that the majority of the respondents had are educated with 44.3% having tertiary education.

Major hypothesis: There are no significant differences in intervention strategies used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Sub-hypothesis 1: There is no significant difference in the use of drugs treatment as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Table 4.1.2: Summary of Chi-square result of drugs used by doctors in management for neuropathic pain in UATH

Variables	Agree (%)	Disagree (%)	Df	χ^2	Cum. χ^2	Probability
Tricyclic A	84 (68.9%)	38(31.1%)		17.34 ^a		
Anticnvlst	96(78.7%)	26(21.3%)	1	40.16 ^a	132.343 ^a	0.001
SNRI	82(67.2%)	40(32.8%)		14.46 ^a		
Opiods	24(19.7%)	98(80.3%)		44.88		
Topical C	38(31.1%)	84(68.9%)		17.34		

$\chi^2_{table} = 3.841$, **df = 1, ^a Indicates where the significant difference exists at **p= 0.000 > 0.05****

Table 4.1.2 reveals that 84 (68.9 %) of the respondents agreed and 38 (31.1%) disagreed on doctors recommendation to take tricyclic antidepressants for treatment of diabetic neuropathy. From the table, it is indicated that the number of respondents that agreed are more than those that disagreed. On the use of anticonvulsants, the table reveals that 96 (78.7 %) of the respondents agreed and 26 (21.3%) disagreed on doctors recommendation. From the table, it is indicated that the number of respondents that agreed are more than those that disagreed. The table also reveals that 82 (67.2%) of the respondents agreed and 40 (32.8%) disagreed on doctors recommendation to take serotonin – norepinephrine reuptake inhibitors. From the table, it is indicated that the number of respondents that agreed are more than those that disagreed. From the table, 24 (19.7%) of the respondents agreed and 98 (80.3%) disagreed on doctors recommendation to take opioids. From the table, it is indicated that the number of respondents that agreed are less than those that disagreed. Finally, the table also reveals that 38 (31.1 %) of the respondents agreed and 84 (68.9%) disagreed on doctors recommendation to apply topical

creams. From the table, it is indicated that the number of respondents that agreed are less than those that disagreed.

From the above, it can be seen that doctors in UATH significantly adopt the use of tricyclic antidepressants, anticonvulsants and SNRI as drug interventions in the management of DPN. Statistical analysis indicated χ^2 value of 132.343 at $df = 1$ and $p < 0.05$. This indicated that doctors in UATH significantly adopt the use of drug as an intervention in the management of DPN. The null hypothesis is therefore rejected on the basis that drugs treatment is a significant intervention used by doctors in the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Sub- hypothesis 2: There is no significant difference in the use of dietary control as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Table 4.1.3: Summary of Chi-square result of diet as an intervention used by doctors in management for neuropathic pain in UATH

Variables	Agree (%)	Disagree (%)	df	χ^2	Cum. χ^2	Probability
Control of carbohydrate intake	122 (100%)	0 (0%)	1	122 ^a	314.531 ^a	0.001
Control of alcohol intake	122(100%)	0 (0%)		122 ^a		
Use of supplements	12 (9.8%)	110 (90.2)		78.72		

$\chi^2_{table} = 3.841$, $df = 1$, ^a Indicates where the significant difference exists at $p = 0.000 > 0.05$

Table 4.1.3 reveals that 122 (100 %) of the respondents agreed and 0 (0%) disagreed on doctors recommendation on control of carbohydrate intake to reduce glucose level. From the table, it is indicated that all respondents agreed and none disagreed. On alcohol intake, the table reveals that 122 (100 %) of the respondents agreed and 0 (0%) disagreed on doctors recommendation. From the table, it is indicated that all respondents agreed

and none disagreed on drinking alcohol. Finally, the table also reveals that 12 (9.8%) of the respondents agreed and 110 (90.2%) disagreed on doctors recommendation on use of supplements. From the table, it is indicated that the number of respondents that agreed are far less than those that disagreed.

From the above, it can be seen that doctors in UATH significantly adopt and recommend to diabetic neuropathic patients controlled intake of carbohydrates and alcohol intake and also checking glucose levels as diet interventions in the management of DPN and however they do not recommend the use of diet supplements. Statistical analysis indicated χ^2 value of 314.531 at $df = 1$ and $p < 0.005$. The null hypothesis is therefore rejected on the basis that diet treatment is a significant intervention used by doctors in the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Sub- hypothesis 3: There is no significant difference in the use of exercise therapy as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Table 4.1.4: Summary of Chi-square result of exercise therapy used by doctors for management of neuropathic pain in UATH

Variables	Agree (%)	Disagree (%)	Df	χ^2	Cum. χ^2	Probability
Walking	122 (100%)	0(0%)		122 ^a		
Strengthening	57(46.7%)	65(53.3%)	1	0.52	296.661 ^a	0.0001
Swimming	5 (4.1%)	117(95.9%)		102.8		
Cycling	12 (9.8%)	110(90.2%)		78.72		

$\chi^2_{table} = 3.841$, $df = 1$, ^a Indicates where the significant difference exists at $p =$

0.0001 > 0.05

Table 4.1.4 reveals that 122 (100 %) of the respondents agreed and 0 (0%) disagreed on doctors recommendation of walking as a form of exercise therapy. From the table, it is indicated that all of the respondents agreed and none disagreed. On strengthening as a form of exercise therapy, the table reveals that 57 (46.7 %) of the respondents agreed and 65 (53.3%) disagreed on doctors recommendation of strengthening exercise as a form of therapy. From the table, it is indicated that the number of respondents that agreed are slightly less than those that disagreed. The table also reveals that 5 (4.1%) of the respondents agreed and 117 (95.9%) disagreed on doctors recommendation to take swimming as a form of exercise therapy for DPN patients. From the table, it is indicated that the number of respondents that agreed are far less than those that disagreed. From the table, 12 (9.8%) of the respondents agreed and 110 (90.2%) disagreed on doctors recommendation on cycling exercise as a form of therapy for DPN patients. From the table, it is indicated that the number of respondents that agreed are far less than those that disagreed.

From the above, it can be seen that doctors in UATH significantly adopt the use of walking as a form of exercise and to a lesser extent the use of strengthening exercise which was recommended but not significantly adopted as an interventions in the management of DPN. Swimming is not significantly adopted by UATH doctors for diabetic neuropathic patients attending the clinic. The null hypothesis is therefore rejected on the basis that exercise intervention is significantly adopted as an intervention by doctors in the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Sub- hypothesis 4: There is no significant difference in the use of combined treatment as an intervention strategy used by doctors for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

Table 4.1.5: Summary of ANOVA Result of Combined Treatment Strategies Used by Doctors for Management of Neuropathic Pain in UATH

Combined therapy				
Sum of Squares	df	Mean Squares	F	Prob.
Between Groups	40.182	13.394	9.209	0.0001
Within Groups	173.145	1.455		
Total	213.327			

$F_{table} = 2.21, df; 3, 119, p < 0.05, \text{Significant.}$

ANOVA was conducted on combined treatment as an intervention strategy to determine the differences among the various intervention strategies used by doctors in management of DPN in UATH. Statistical analysis indicated that $F = 9.209, df; 3, (p < 0.05)$. Therefore,

the null hypothesis is rejected on the account that significant difference exist among the combined treatment as an intervention strategy used by doctors in the management of DPN in UATH.

In order to ascertain and determine the direction of significant differences of combined therapy as an intervention strategy, a Tukey Post -Hoc test was conducted and the results are presented in Table 4.1.6.

Table 4.1.6: The Result of the Post-Hoc test of Combined Therapy

(I) Intervention Strategies	(J) Intervention Strategies	Mean Diff.(I – J)	Std. Error	Sig.
Drugs	Diet	3.6000*	1.23088	0.001
	Exercise	3.8000*	1.23088	0.001
Diet	Drugs	-3.6000*	1.23088	0.001
	Exercise	0.2000	1.23088	0.998
Exercise	Drugs	-3.8000*	1.23088	0.001
	DIET	-0.2000	1.23088	0.998

From table 4.1.6, statistical analysis indicated that the significant differences exist in combined therapy. Therefore the null hypothesis was rejected. The table reveals that significant differences exist between drugs and diet. There is significant difference between drugs and exercise. But, no significant difference exists between diet and exercise.

4.2 Discussion

Background information of the subjects in this study showed that their age range varies between 30 years and above, this is consistent with some earlier descriptions of diabetic neuropathic patient. Mokdad *et al.* (2001) and Marthur (2006) reported that DPN usually occurs in patient in their middle age or old age. The study also showed that there were more females than males. The female preponderance of DPN observed in this study was in line with the findings of Federal Ministry of health (FMoH, 1992;& Osisianya *et al.* 2006).

The study investigated the assessment of the intervention strategies in the management of diabetic neuropathic patients in University of Abuja Teaching Hospital.

With regards to the use of drugs only for management of DPN patients, several medications (Amitriptyline, Pregabalin, Gabapentin, Doloxetine and Tramadol) were used to relieve nerve pain, but they don't work for everyone and most have side effects that must be weighed against benefits they offer. Large-scale clinical trials have shown that pharmacological treatment can reduce the morbidity and mortality associated with metabolic and cardiovascular diseases and that long-term or lifelong treatment is often indicated (Bell, 2004; Balkrishnan, 2004). From the outcome of this study, it was noted that anticonvulsants like pregabalin and gabapentine, antidepressants like amitriptyline and imipramine, and duloxetine a serotonin – norepinephrine reuptake inhibitor were the drugs prescribed and recommended by the doctors in UATH for the management of pain in DPN patients. This is in line with the clinical guideline regimen for the management of DPN as recommended by National Institute for Health and Care (NICE, 2013), American Association of Neurology (AAN), American Association of Neuromuscular and

Electrodiagnostic Medicine (AANEM) and American Academy of Physical Medicine and Rehabilitation (AAPMR) (2014). These guidelines suggest using tricyclic agents (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) or γ -aminobutyric acid (GABA) analogues (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments (Spallone, 2012). The guideline is based on a systematic review of numerous pharmacological and non pharmacological agents, with the aim of guiding and assisting physicians to create a treatment plan that helps reduce pain and improve physical function and quality of life in patients who have this condition.

In a review of 6 trials (2220 patients) on duloxetine's effects on painful diabetic peripheral neuropathy (3 trials) and fibromyalgia (3 trials), Lunn *et al* (2014) concluded that 60 mg of duloxetine daily can relieve the pain of peripheral neuropathy in the short-term, calculating a 1.65 risk ratio for a 50% pain reduction at 12 weeks. There was no difference identified between gabapentin and tricyclic antidepressants in the achievement of pain relief of diabetic neuropathy or postherpetic neuralgia in a study by Chou, Carson and Chan in 2009. The authors also performed a meta-analysis of head-to-head trials comparing the results of gabapentin and tricyclic antidepressants for pain relief in diabetic neuropathy.

Initial selection of first line treatment is influenced by the assessment of contraindications, consideration of co-morbidities and cost; for example, in diabetic patients with a history of heart disease, elderly patients on other concomitant medications such as diuretics and antihypertensives, patients with co-morbid orthostatic hypotension and others, TCA have relative contraindications. In patients with liver disease, duloxetine

should not be prescribed, and in those with oedema, pregabalin or gabapentin should be avoided (Tavakoli et al. 2008).

The SNRI duloxetine was the first drug to be approved for DPN by the US Food and Drug Administration in 2004 based on data from large randomized controlled trials (Tavakoli et al. 2008). In the first placebo-controlled double-blind trial, patients treated with duloxetine at 60 mg and 120 mg reported significant improvement in average pain scores continuing throughout the study (Goldstein et al. 2005). These findings are supported by a recent Cochrane Collaboration review that analysed data from eight studies, including 2728 participants, and concluded that 60 mg and 120 mg daily doses of duloxetine were efficacious in the management of PDN, but lower doses were not associated with improvement. Minor side effects were commonly present and occurred more frequently with higher doses but major side effects were rare (Lunn et al. 2014). Somnolence and constipation were reported in 20% and 14% of patients receiving 60 mg daily duloxetine (Goldstein et al. 2005). In the UK, duloxetine has been found to be a cost-effective agent for PDN (Beard et al. 2008) and was indeed endorsed by NICE (Clinical Guideline 173) in November 2013.

Regarding physical exercise, it is an effective treatment that can help restore balance and sensation that has been lost in DPN. The present study showed that doctors at UATH recommend physical exercise as part of the interventions in the management of DPN. Walking and strengthening exercises were the selected few that are most recommended, though not on their own but in combination with drugs. While swimming and cycling were the least recommended by the doctors, likely due to some environmental and

cultural factors. This is in contrast with the recommended guidelines by NICE, AAN, AANEM and AAPMR (2014), who strongly recommend swimming and cycling as a basic component for the exercise intervention of the management of DPN. Physical exercise help DPN patients regain motions that have been lost or improve balance when walking, its main goal therefore is maintaining and improving range of motion, as well as strengthening muscles. Inactivity was found to have significant effect on diabetes control. Many patients with poor diabetes control were very inactive. Low levels of physical activity as in sedentary lifestyle such as excessive watching of television have been implicated as an important risk factor for both obesity and diabetes (Hu, Li, Colditz, Willett, Manson, (2003). Physical activity is widely endorsed for persons with diabetes by the American Institute for Cancer Research (AICR, 2007). Larson *et al.* (1999) affirms that physical exercise increases the number and binding capacity of insulin receptors, assists in lowering blood sugar level and reduces insulin requirements in persons who use insulin. It also reduces blood lipid level in those who engage in regular exercise thereby assisting in weight control and improving muscle strength and flexibility.

Long-term aerobic exercise training can modify the natural history of DPN (Sayed and Hoda, 2008). Exercises which are based on strengthening, aerobic and functional program were feasible and acceptable for people with neuropathy and participation in these exercises may be successful in reducing chronic disablement (Balducci, Iacobellis, Parisi, Di Biase, Calandriello, Leonetti, and Fallucca, 2006). Unfortunately, the finding of this study on use of exercise as a form of intervention is not quite supportive.

From another study conducted by Sayed and Hoda in 2008, they concluded that physical exercise therapy interventions continue to generate new therapies and strategies in the

management of diabetic foot ulceration in the fields of wound healing and diabetic foot disease.

Furthermore, regarding dieting, Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications like neuropathy. It is, therefore, important at all levels of diabetes prevention. MNT is also an integral component of diabetes self-management education (or training) that is employed in hospitals recommended by the American Diabetes Association. This is in line with the present study findings, that doctors in UATH recommended dieting in the control of blood sugar levels, though diet supplements were the least recommended.

Fadupin and Keshinro (2001) observed that most hospitals in Nigeria do not employ dieticians. The situation has not changed much and this may have accounted for the dietary counseling of the subjects by non nutrition expert. This may also be responsible for the poor nutrition knowledge of the subjects. Many graduate nutritionists / dieticians are now available in Nigeria, but they are yet to be employed in most Nigerian hospitals. It is necessary that hospitals should be encouraged to engage the services of qualified exercise scientists, nutritionists/ dieticians among others.

The use of combined therapy remains the best treatment option in the management of diabetic neuropathy as seen, especially in combination with drugs. This is in line with the clinical guideline regimen for the management of DPN as recommended by National Institute for Health and Care (NICE, 2013), American Association of Neurology (AAN),

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and
American Academy of Physical Medicine and Rehabilitation (AAPMR) (2014).

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.0 Summary

The study investigated the intervention strategies used for the management of diabetic neuropathic patients in University of Abuja Teaching Hospital. To achieve the purpose of the study, two research questions were raised; one major hypothesis and four sub-hypotheses were formulated. According to the literature review, different types of diabetes, their epidemiology and pathophysiology were reviewed. Assessment and diagnosis of DPN were stated to include various diabetic neuropathic interventions like the pathogenic treatments targeting the underlying pathophysiological processes and symptomatic treatments aimed at alleviating the painful symptoms of PDN were also reviewed. Descriptive design of survey type was used for the study. The population of the study comprised 145 subjects who were exclusively diabetic patients with neuropathic pain at the Teaching Hospital, from January 2015 to date. A researcher developed questionnaire which was designed in line with the four points modified Likert scale was used as instrument for data collection. It was validated and subjected to a test-retest reliability method that yielded a reliability index of 0.78. Frequency counts and percentages were used to analyze the demographic variables while Chi-square was used to test the hypotheses of the study at 0.05 level of significance. The data from 122 respondents who duly completed and returned the questionnaire forms were analyzed and reported. The findings of the study showed that doctors in UATH significantly adopt the use of drugs, diet, exercise and combined therapy as interventions in the management of

DPN. The result also revealed that dieting and exercise were to a lesser extent adopted and recommended by the doctors in UATH.

5.1 Conclusions

On the basis of the findings of this study, the following conclusions were drawn:

1. Doctors in University of Abuja Teaching Hospital significantly adopt the use of drugs as an intervention strategy in the management of Diabetic Neuropathy.
2. Doctors in University of Abuja Teaching Hospital adopt the use of dieting as an intervention strategy in the management of Diabetic Neuropathy.
3. Doctors in University of Abuja Teaching Hospital adopt the use of exercise as an intervention strategy in the management of Diabetic Neuropathy.
4. Doctors in University of Abuja Teaching Hospital significantly adopt the use of drugs, dieting and exercise as combined intervention strategies in the management of Diabetic Neuropathys.

5.2 Recommendations

Based on the findings and conclusions of this study, the following recommendations were made:

1. Doctors should intensify the need for diabetic neuropathic patients to adhere strictly to controlling their blood glucose level through adoption of appropriate dietso as not to exacerbate their condition.

2. There is need for regular and proper counseling of DPN patients by doctors on the importance of exercise in the control, management and cure of diabetic neuropathy in University of Abuja Teaching Hospital.

3. There is need to engage in an intensive goal oriented sensitization campaign and embark on educational programmes that will influence the use of diet and exercise by diabetic neuropathic patients in the care, management and cure of the disorder among doctors and health professionals in University of Abuja Teaching Hospital.

5.3 Recommendation for Further Studies

From the outcome of this day study, the following may be recommended:

1. Further studies on diet and exercise as sole interventions for the cure of diabetic neuropathic disorders should be carried out.
2. Use of different interventions in the management and cure of diabetic disorders like diabetic retinopathy and nephropathy should also be looked into.

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APPENDIX I

CLIENTS CONSENT FORM

I after having been properly counseled and given necessary information do willingly consent to participate in the study. Also, I am aware that the information obtained from this research will be treated with absolute confidentiality.

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.....

Participants

Sign/Thumb

Researchers Sign

APPENDIX II

FACULTY OF EDUCATION

DEPARTMENT OF PHYSICAL AND HEALTH EDUCATION

BAYERO UNIVERSITY KANO

P. O. BOX 3011, KANO, KANO STATE NIGERIA

QUESTIONNAIRE ON EVALUATION OF DIFFERENT DIABETIC INTERVENTIONS IN THE MANAGEMENT OF DIABETIC NEUROPATHY

Dear Sir/Ma,

This questionnaire is designed to obtain relevant information on “Assessment of Intervention Strategies in the Management of Diabetic Neuropathy in University of Abuja Teaching Hospital Gwagwalada, Abuja”.

The study is purely for academic purpose in partial fulfillment of the requirements for the award of Master of Science degree in Health Education and respondents are kindly requested to answer the questions as honestly as possible, and it does not require names.

All information provided shall be treated with utmost confidentiality.

It is also believed that the outcome of the study will be beneficial to your health provider who may be further informed on how to manage your condition further.

Yours sincerely,

Hajara Abubakar Sadiq

SPS/12/MHE/00034

SECTION A: BIO DATA

Instruction: Please write or tick (✓) the answer as appropriate.

1. Sex: (a). Male () (b). Female ().
2. Age: (a). 15-19yrs () (b). 20-30yrs () (c). 30yrs and above ().

3. Education Qualification: (a). Below Primary Education () (b). Primary Education () (c). Secondary Education () (d). Tertiary Education ().

SECTION B

Please tick accordingly; SA-Strongly Agree, A-Agree, D- Disagree, SD-Strongly Disagree

PHYSICAL ACTIVITIES INTERVENTION		SA	A	D	SD
1	Doctors in UATH recommended 30-60min/wk on exercise.				
2	Doctors in UATH recommended I perform stretching or strengthening				

	exercises (range of motion, using weights, etc.)				
3	Doctors in UATH recommended walking exercise				
4	Doctors in UATH recommended swimming or performing aquatic exercise				
5	Doctors in UATH recommended cycling (including stationary exercise bikes) and the use of aerobic exercise equipment (e.g stairmaster).				
DIETARY INTERVENTIONS					
		SA	A	D	SD
1	Doctors in UATH recommended I control my carbohydrate intake				
2	Doctors in UATH recommended I don't drink alcohol				
3	Doctors in UATH recommended I check my cholesterol level				
4	Doctors in UATH recommended I take other supplements(neem,				

	moringa (zogale), curcumin etc) that will help reduce my glucose level and pain				
5	Doctors in UATH recommended I take some vitamin supplements (vit B12, benfotiamine etc) and vegetables to reduce my glucose level and pain				

SECTION B: DRUG TREATMENT FOR NEUROPATHIC PAIN

		SA	A	D	SD
1	Amitriptyline, Nortriptyline, is one of the drugs prescribed by Doctors in UATH.				
2	Pregabalin, Gabapentin is one of the drugs prescribed by Doctors in UATH.				
3	Doloxetone is one of the drugs prescribed by Doctors in UATH.				
4	Tramadol, Morphine is one of the drugs prescribed by Doctors in				

	UATH.				
5	Capsaicin Cream, Lidocaine is one of the drugs prescribed by Doctors in UATH.				

SECTION C: COMBINED THERAPY

		SA	A	D	SD
1	Doctors in UATH recommended the use of both drugs and exercise to reduce my glucose level and pain.				
2	Doctors in UATH recommended the use of both drugs and dieting to reduce my glucose level and pain.				
3	Doctors in UATH recommended				

	the use of both dieting and exercise to reduce my glucose level and pain.				
4	Doctors in UATH recommended the use of drugs, dieting and exercise to reduce my glucose level and pain.				