Preview of the Medifocus Guidebook on: Peripheral Neuropathy

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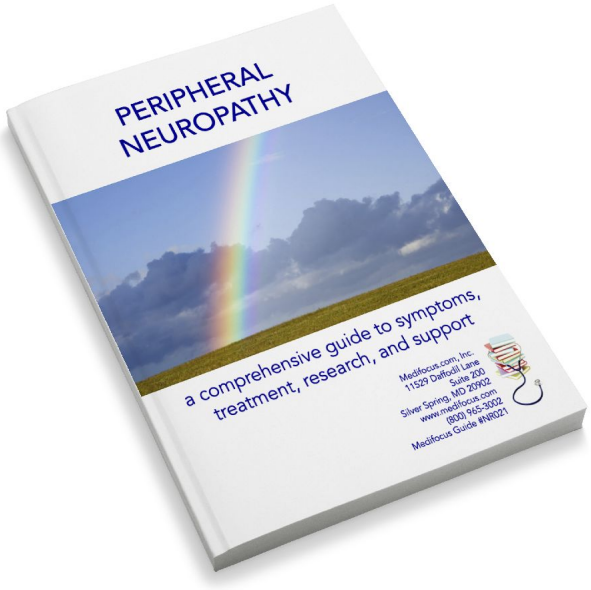

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Peripheral Neuropathy**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

To purchase the **COMPLETE** Medifocus Guidebook on Peripheral Neuropathy (165 pages; Updated January 29, 2017), please:

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Table of Contents

1 - Background Information

Introduction

Chronic or life-threatening illnesses can have a devastating impact on both the patient and the family. In today's new world of medicine, many consumers have come to realize that they are the ones who are primarily responsible for their own health care as well as for the health care of their loved ones.

When facing a chronic or life-threatening illness, you need to become an educated consumer in order to make an informed health care decision. Essentially that means finding out everything about the illness - the treatment options, the doctors, and the hospitals - so that you can become an educated health care consumer and make the tough decisions. In the past, consumers would go to a library and read everything available about a particular illness or medical condition. In today's world, many turn to the Internet for their medical information needs.

The first sites visited are usually the well known health "portals" or disease organizations and support groups which contain a general overview of the condition for the layperson. That's a good start but soon all of the basic information is exhausted and the need for more advanced information still exists. What are the latest "cutting-edge" treatment options? What are the results of the most up-to-date clinical trials? Who are the most notable experts? Where are the top-ranked medical institutions and hospitals?

The best source for authoritative medical information in the United States is the National Library of Medicine's medical database called PubMed®, that indexes citations and abstracts (brief summaries) of over 7 million articles from more than 3,800 medical journals published worldwide. PubMed® was developed for medical professionals and is the primary source utilized by health care providers for keeping up with the latest advances in clinical medicine.

A typical PubMed® search for a specific disease or condition, however, usually retrieves hundreds or even thousands of "hits" of journal article citations. That's an avalanche of information that needs to be evaluated and transformed into truly useful knowledge. What are the most relevant journal articles? Which ones apply to your specific situation? Which articles are considered to be the most authoritative - the ones your physician would rely on in making clinical decisions? This is where *Medifocus.com* provides an effective solution.

Medifocus.com has developed an extensive library of *MediFocus Guidebooks* covering a wide spectrum of chronic and life threatening diseases. Each *MediFocus Guidebook* is a

high quality, up- to-date digest of "professional-level" medical information consisting of the most relevant citations and abstracts of journal articles published in authoritative, trustworthy medical journals. This information represents the latest advances known to modern medicine for the treatment and management of the condition, including published results from clinical trials. Each *Guidebook* also includes a valuable index of leading authors and medical institutions as well as a directory of disease organizations and support groups. *MediFocus Guidebooks* are reviewed, revised and updated every 4-months to ensure that you receive the latest and most up-to-date information about the specific condition.

About Your MediFocus Guidebook

Introduction

Your *MediFocus Guidebook* is a valuable resource that represents a comprehensive synthesis of the most up-to-date, advanced medical information published about the condition in well-respected, trustworthy medical journals. It is the same type of professional-level information used by physicians and other health-care professionals to keep abreast of the latest developments in biomedical research and clinical medicine. The *Guidebook* is intended for patients who have a need for more advanced, in-depth medical information than is generally available to consumers from a variety of other resources. The primary goal of a *MediFocus Guidebook* is to educate patients and their families about their treatment options so that they can make informed health-care decisions and become active participants in the medical decision making process.

The *Guidebook* production process involves a team of experienced medical research professionals with vast experience in researching the published medical literature. This team approach to the development and production of the *MediFocus Guidebooks* is designed to ensure the accuracy, completeness, and clinical relevance of the information. The *Guidebook* is intended to serve as a basis for a more meaningful discussion between patients and their health-care providers in a joint effort to seek the most appropriate course of treatment for the disease.

Guidebook Organization and Content

Section 1 - Background Information

This section provides detailed information about the organization and content of the *Guidebook* including tips and suggestions for conducting additional research about the condition.

Section 2 - The Intelligent Patient Overview

This section of your *MediFocus Guidebook* represents a detailed overview of the disease or condition specifically written from the patient's perspective. It is designed to satisfy the basic informational needs of consumers and their families who are confronted with the illness and are facing difficult choices. Important aspects which are addressed in "The Intelligent Patient" section include:

- The etiology or cause of the disease
- Signs and symptoms
- How the condition is diagnosed
- The current standard of care for the disease
- Treatment options

- New developments
- Important questions to ask your health care provider

Section 3 - Guide to the Medical Literature

This is a roadmap to important and up-to-date medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest developments and breakthroughs in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new clinical developments, and advances in research. To facilitate your review and analysis of this information, the articles are grouped by specific categories. A typical *MediFocus Guidebook* usually contains one or more of the following article groupings:

- *Review Articles:* Articles included in this category are broad in scope and are intended to provide the reader with a detailed overview of the condition including such important aspects as its cause, diagnosis, treatment, and new advances.

- *General Interest Articles:* These articles are broad in scope and contain supplementary information about the condition that may be of interest to select groups of patients.

- *Drug Therapy:* Articles that provide information about the effectiveness of specific drugs or other biological agents for the treatment of the condition.

- *Surgical Therapy:* Articles that provide information about specific surgical treatments for the condition.

- *Clinical Trials:* Articles in this category summarize studies which compare the safety and efficacy of a new, experimental treatment modality to currently available standard treatments for the condition. In many cases, clinical trials represent the latest advances in the field and may be considered as being on the "cutting edge" of medicine. Some of these experimental treatments may have already been incorporated into clinical practice.

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Article title
- Author Name(s)
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)

- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the corresponding URL address that is provided for each cited article. If you purchased a printed copy of a *MediFocus Guidebook*, you can still access the article abstracts online by entering the individual URL address for a particular article into your web browser.

Section 4 - Centers of Research

We've compiled a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of the specific medical condition. The "Centers of Research" directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of the condition.

Inclusion of the names of specific doctors, researchers, hospitals, medical centers, or research institutions in this *Guidebook* does not imply endorsement by Medifocus.com, Inc. or any of its affiliates. Consumers are encouraged to conduct additional research to identify health-care professionals, hospitals, and medical institutions with expertise in providing specific medical advice, guidance, and treatment for this condition.

Section 5 - Tips on Finding and Choosing a Doctor

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver high-level, quality medical care in accordance with curently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it. This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Section 6 - Directory of Organizations

This section of your *Guidebook* is a directory of select disease organizations and support groups that are in the business of helping patients and their families by providing access to information, resources, and services. Many of these organizations can answer your questions, enable you to network with other patients, and help you find a doctor in your geographical area who specializes in managing your condition.

2 - The Intelligent Patient Overview

PERIPHERAL NEUROPATHY

Introduction to Peripheral Neuropathy

What is Peripheral Neuropathy?

Peripheral neuropathy (PN) is a term used to describe damage to nerves of the peripheral nervous system, which leads to symptoms such as pain, numbness, tingling, burning, and weakness. Peripheral neuropathy most commonly affects the peripheral limbs, namely hands, arms, feet and legs. Peripheral neuropathy can be caused by a variety of precipitating factors including trauma, infection, metabolic disorders (e.g., diabetes), alcohol abuse, and cancer chemotherapy. It can also be *idiopathic*, meaning that it arises from an unknown cause.

One of the most important functions of peripheral nerve cells is to alert a person to tissue injury and noxious stimuli or events in their environment. Normally, pain is a signal of imminent or actual harm to the body that initiates protective reflexes to prevent or minimize that danger. When tissue damage occurs, the resulting pain prompts special attention to the affected area and the person responds either by removing the source of danger (e.g., pulling a hand away from a hot object) or by initiating treatment quickly. The pain which is felt in response to a harmful stimulus is known as *nociceptive pain*. It is caused by stimulation of certain pain receptors and is generally described as sharp, aching, or throbbing. It is also the type of pain felt in some chronic, painful conditions (e.g., arthritis).

However, when pain occurs in the absence of dangerous stimuli, does not prompt protective reflexes, nor subsides when the danger is past or when the injury has healed, it is said to be "maladaptive" or "dysfunctional" and is called *neuropathic pain*. The nervous system malfunctions and becomes the *cause* of the pain. This type of pain serves no protective or biological function. It may or may not be triggered by an injury and can persist for years or decades. It is often described as burning, electric, tingling and/or shooting pain and can be continuous or intermittent. While symptoms of neuropathic pain tend to predominate in the peripheral limbs, they can also appear in different locations (e.g., in the cranial nerve as *trigeminal neuralgia*).

Peripheral neuropathy can significantly impact an individual's quality of life and daily activities by causing major disruptions including:

- Sleep disturbances
- Mood changes
- Impairment of social, occupational, and recreational functioning

The Nervous System

The nervous system controls the smooth functioning of all systems in the body as well as all interactions between the human being and the environment. It consists of two networks:

- Central nervous system - includes the brain and spinal cord
- Peripheral nervous system - includes the nerves that lead from the brain and spinal cord to all parts of the body. This is the system affected by peripheral neuropathy. There are two components to the peripheral nervous system:

    - *somatic nervous system* - regulates body movement through control of skeletal muscles and connects the brain to the outside environment through the five senses. It is the "voluntary" nervous system that enables people to react to environmental stimuli.
    - *autonomic nervous system* - controls automatic, involuntary functions including heart rate, blood pressure, breathing, digestion, and bladder function. This system is responsible for maintaining *homeostasis*, the state of equilibrium where all body systems are working and interacting correctly.

An extensive system made up of three types of specialized nerves makes up the peripheral nervous system:

*_Motor nerves_ - carry messages from the brain to organs, muscles, and glands, and are responsible for the ability to move any part of the body. These are called _efferent nerves_. * _Sensory nerves_ - carry information from organs (e.g., the skin) to the central nervous system where it is processed into sensation (e.g., touch, temperature changes, and vibrations). These are called _afferent nerves_. * _Autonomic nerves_ - control involuntary functions such as heart rate, digestion, respiration rate, and perspiration.

Each peripheral nerve cell (*neuron*) in the human body has three parts:

- Cell body (also called *soma*), which is similar to the cell body of all other cells.
- Dendrites - fibers of varying sizes which extend from the cell body and are the sensory terminals of the neuron. They receive messages from neighboring cells and transmit them to the cell body.
- Axon (also called a *nerve fiber*) - a long slender projection that extends from the cell body and transfers a signal from the cell body to another nerve or muscle cell. Axons can be either *myelinated* (insulated by the myelin sheath made up of specialized cells) or *unmyelinated*. The presence or absence of myelin affects the speed of transmission of impulses; conduction speed is significantly faster in myelinated cells.

Nerve fibers may be either *large* or *small*.

Large Nerve Fibers

Large fibers are long nerve fibers that are myelinated and enable very fast conduction of impulses

to the brain and spinal cord. They carry non-nociceptive information and are not normally associated with pain. Lesions or injury to large fibers can affect many functions including:

- Motor function
- Vibration perception
- Positional sense
- Perception of temperature

Symptoms associated with large fiber neuropathy include:

- Numbness
- Tingling
- Weakness
- Loss of deep reflexes

Small Nerve Fibers

Small nerve fibers may or may not be myelinated and each type involves different sensations. Regardless of whether or not they are myelinated, they contain nociceptors which are highly sensitive to *pain* and *paresthesia* (abnormal sensations such as tingling, pricking, or burning).

Symptoms of small fiber neuropathy are many and include:

- Pain described as burning, stabbing, prickling, jabbing, or lancinating (piercing)
- Sensation of "broken glass", "burning sand", or "ice pick in the bone"
- Tight band-like pressure
- Insensitivity to heat and cold
- Autonomic dysfunction (malfunctioning of the autonomic nervous system)

While small fiber neuropathy may be caused by conditions such as diabetes or HIV, the cause of most cases of small fiber peripheral neuropathy is unknown and is called *idiopathic peripheral neuropathy*. It is estimated that an underlying cause for small fiber neuropathy is found in less than 10% of patients. Small fiber neuropathy is the most common type of PN in people over the age of 50 and is often unrecognized by physicians. It is very painful to the point of being debilitating and responds slowly to medication, if at all.

In peripheral neuropathy involving both large and small fibers, small fiber damage usually precedes large fiber dysfunction and occurs typically in the lower limbs.

What Happens in Peripheral Neuropathy?

Peripheral neuropathy develops as a result of injury or damage to any of the three types of nerves in the peripheral nervous system. Symptoms of an individual's peripheral neuropathy depend upon which types of nerves are injured, for example:

- Sensory nerves - Damage to sensory nerves can produce symptoms such as pain, numbness,

tingling, burning, or a loss of sensation or feeling. The pain usually begins in the hands or feet and progresses towards the trunk of the body. Lack of sensation can cause other complications relating to recurrent injuries that may go unnoticed, (e.g., awareness of cuts or burns to the skin) and can lead to ulcers or poor healing of wounds. The nerve damage in sensory peripheral neuropathy may be found in either large fibers or small fibers. The symptoms of sensory peripheral neuropathy can be intermittent or continuous and can significantly interfere with quality of life.

- Motor nerves - Damage to motor nerves results in decreased movement or control of muscles. Since movement is important for the health of many organ systems (such as promoting increased blood circulation), damage to motor function can also lead to abnormal changes in muscle, bone, skin, and other organs. Symptoms of damage to peripheral motor nerves usually begin as weakness or heaviness of the hands and/or feet and may deteriorate over time.

- Peripheral nerves that link to the *autonomic nervous system* affect involuntary body functions and damage can result in:

    - cardiac symptoms (e.g., heart rate irregularities, orthostatic hypotension (drop in blood pressure when standing up from a sitting position)
    - impaired ability to regulate body temperature
    - blurred vision
    - reduced sweating
    - dizziness
    - bowel/bladder dysfunction
    - sexual dysfunction

There are many types of neuropathy included under the category of peripheral neuropathy and the etiology, symptoms, progression rate, pattern of symptoms, recurrence, and response to treatment vary widely.

Classification of Peripheral Neuropathy

There are several different ways to classify peripheral neuropathy. One of the most common classification systems takes into account the pattern and distribution of the pain and includes:

- Mononeuropathy
- Mononeuropathy multiplex
- Polyneuropathy

Mononeuropathy

Mononeuropathy is characterized by involvement of a single peripheral nerve. This is most likely to be the result of trauma or nerve entrapment (such as carpal tunnel syndrome, which is the most common cause of mononeuropathy).

Mononeuropathy multiplex

In mononeuropathy multiplex, two or more peripheral nerves in separate parts of the body are affected. The pattern of involvement is random, may appear in many places, and typically evolves quickly. Mononeuropathy multiplex is associated with:

- Vasculitis - inflammation in the part of the vascular system that is innervated by the affected nerves. Vasculitis could also be systemic and affect the vascular system throughout the body. It therefore needs to be diagnosed and treated quickly.
- Diabetic *amyotrophy* - a type of neuropathy characterized by acute pain, weakness, and/or wasting of the muscles of the lower extremity
- *Sarcoidosis* - inflammation that produces tiny lumps of cells in various organs in the body
- Lyme disease
- Lymphoma
- Carcinoma
- HIV
- Amyloidosis - amyloid protein deposits in limited organs or throughout the body
- Polyarteritis nodosa - An autoimmune disease that causes inflammation of the small and medium-sized arteries that can lead to problems with muscles, joints, and other organs

Polyneuropathy

Polyneuropathy affects multiple nerves, may affect more than one extremity (legs and arms) and often occurs on both sides of the body (symmetric). Symptoms appear more commonly in the legs than the arms and usually are felt first in the toes and soles of the feet. It is the most common type of idiopathic peripheral neuropathy, meaning that neuropathy develops spontaneously from an unknown cause. Polyneuropathy is also associated with diabetes, alcoholism, vitamin B deficiency, and HIV. It may also involve the autonomic nervous system.

Most polyneuropathies evolve slowly, involve sensory and motor nerves, and progress symmetrically. Polyneuropathies may involve more than one nerve (sensory or motor) and large and small fibers, but there is usually one (e.g., sensory or motor, large fiber or small fiber) that is predominant.

The most common type of polyneuropathy is called *distal symmetric polyneuropathy*. It involves long sensory nerves and symptoms usually appear first in the toes and the soles of the feet. Early symptoms include numbness, tingling, paresthesia, and burning. As the name implies, symptoms are symmetric and involve both legs. Distal symmetric polyneuropathy is associated with:

- Diabetes
- Idiopathic neuropathy
- Connective tissue disease
- Inherited neuropathies
- HIV
- Cancer
- Chemotherapy
- Metabolic disorders

Polyneuropathy may be *acute* or *chronic*.

Acute Polyneuropathy

This type of polyneuropathy evolves suddenly and tends to progress rapidly. Approximately half of individuals with acute polyneuropathy have a history of respiratory or gastrointestinal infections within two to three weeks prior to onset. Acute polyneuropathy is associated with:

- Guillain-Barre Syndrome - a disorder in which the body's immune system attacks part of the peripheral nervous system. Symptoms appear suddenly and progress quickly, beginning with weakness or tingling sensations in the leg and, in some cases, progressing to the arms and upper body. This condition requires immediate diagnosis and treatment since it can deteriorate quickly and cause paralysis and respiratory insufficiency if respiratory muscles are affected. Symptoms resolve slowly as damaged nerves heal. Approximately 25-30% of patients with Guillain-Barre syndrome require ventilation support (breathing support).
- Porphyria - a group of genetic disorders caused by problems with how the body makes a substance called *heme*, a component of hemoglobin
- Diphtheria
- Vasculitis
- Tumor
- Certain medications

Chronic Polyneuropathy

Chronic polyneuropathy typically develops over a long period of time and the symptoms can remain for years. Two of the more common types of chronic polyneuropathy include:

- *Chronic demyelinating polyneuropathy* - *demyelination* refers to the destruction and loss of myelin from the sheath surrounding the axon and affects both near and far segments of the nerve. It is characterized by progressive weakness and impaired sensory function in the legs and arms. It is more common in males than females and in young adults than older people. This condition may be either *genetic* or *acquired*. The acquired form is known as *chronic inflammatory demyelinating polyneuropathy* (CIDP).
- *Chronic distal polyneuropathy* - this is the most common type of polyneuropathy and is characterized by ascending nerve damage, meaning that the nerve fibers most distant from the brain and spinal cord are affected first. Pain or other symptoms may appear in both feet and gradually progress up the legs and then appear in the fingers, hands, and arms. It may be idiopathic or associated with many conditions including:

    - diabetes (most common)
    - nutritional deficiencies (e.g. vitamin B12)
    - cancer
    - renal failure
    - medication toxicity
    - alcohol abuse

Chronic polyneuropathy may develop over a period of months or years. It can involve large and/or

small fibers and can affect sensory, motor, and/or autonomic pathways. Symptoms are symmetrical and typically start distally (usually in the feet) with pain, numbness, or burning. Progression of symptoms is slow and typically follows a pattern of gradually moving up both legs, followed by the fingers, hands, and arms. Chronic polyneuropathy usually does not result in serious physical disability although quality of life can be significantly impacted, especially due to pain and *dysesthesia* (distorted response to sense of touch where innocuous stimuli are perceived as very painful).

Approximately 20-25% of cases are thought to be idiopathic, where, no cause can be found. Most cases of idiopathic peripheral neuropathy involve sensory nerves. Idiopathic peripheral neuropathy affects primarily older patients.

While acute neuropathies tend to appear suddenly, progress rapidly, be potentially life-threatening, and resolve slowly, chronic neuropathies progress slowly and worsen over time, but are typically not fatal. Some patients find that symptoms plateau at a given point, while other patients experience symptoms that relapse and remit.

For more in-depth information regarding various types of peripheral neuropathy, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/19272511

Onset and Progression of Peripheral Neuropathy

The onset and progression of peripheral neuropathy varies based on its underlying cause. Examples include:

- With trauma or circulatory problems, the onset of peripheral neuropathy symptoms will be acute or sudden, with the most severe symptoms occurring at the onset.
- Inflammatory and some metabolic neuropathies have a subacute course extending over days to weeks. A chronic course over weeks to months usually indicates a toxic or metabolic neuropathy. A chronic, slowly progressive neuropathy over many years occurs with most hereditary neuropathies such as Charcot-Marie-Tooth Syndrome.
- Demyelinating neuropathies are commonly inflammatory and treatable. They may present either with acute or chronic symptoms. Acute presentation of symptoms is seen with conditions such as with Guillain-Barre syndrome where symptoms of weakness and sensory disturbances worsen and reach a peak over one month, while chronic inflammatory demyelinating polyneuropathy (CIDP) may evolve over a longer period (more than four weeks).
- Idiopathic peripheral neuropathy progresses slowly or may not progress at all after the initial symptoms appear. Symptoms may barely be noticeable when they first appear. Initial sensations may be intermittent and can include tingling, numbness, or other feelings in the feet/toes or hands/fingers. Symptoms usually progress from the periphery towards the center of the body. Some individuals experience intensification of their symptoms at night. Skin may become increasingly sensitive and the slightest touch can cause excruciating pain. Many people have pain or burning distributed in the pattern of wearing an invisible stocking or glove. The pain or sensations can increase in frequency and duration and can also change in quality to include new symptoms. Individuals experience their own unique patterns of

pain progression.

If motor nerves are involved, individuals may experience weakness in the legs or arms and a sense of heaviness when trying to lift them. This also effects balance and increases the danger of falling and fracture. If autonomic nerves are involved, individuals may progress to having related symptoms (e.g., bowel or bladder problems, impotence, cardiac symptoms, and/or reduced sweating).

Acute peripheral neuropathy (such as Guillain-Barre Syndrome) must be diagnosed and treated quickly as the symptoms develop rapidly and can potentially become life-threatening. Other types of peripheral neuropathy may be self-limiting, such as neuropathy related to a treatable underlying medical condition. Yet other individuals who suffer from neuropathy may find that their symptoms relapse and remit over the years. Peripheral neuropathy is a condition that causes significant morbidity (disease) for patients but typically is not associated with mortality.

Risk Factors for Peripheral Neuropathy

A *risk factor* is anything that increases a person's chances of getting a particular disease. Risk factors for peripheral neuropathy include:

- Diabetes
    - peripheral neuropathy occurs in up to 60% of patients with diabetes (type 1 or type 2)
    - poorly controlled diabetes and prediabetes (elevated blood sugar but not yet at the level of full diabetes) greatly increase the risk of peripheral neuropathy
- Autoimmune diseases
    - systemic lupus erythematosus
    - rheumatoid arthritis
    - Guillain-Barre syndrome
- Metabolic diseases
    - hypothyroidism
    - amyloidosis
- Hereditary disorders
    - Charcot-Marie-Tooth disease (CMT) - extreme atrophy (wasting) of muscles in the lower legs and feet, numbness in lower legs, and loss of tendon reflexes
    - Dejerine-Sottas Syndrome - a subtype of CMT that involves earlier onset (children) and more severe and rapid progression than classic CMT
- Infectious diseases

    - lyme disease
    - HIV/AIDS
    - hepatitis B
    - leprosy

- Ischemic disorders - a lack of sufficient oxygen delivery to tissue due to interrupted blood flow caused by blockage in blood vessels

- Chronic kidney or liver failure
- Trauma or compression of a nerve - this is the most common cause of nerve injury
- Repetitive motion stress or carpal tunnel syndrome
- Vitamin deficiency (especially vitamin B12)
- Alcohol abuse - poor health and nutrition in alcoholics leads to vitamin deficiencies associated with peripheral neuropathy
- Paraneoplastic disorders (tumors)
- Toxic substance exposure
- Chemotherapy drugs used for cancer treatment, including:

    - vinca alkaloids (such as vincristine)
    - platinum-based drugs (such as cisplatin)
    - taxanes (such as paclitaxel)

Incidence of Peripheral Neuropathy

The incidence of peripheral neuropathy in general is not known with any degree of certainty. It has been estimated that more than 20 million Americans have some form of peripheral neuropathy (8% of adults over the age of 55). The prevalence of peripheral neuropathy worldwide has been estimated to range from 2% to 10% of the population. Peripheral neuropathy affects both genders at all ages, but symptoms are unique to each individual in terms of frequency, quality, and severity of pain. Idiopathic peripheral neuropathy typically affects adults over the age of 50. Although estimates vary widely, approximately 25-60% of diabetics are thought to have diabetic peripheral neuropathy.

The American Academy of Family Physicians reports that the primary worldwide cause of treatable neuropathy is leprosy, but that neuropathies associated with human immunodeficiency virus (HIV) infection account for an increasing number of cases.

Diabetic Neuropathy

Diabetes mellitus (type 1 and type 2) is the most common cause of peripheral neuropathy in Western countries and accounts for more diabetes-related hospitalizations than any other complication. As of 2009, it was thought that in the U.S., diabetic neuropathy had an annual cost of $4-14 billion. Peripheral neuropathy is one of the most common long-term complications of diabetes and may be the most costly complication as well. It occurs equally with type 1 and type 2 diabetes and has more of an effect on the quality of life of diabetics than any other aspect of the

condition, such as dietary restrictions.

The American Academy of Family Physicians (AAFP) reports that peripheral neuropathy is a complication that occurs in 30-50% of diabetic patients and is characterized by the loss of sensation in a "stocking-glove" pattern, starting with the toes and feet, and spreading towards the trunk. Approximately 10-20% of diabetic patients suffer from diabetic peripheral neuropathic pain which is characterized by burning, tingling, or aching discomfort that worsens at night. In addition, these patients may experience allodynia (pain with light touch) and hyperalgesia (increased sensitivity to pain). Functionality, mood, and sleep patterns are also typically affected by diabetic neuropathic pain.

The cause of diabetic neuropathy is not completely understood but some researchers theorize that the metabolic consequences of *insulin deficiency* and *hyperglycemia* (higher than normal levels of sugar in the blood) are related to the initial damage to the nerve fibers, and that vascular insufficiency (insufficient blood circulation), which is common in diabetes, may accelerate the neuropathic injury.

Additional factors related to the development of diabetic peripheral neuropathy include duration of diabetes and obesity. The highest rates of peripheral neuropathy are in people who have had diabetes more than 25 years. Age is also a factor as the number of people affected by diabetic neuropathy increases with age (approximately 50% of diabetics over the age of 60) since it can develop several years after the onset of diabetes. It appears that hypertension, smoking, and dyslipidemia (high blood cholesterol and triglycerides) may also elevate the risk of developing diabetic peripheral neuropathy. There is ongoing debate as to whether progression of diabetic neuropathy is closely related to controlling the level of glucose in the blood (glycemic control). It is important to distinguish the origin of the symptoms of peripheral neuropathy in the diabetic patient, since up to 10% of diabetics may have signs of peripheral neuropathy from non-diabetic causes.

Common characteristics of diabetic neuropathy include:

- Numbness, reduced sensation, and/or pain
- Burning, "pins-and-needles", shooting pains, and hyperesthesia (abnormal increased sensitivity to stimuli of the senses) are reported by some patients
- Pain which intensifies at night and may disrupt sleep
- Swaying of the body resulting from difficulty maintaining posture
- Hyperextension of the big toe and clawing of the toes
- Reduced thickness of plantar tissue (undersurface of the foot)
- Foot ulcers

Foot ulcerations are the most serious complication associated with diabetic neuropathy and they are caused by:

- Loss of sensation in the feet (individual may not be aware of injury or pressure sores)
- Autonomic involvement (e.g., dry, chapped skin that does not heal)
- Abnormalities of movement that may cause pressure points on different parts of the foot
- Poor circulation to the extremities

Diabetic foot ulcers can lead to the onset of gangrene and may require amputation. The presence of neuropathy significantly increases the risk of amputation. By some estimates, diabetic neuropathy is responsible for up to 75% of non-trauma related amputations among diabetics. This highlights the need for diabetic patients to be screened for any signs of neuropathy even if there is no clinical evidence of neuropathy, since early symptoms may be subacute or mild.

The progression of diabetic neuropathy differs for type 1 and type 2 diabetes. In type 1 diabetes, there is typically a rapid deterioration of nerve function soon after the onset of neuropathy followed by slower progression thereafter, whereas in type 2 diabetes, the nerve damage and symptoms of neuropathy are often present at diagnosis and progress thereafter at a steady rate.

Diabetic neuropathy is typically a sensory neuropathy but often affects the autonomic nervous system as well. Nearly 50% of diabetics with neuropathy may have symptoms of autonomic peripheral neuropathy which can be mild or subclinical but, nevertheless, potentially life-threatening. Autonomic-related symptoms associated with cardiac disease, (e.g., silent cardiac ischemia, orthostatic hypotension) can be fatal or can cause significant morbidity. Cardiac disease accounts for up to 25% of deaths of diabetic patients over a 10-year period from the time of diagnosis and is an independent risk factor for stroke.

As described above, diabetic peripheral neuropathy can affect small fibers or large fibers. *Small fiber* pain is not well understood. Small nerve fiber dysfunction often occurs quite early in diabetes with symptoms of pain of varying degrees of intensity and severity as well as exaggerated reactivity to touch (*hyperalgesia*). Diabetic neuropathy seems to progress as small fibers called *c-fibers* are damaged. As it progresses, there is a loss of sensory-related symptoms such as decreased sensitivity to:

- Heat
- Pinprick
- Temperature recognition of warm and cold stimuli

When the situation becomes chronic, there is no longer need for a stimulus to cause pain or hyperalgesia - the pain is always present. Eventually, the fibers may die, at which time the individual may no longer experience pain, but rather numbness.

Large fibers are myelinated and injury to these nerve fibers results in varying degrees of severity of symptoms such as:

- Impaired sense of vibration
- Impaired sense of pressure or touch
- Loss of 2-point discrimination - the ability to distinguish between being touched at one or two points close to each other with a sharp object such as a pin
- Dull pain in the bones of the lower leg or foot
- 'Hot foot' due to increased blood flow
- Shortened Achilles tendon
- Impaired muscle coordination

Most cases of diabetic neuropathy are a mixture of large and small fiber damage. Many individuals experience the "stocking-glove" pattern of pain in the legs as an early sign of sensory loss and eventually symptoms may appear in their hands as well. While symptoms from large fiber involvement (e.g., weakness, poor coordination) affect daily activities and may make a person more prone to falling, the effects of small fiber damage are more debilitating and significantly affect the overall wellbeing of the person since the pain may be very intense, frequent, and/or last a long time. Motor involvement is usually less severe than sensory involvement and is usually restricted to lower limbs.

Although some pain in diabetic neuropathy may resolve on its own, if the pain persists for more than three to six months, it is less likely to disappear and is considered chronic.

Though there are several types of neuropathy associated with diabetes, the more common forms include:

Diabetic Peripheral Neuropathy

Also called distal symmetric polyneuropathy, or sensorimotor neuropathy, this is the most commonly recognized form of diabetic neuropathy. It often appears with the beginning of insulin therapy for diabetes (called "insulin neuritis") or with stress. Pain may be of any quality (e.g., burning, stabbing) and accompanied by paresthesia (e.g., tingling, pins and needles). The skin (particularly of the lower legs) may be hypersensitive to any touch and even the slightest disturbance such as a light breeze, may be excruciating (allodynia). Individuals may also suffer from heightened sensitivity to pain (hyperalgesia). Loss of sensitivity to light touch and temperature is often an early symptom of neuropathy and may be followed by ataxia (lack of coordination), which increases the risk of falls and fractures. Symptoms are usually worse at night.

Diabetic peripheral neuropathy may also cause muscle weakness and loss of reflexes, especially of the ankle. As a result, individuals may shift or modify their normal walking pattern, placing pressure on different areas of the foot, all of which may lead to foot deformities and hammertoes. Because diabetic peripheral neuropathy may cause numbness, pressure points on the foot or injuries may go unnoticed, leading to the formation of blisters and sores. The development of numbness in the feet is very important to note since it is usually the precursor to foot problems that can ultimately lead to ulceration, gangrene, and/or amputation.

The acute stage of diabetic neuropathy may resolve spontaneously or the neuropathy may become chronic. Symptoms can be successfully managed for many patients.

Chronic polyneuropathy often occurs up to several years after the onset of diabetes and persists longer than six months. It may be very debilitating and treatment may lead to addiction or abuse of powerful drugs used in an attempt to alleviate the pain. It may be resistant to treatment and, understandably, has a strong negative impact on the quality of life of the individual.

When symptoms are extreme, they may lead to weight loss and depression. This situation is called *diabetic neuropathic cachexia* and it occurs more often in diabetic males than in diabetic females. Diabetic neuropathic cachexia usually responds to symptomatic treatment.

Diabetic Autonomic Neuropathy

The symptoms of autonomic neuropathy described above (e.g., cardiac symptoms, bowel and bladder dysfunction, blurred vision, and reduced perspiration) affect up to 50% of diabetic patients.

In addition, diabetic autonomic neuropathy can also lead to *hypoglycemic unawareness*. Normally, symptoms such as shaking or sweating occur when blood glucose levels drop below 70 mg/dL and they serve as warning signals of impending hypoglycemia. However, in diabetic patients with autonomic neuropathy, these warning symptoms may not occur making hypoglycemia difficult to identify when it develops.

Diabetic Proximal Neuropathy

This is also known as *lumbrosacral plexus neuropathy*, *plexus neuropathy*, or *diabetic amyotrophy* . Proximal neuropathy typically occurs on one side of the body and begins with pain in the thigh, hip, buttock, or leg. It is more common in individuals with type 2 diabetes or older diabetic adults. Proximal neuropathy also causes weakness in the leg, making it difficult to change from a sitting to a standing position without help. Individuals may be treated for weakness or pain.

Diabetic Focal Neuropathy

Focal neuropathy is a mononeuropathy that affects a single nerve and occurs in older adults with diabetes. The most commonly affected nerves are in the head, torso, or legs. Focal neuropathy often comes on suddenly and is usually characterized by intense acute pain and muscle weakness that usually resolves within six to eight weeks.

Symptoms of focal neuropathy include:

- Inability to focus the eye
- Double vision
- Aching behind one eye
- Bell's palsy (paralysis on one side of the face)
- Severe pain in the lower back or pelvis
- Pain in the front of a thigh
- Pain on the outside of the shin or inside of the foot
- Chest or abdominal pain that is sometimes mistaken for heart disease, a heart attack, or appendicitis

Focal neuropathy also includes radiculopathy and entrapment syndromes (e.g. carpal tunnel syndrome). Carpal tunnel syndrome causes tingling, numbness, and/or muscle weakness in the hand and occurs approximately three times more often among diabetics than in the general population. Other locations of entrapment syndrome include nerves outside the shin or on the inside of the foot ("tarsal tunnel syndrome").

In general, resolution or remission of pain from diabetic peripheral neuropathy appears to be

related to:

- Change of metabolic status (e.g., glycemic control)
- Weight loss
- Sensory loss that is not severe

Medical professionals involved in the care and treatment of diabetic neuropathy include an endocrinologist, neurologist, rehabilitation specialist, and physical and/or occupational therapist. Other professionals who may be involved include a social worker or vocational counselor.

To read more about diabetic peripheral neuropathy, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/18227494

Prediabetes and Peripheral Neuropathy

Increasing attention is being placed on a condition identified as *prediabetes* where blood glucose levels are higher than normal but not yet at the level of diabetes - i.e. between 140-200 mg/dL by an oral glucose tolerance test (OGTT), or between 100-126 mg/dL by a fasting plasma glucose test (FPG). Prediabetes is indicative of a condition called *insulin resistance* where the cells of the body do not use insulin properly to help absorb glucose that they need for energy. As a result, they continually send out a signal for more insulin. The pancreas produces more insulin to keep up with demand, but the levels of glucose in the blood continue to rise (*hyperglycemia*) which results in *impaired glucose tolerance* (IGT), another term for prediabetes.

There is increasing evidence that hyperglycemia resulting from insulin resistance is enough to damage or injure the very distal long axons of unmyelinated or slightly myelinated small fibers (toes and feet), and causes the first symptoms of peripheral neuropathy. It appears that the neuropathy of prediabetics is the same type as that of diabetics and causes the same symptoms, such as tingling, paresthesia, pain, and autonomic dysfunction, although perhaps not as intense or as widespread. There is also data to indicate that impaired glucose tolerance is more common among people with idiopathic peripheral neuropathy than commonly thought (up to 45% or more in one study) vs. impaired glucose tolerance in the general population (up to 14%).

In addition, IGT is one of a group of conditions that make up the *metabolic syndrome*, also common in prediabetics. The metabolic syndrome includes:

- Excess weight around the waist
- High triglycerides
- *Dyslipidemia* - low HDL (high-density lipoproteins) - the "good" cholesterol
- High blood pressure
- High fasting blood glucose levels

Investigators continue to examine the relationship between glucose intolerance, metabolic syndrome, and peripheral neuropathy.

The most effective management of prediabetes, advocated by the Diabetes Prevention Program, is

dietary changes and exercise. Evidence points to improvement of symptoms of peripheral neuropathy following these steps.

To read more about prediabetes and peripheral neuropathy, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/18195653

Cancer- and Chemotherapy-Induced Peripheral Neuropathy

Peripheral neuropathy is associated with several types of cancers and is thought to affect as many as 5% of cancer patients. Cancer-related neuropathies are usually caused by the spread of cancer to the nervous system or compression of a tumor on a nerve.

However, most cases of peripheral neuropathy experienced by cancer patients are caused not by the cancer itself, but by neurotoxic side effects of the chemotherapy used to treat the cancer. While chemotherapy is designed to destroy cancer cells, it also damages or destroys other healthy cells in the body, including peripheral nerve cells. Overall, the incidence of chemotherapy-induced neuropathy is thought to occur in 30-40% of cancer patients.

Chemotherapeutic agents interfere with the metabolic needs of the nerve cells which, in many cases, leads to degeneration or injury to the axon, myelin sheath, or cell body of sensory, motor and/or autonomic neurons. This causes intense, debilitating pain that can severely impact quality of life. In addition, chemotherapy-induced neuropathy is a dose-limiting factor, meaning that the dose of the particular chemotherapy must be reduced or stopped due to the intensity of the pain, which can adversely affect the efficacy of chemotherapy and ultimately, the survival of the patient.

Typically the neuropathy is a symmetrical, distal polyneuropathy that follows the 'stocking-glove' pattern where symptoms first appear at the most distal points which are the most vulnerable to injury (toes then fingers), and progress proximally towards the center of the body, a pattern called "dying back". The earliest symptoms, such as paresthesia, numbness, and pain in the hands and feet may occur between the first and third cycle of some chemotherapeutic agents. Pain is a particularly difficult symptom that many patients find hard to describe and is associated with depression more than any other type of pain. In particular, small fiber neuropathy, in addition to pain, causes distal impairment of temperature and sensitivity to pinprick. There also may be pain at light touch (allodynia) and in response to warm or cold stimuli. Most chemotherapy-induced neuropathies are mixed fiber neuropathies (large and small fibers).

Motor neuropathy is not as common as sensory neuropathy early in the chemotherapy-induced neuropathy process. If it develops, it usually occurs later, since motor axons are myelinated, which offers some protection from initial injury, whereas most sensory neurons are unmyelinated. Symptoms of motor neuropathy include weakness, muscle wasting, cramps, or fasciculation (muscular twitching).

Some chemotherapy-induced neuropathies are dose-related and worsen with cumulative doses. Some appear after the first dose while others may appear following several doses of medication

and may even develop after chemotherapy has been stopped, a process known as "coasting". Sensory symptoms are characterized as either *negative* (such as numbness), or *positive* (such as pain and paresthesia). Sensory disturbances are common to almost all chemotherapy-related neuropathies and have a significant impact on quality of life.

The appearance of peripheral neuropathy associated with chemotherapy generally follows a pattern, namely:

- Symptoms initially appear distally in toes and feet and progress proximally.
- When the symptoms have progressed up the legs to approximately the level of the knees or above, symptoms may begin to be felt in the fingertips.
- Symptoms may form a "tear-drop" pattern around the abdomen.
- Patients may experience *myalgia* (muscle pain) or muscle cramps that are exacerbated by activity.
- Autonomic symptoms such as dry mouth or orthostatic hypotension (drop in blood pressure when changing from a sitting to standing position) may develop.
- Pain may develop with some neuropathies and may be severe.

Chemotherapy agents that are neurotoxic include:

- Platinum-based drugs (cisplatin, oxaliplatin, and carboplatin):
    - These are highly associated with small fiber sensory neuropathy, though large fiber nerves may be affected.
    - Platinum-based drugs are uniquely identified by pure sensory involvement
    - Up to 60% of patients receiving platinum-based medications suffer from peripheral neuropathy.
    - Symptoms may persist or progress for several months beyond the treatment period.
    - Platinum drugs are dose-limiting for many patients, which may affect efficacy of therapy as well as survival.
    - Coasting (reaching an improvement plateau) has been reported when oxaliplatin or cisplatin are discontinued, where neuropathy may progress for up to two months. After a plateau, there may be gradual improvement, although many patients continue to experience residual pain that may last for several years after cessation of therapy.
    - Cisplatin-related neuropathy is closely related to the total cumulative dose and symptoms typically appear three to six months after treatment begins; all sensory modalities are involved but loss of large fiber sensory function is often prominent.
    - Oxaliplatin-related neuropathy develops in 60-80% of patients and is the most frequent reason for dose-limitation. Paresthesias occur within 30-60 minutes of administration, usually in the second or third course of therapy. They are described as tingling or burning and are induced by contact with cold surfaces or liquids and occur in the throat, mouth, face, and hands.
    - Carboplatin is less neurotoxic at lower doses, but high doses produce a neuropathy that is similar to that of cisplatin. Approximately 20% of patients develop moderate to severe neuropathy when carboplatin is combined with paclitaxel.
- Taxanes (paclitaxel and docetaxel):

- Taxanes cause degeneration and demyelination of the axon.
- They affect autonomic cardiovascular function (e.g., blood pressure).
- Symptoms may include burning, dysesthesia (abnormal, unpleasant sensation), or paresthesia (prickling or numbness).
- Acute tingling in fingertips and toes may occur within 24 hours of the paclitaxel infusion.
- Sensory loss from paclitaxel develops in up to 70% of patients.
- Neuropathy from paclitaxel appears in some patients after the first dose and tends to increase with prolonged treatment.
- Sensory loss from docetaxel occurs in up to 50% of patients.
- Docetaxel is not as neurotoxic as paclitaxel and patients may experience spontaneous recovery when treatment is discontinued.
- In general, patients may experience improvement in symptoms from neuropathy when therapy is delayed or completed.
- When combined with platinum-based drugs, a high percentage of patients develop sensorimotor neuropathy.

- Vinca alkaloids (vinorelbine, vincristine, vindesine, and vinblastine):

  - All vinca-based drugs produce a dose-related sensorimotor neuropathy, with vinorelbine and vinblastine being less toxic than vincristine and vindesine.
  - Paresthesia (abnormal sensations; tingling) and pain in the hands and feet are early symptoms in up to 60% of patients.
  - Muscle weakness and muscle cramps are frequent symptoms.
  - These are considered to be the least neurotoxic of the chemotherapeutic agents.

- Newer agents

  - Thalidomide causes neuropathy in approximately 20-40% of patients. Its effects on the nervous system are long-lasting and while some patients recover slowly, others do not recover at all. Although early symptoms include numbness and paresthesia in hands and feet as well as leg cramps, the predominant feature is a sensory neuropathy with the loss of all sensory modalities. Thalidomide-associated neuropathy typically increases with age and cumulative dose over the duration of treatment.
  - Lenolidamide is a more potent analog of thalidomide but less toxic for neuropathy and somnolence.
  - Bortezomib-related neuropathy is dose-related and cumulative. Severe neuropathy is typically sensory, begins distally, and often involves cessation of treatment due to neuropathic pain. Motor function usually remains normal. Neuropathy is reversible and symptoms usually dissipate after cessation of treatment.
  - Etoposide is associated with a mild, sometimes moderate sensorimotor neuropathy.
  - Gemcitabine results in mild paresthesias during treatment in approximately 10% of cases.
  - Cytosine arabinoside (ara C) causes a demyelinating polyneuropathy in approximately 1% of patients.
  - Bivacizumab is a new biological agent that has been associated in case reports with

optic neuropathy.
- ZD6474 (Zactima) has been shown to be effective with relapsed multiple myeloma, colon, and lung cancers, but is associated with Grade 1-2 sensory neuropathy in approximately 20% of patients.

In addition to pain and numbness, other neuropathic symptoms associated with chemotherapy include:

- Allodynia (pain due to a stimulus which does not usually cause pain, e.g., light touch)
- *Acroparesthesia* (tingling/numbness, stiffness in fingers, hands, forearms, and legs); this is often the earliest and most persistent symptom
- Muscle weakness
- Hypoflexia (diminished muscle reflexes)
- Autonomic symptoms such as:

    - postural hypotension - drop of blood pressure with postural or positional change; it is one of the most common manifestations of autonomic involvement
    - cardiac irregularities
    - bladder/bowel dysfunction

Recovering from chemotherapy-related peripheral neuropathy can be very slow and sometimes symptoms may be even more intense during the recovery period. Regenerating nerves can cause cramping and paresthesia that are severe and significantly interfere with daily activities. Patients who had previous neuropathy are at highest risk for developing chemotherapy-related peripheral neuropathy. As cancer treatment evolves with the use of higher doses of drugs and combinations of increasingly potent drugs, the number of cases of chemotherapy-related peripheral neuropathy is expected to increase.

To read more about chemotherapy-related peripheral neuropathy, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/20156778

Peripheral Neuropathy and Pregnancy

Although peripheral neuropathy is not common in pregnancy, it is important that if it does occur, it be recognized and treated quickly since it has the potential (though a rare occurrence) to harm the mother and the fetus. Typically, symptoms associated with peripheral neuropathy during pregnancy are more bothersome than dangerous and they usually resolve after birth.

Neuropathies that may occur during pregnancy include:

- Mononeuropathy

    - Facial nerve (Bell's palsy) - Risk for developing this condition during or immediately following pregnancy is three times higher than for women who are not pregnant; the

most common period for development of Bell's palsy is in the third trimester or two weeks following birth (postpartum). Typically there is complete or near complete recovery of facial strength. Treatment includes steroids to control overall symptoms and ocular lubrication to manage dry eye.

- Carpal tunnel syndrome - The incidence of carpal tunnel syndrome is higher among pregnant women than among the general population. It typically presents as pain at night and sensory abnormalities such as loss of sensation along the median nerve of the arm. Management is usually conservative since symptoms almost always resolve after childbirth. One study showed that 76% of cases resolved up to one month postpartum. Treatment includes wearing wrist orthoses, controlling edema, and avoiding occupational or other activities which exacerbate the condition.

- Polyneuropathy

  - Acute Immune Demyelinating Polyneuropathy (AIDP), also known as *Guillain-Barre syndrome*, presents with an ascending symmetric weakness of the legs that can be quite severe, and paresthesia. Reflexes are usually lost. AIDP develops most often in the third trimester. It is often preceded (approximately 65% of cases) by a viral syndrome. Respiratory function may be compromised and mechanical ventilation may be necessary in late pregnancy, a situation which raises the mother's risk for several other problems such as premature labor or thromboembolism. Management includes prevention of embolism and its complications, good hydration, continued observation for signs of autonomic dysfunction, plasmapheresis (a blood purification procedure), and/or intravenous immunoglobulin (IVIG).
  - Chronic Immune Demyelinating Polyneuropathy (CIDP) - a sensory motor neuropathy. Onset is slower than AIDP and may follow a relapsing-remitting course. Symptoms may worsen during the last trimester or in the postpartum period. As with women who are not pregnant, management may include IVIG, plasmapheresis, and/or steroids.
  - Diabetic neuropathy - a sensorimotor neuropathy that usually does not worsen during pregnancy but has a higher risk of developing during the postpartum period than in nondiabetic pregnant women. There is a direct relationship between the development or exacerbation of diabetic neuropathy during or immediately following pregnancy and glycemic control.
  - *Nutritional neuropathy* - typically related to a vitamin deficiency, most commonly vitamin B1 (thiamine) and vitamin B6. Thiamine deficiency causes sensorimotor neuropathy which is usually managed with intravenous thiamine and better attention to the inclusion of thiamine in the diet. Neuropathy almost always improves with treatment.
  - *Toxic neuropathy* - usually related to medications taken by the mother. It has been associated with *nitrofurantoin* (Macrobid™, Furadantin™), an antibiotic prescribed for urinary tract infections. There is concern that the fetus may also develop neuropathy if this drug is given during the first trimester. Symptoms for the mother can be profound and may linger even after the medication is discontinued.
  - Hereditary polyneuropathy -a demyelinating polyneuropathy such as Charcot-Marie-Tooth_ (CMT), which may become exacerbated during pregnancy in women who developed symptoms earlier in life. Approximately one-third of women

with CMT experience a worsening of their symptoms during pregnancy. The greatest difficulty caused by symptoms of demyelinating polyneuropathy relates to walking, as women may fall or lose their balance.

For further information about peripheral neuropathy and pregnancy, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/18194755

3 - Guide to the Medical Literature

Introduction

This section of your *MediFocus Guidebook* is a comprehensive bibliography of important recent medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest advances in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new developments, and advances in research.

To facilitate your review and analysis of this information, the articles in this *MediFocus Guidebook* are grouped in the following categories:

- Review Articles - 59 Articles
- General Interest Articles - 33 Articles
- Clinical Trials Articles - 29 Articles
- Diabetic Neuropathy Articles - 23 Articles
- Chemotherapy and Neuropathy Articles - 6 Articles

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Title of the article
- Name of the authors
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)
- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the URI that is provided for each cited article. If you purchased a printed copy of the *MediFocus Guidebook*, you can still access the abstracts online by entering the individual URI for a particular abstract into your computer's web browser.

Recent Literature: What Your Doctor Reads

Database: PubMed <January 2012 - January 2017>

Review Articles

1.

Chemotherapy-induced peripheral neuropathy: Current status and progress.

Authors: Brewer JR; Morrison G; Dolan ME; Fleming GF
Institution: Section of Hematology-Oncology, Department of Medicine, University of Chicago Medical Center, 5841 S. Maryland Ave, Chicago, IL 60637, United States.; Section of Hematology-Oncology, Department of Medicine, The University of Chicago, Knapp Center for Biomedical Discovery, 900 East 57th Street, Chicago, IL 60637, United States. Electronic address: gfleming@medicine.bsd.uchicago.edu.
Journal: Gynecol Oncol. 2016 Jan;140(1):176-83. doi: 10.1016/j.ygyno.2015.11.011. Epub 2015 Nov 7.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=NR021&ID=26556766

2.

Management of critical limb ischemia in the patient with diabetes.

Authors: Forsythe RO; Hinchliffe RJ
Institution: Centre for Cardiovascular Science, University of Edinburgh, Chancellor's Building, Edinburgh, UK - rhinchli@sgul.ac.uk.
Journal: J Cardiovasc Surg (Torino). 2016 Apr;57(2):273-81. Epub 2015 Dec 2.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=NR021&ID=26632661

The **Guide to the Medical Literature** in the complete **Medifocus Guidebook on Peripheral Neuropathy** includes the following sections:

- Review Articles - 59 Articles
- General Interest Articles - 33 Articles
- Clinical Trials Articles - 29 Articles
- Diabetic Neuropathy Articles - 23 Articles
- Chemotherapy and Neuropathy Articles - 6 Articles

To Order the Complete **Guidebook on Peripheral Neuropathy** Click Here
Or Call 800-965-3002 (USA) or 301-649-9300 (Outside USA)

4 - Centers of Research

This section of your *MediFocus Guidebook* is a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition. The *Centers of Research* directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of this disorder.

Use the *Centers of Research* directory to contact, consult, or network with leading experts in the field and to locate a hospital or medical center that can help you.

The following information is provided in the *Centers of Research* directory:

- **Geographic Location**
    - United States: the information is divided by individual states listed in alphabetical order. Not all states may be included.
    - Other Countries: information is presented for select countries worldwide listed in alphabetical order. Not all countries may be included.
- **Names of Authors**
    - Select names of individual authors (doctors, researchers, or other health-care professionals) with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition, who have recently published articles in leading medical journals about the condition.
    - E-mail addresses for individual authors, if listed on their specific publications, is also provided.
- **Institutional Affiliations**
    - Next to each individual author's name is their **institutional affiliation** (hospital, medical center, or research institution) where the study was conducted as listed in their publication(s).
    - In many cases, information about the specific **department** within the medical institution where the individual author was located at the time the study was conducted is also provided.

Centers of Research

United States

AL - Alabama

Name of Author	Institutional Affiliation
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The **Centers of Research** in the complete **Medifocus Guidebook on Peripheral Neuropathy** includes the following sections:

- Centers of Research for relevant states in the United States
- Centers of Research listed for relevant countries outside the United States

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5 - Tips on Finding and Choosing a Doctor

Introduction

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver a high level and quality of medical care in accordance with currently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it.

The process of finding and choosing a physician to manage your specific illness or condition is, in some respects, analogous to the process of making a decision about whether or not to invest in a particular stock or mutual fund. After all, you wouldn't invest your hard eared money in a stock or mutual fund without first doing exhaustive research about the stock or fund's past performance, current financial status, and projected future earnings. More than likely you would spend a considerable amount of time and energy doing your own research and consulting with your stock broker before making an informed decision about investing. The same general principle applies to the process of finding and choosing a physician. Although the process requires a considerable investment in terms of both time and energy, the potential payoff can be well worth it--after all, what can be more important than your health and well-being?

This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Tips for Finding Physicians

Finding a highly qualified, competent, and compassionate physician to manage your specific illness or condition takes a lot of hard work and energy but is an investment that is well-worth the effort. It is important to keep in mind that you are not looking for just any general physician but rather for a physician who has expertise in the treatment and management of your specific illness or condition. Here are some suggestions for where you can turn to identify and locate physicians who specialize in managing your disorder:

- **Your Doctor** - Your family physician (family medicine or internal medicine specialist) is a good starting point for finding a physician who specializes in your illness. Chances are that your doctor already knows several specialists in your geographic area who specialize in your illness and can recommend several names to you. Your doctor can also provide you with information about their qualifications, training, and hospital affiliations.

The **Tips on Finding and Choosing a Doctor** in the complete **Medifocus Guidebook on Peripheral Neuropathy** includes additional information that will assist you in locating a highly qualified and competent physician to manage your specific illness.

To Order the Complete **Guidebook on Peripheral Neuropathy** Click Here
Or Call 800-965-3002 (USA) or 301-649-9300 (Outside USA)

6 - Directory of Organizations

American Academy of Neurology
1080 Montreal Avenue; St. Paul, Minnesota 55116
800.879.1960 651.695.2717
memberservices@aan.com
www.aan.com

American Academy of Pain Management
13947 Mono Way; #A; Sonora, CA 95370
209.533.9744
aapm@aapainmanage.org
www.aapainmanage.org

American Academy of Pain Medicine
4700 W. Lake; Glenview, IL 60025
847.375.4731
info@painmed.org
www.painmed.org

American Association of Neurological Surgeons
5550 Meadowbrook Drive; Rolling Meadows, IL 60088
888.566.2267
info@aans.org
www.neurosurgerytoday.org

American Chronic Pain Association
POB 850; Rocklin, CA 95677
800.533.3231
ACPA@pacbell.net
www.theacpa.org

American Diabetes Association
1701 North Beauregard Street; Alexandria, VA 22311
800.342.2383
askada@diabetes.org
www.diabetes.org

The **Directory of Organizations** in the complete **Medifocus Guidebook on Peripheral Neuropathy** includes a list of selected disease organizations and support groups that are helping people diagnosed with Peripheral Neuropathy.

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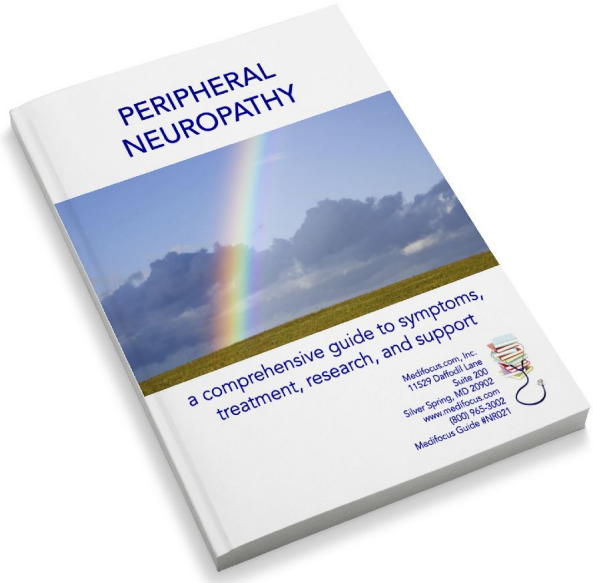

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Peripheral Neuropathy**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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