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Medications for diabetic neuropathic pain

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Advances in the management of painful diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN), one of the most common complications that occur in patients with diabetes mellitus (DM), leads to an increase in morbidity and mortality rate. This article will review the pathophysiological mechanisms, the current pharmacological treatment strategies for painful DPN, as well as the protocols for prevention and potential future therapeutic options for treatment.

Epidemiology

It has been shown that DPN can occur in as many as 50% of patients with DM.[1] Indeed some studies have demonstrated that clinical and sub-clinical neuropathies affect 10-100% of diabetic patients.[2,3]

Compared to Caucasians, Hispanics and African-Americans are more prone to secondary complications and hospitalisations from DPN.[4] It tends to occur earlier in male patients with type 2 DM, while neuropathic pain causes more morbidity in females.[5]

With regard to signs and symptoms, a study from Northwest England, that included 15,692 diabetic patients, indicated that the prevalence of clinical neuropathy was 49%, whereas the prevalence of painful neuropathic symptoms was 34%. The risk of painful neuropathy increases in patients with type 2 DM, in women and those of South Asian ethnicity.[6] DPN can occur at any age but the incidence increases with age.

A study performed in the UK, which included 6487 diabetic patients, showed that the overall prevalence of DPN was 28.5%, reaching 44% in patients between 70-79 years of age [7]

A population-based study of 329 adults with type 1 DM and 70 adults with type 2 DM showed that the incidence of DPN was higher with type 2 compared with type 1 DM (26 vs 8%).[8] The cumulative risk of lower extremity amputation in one report was 11% 25 years after diagnosis of DM.[9]

Classifications

***Distal symmetric sensorimotor poly-neuropathy*:** The most common type of neuropathies affects approximately 50% of diabetic patients. There is progressive loss of sensory axons. In severe cases, the motor axonal nerve may be injured.

***Autonomic neuropathy*:** This affects approximately 7% of diabetic patients, and may cause postural hypotension, gastro-paresis, and enteropathy with constipation or diarrhea.

Poly-radiculopathies: Asymmetric proximal set of conditions. The location of the injury is at the level of the proximal limb and nerve roots.

***Thoracic or lumbar neuropathies*:** DM may damage the thoracic or high lumbar levels nerve roots with subsequent axonal degeneration and frequent contralateral, cephalic, or caudal extension, in about 3% of diabetic patients. These neuropathies are responsible for the poly-radiculopathies.

***Lumbar poly-radiculopathy*:** Also known as diabetic amyotrophy. The exact cause is unclear; the most likely is ischemic injury from non-systemic micro-vasculitis. The clinical presentation of diabetic amyotrophy includes acute asymmetric focal onset of pain, followed by weakness of the proximal leg. Autonomic failure and weight loss may also occur. The contralateral leg may also be affected immediately, within days or later within months to years after the initial attack.

***Thoracic poly-radiculopathy*:** Less common subtype of diabetic polyradiculopathy. Affected patients suffer from severe abdominal pain, sometimes in a band-like pattern.

***Diabetic neuropathic cachexia*:** A rare diffuse type of diabetic poly-radiculopathy; characterised by unintended severe weight loss and depression. It frequently occurs in middle-aged or older males with type 2 DM

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who are on oral hypoglycemic agents. Most patients recover spontaneously within 12-24 months

***Mono-neuropathies*:** Divided into two sub-types, which are cranial and peripheral mononeuropathy. Cranial mono-neuropathy is the most common mononeuropathy that affects the supplier nerves of the extra-ocular muscles, especially cranial nerves III (oculomotor), IV (trochlear and VI (abduces). Diabetic ophthalmoplegia is characterised by unilateral pain, ptosis, and diplopia, with sparing of pupillary function. Facial mono-neuropathy, also known as Bell's palsy, is noticed more in diabetic than in non-diabetic patients. The most frequent peripheral mono-neuropathy is median mono-neuropathy, which occurs at the wrist.

***Multiple mono-neuropathies*:** Also known as mono-neuropathy multiplex or asymmetric poly-neuropathy. Vasculitis could also be considered since it is the major disorder that may cause this syndrome.

Acute painful diabetic neuropathy

There are several types of acute painful DPN syndromes, such as treatment-induced DPN (TIND), diabetic neuropathic cachexia and diabetic anorexia, which is caused by intentional weight loss. Any patient with any of these conditions may suffer from severe neuropathic pain, autonomic dysfunction and a potentially reversible course that may last for many months. TIND that affects small fibers, also known as insulin neuritis, is induced by rapid reduction of blood glucose. The main clinical manifestations are serious, such as treatment-resistant pain and autonomic dysfunction, as well as retinopathy and nephropathy. The exact cause of TIND is unclear; however, suggested mechanisms involve endoneurial edema and ischemia, apoptosis from glucose deprivation, and microvascular neuronal injury due to recurrent hypoglycemia.

Clinical Presentation

The signs and symptoms of DPN differ, depending on nerves injured, and the type of neuropathy. Symmetrical lower-limb poly-neuropathies are the most common clinical manifestations in most patients with DM after a few years. Patients with DPN experience two types of clinical symptoms that are sensory: categorised into negative or positive or motor: categorised into proximal, distal and focal or diffuse. Patients with negative symptoms feel numbness or deadness, which is similar sensation to wearing gloves or socks. On the other hand, patients with positive sensory symptoms feel tingling, burning, an “electric shock” sensation, aching or hypersensitivity to touch. Motor symptoms may affect the hands and impair coordination. Moreover, the motor symptoms may involve the limbs, leading to frequent falling or weakness in the knees.

On the other hand, autonomic neuropathy may involve the large or small nerve fibers of the major organ systems such as the gastrointestinal, cardiovascular and genitourinary systems.

If small nerve fibers are injured, patients may experience GI symptoms such as difficulty in swallowing, abdominal pain, nausea, vomiting and diarrhea, and genitourinary symptoms such as poor urinary flow, impotence and voiding difficulties, or cardiovascular symptoms such as orthostatic hypotension, arrhythmias, increased heart rate and near-syncope. However, if large nerve fibers are injured, patients may experience pain or numbness, uncoordinated movement or muscle fatigue. Severe, painful DPN is characterised by sleeplessness, depression, nervousness, activity impairments and a reduced quality of life. Progressive skin ulcers, amputations and death may occur if DPN remains undiagnosed and untreated.

Diagnosis

Early diagnosis is necessary to prevent severe complications. DPN is highly suspected in any patient with type 1 DM for more than five years or newly diagnosed with type 2 DM, as well as any patient with idiopathic painful neuropathy because of pre-diabetic condition. Until around 1988, the diagnosis of DPN was based on signs and symptoms. Subsequently, an intensive set of criteria was developed to diagnose DPN based on symptom scores. However, they are not particularly useful in clinical practice.

The Michigan Neuropathy Screening Instrument (MNSI) is a simple screening test to diagnose DPN in outpatient clinics. The UK screening test (UKST) is a useful diagnostic test that contains a simple symptom score and physical examination. The tuning fork test is a simple, valid and reliable neurological examination to screen for DPN in clinical practice.

Other conditions that should be eliminated, during the diagnosis of DPN, are chronic inflammatory de-myelinating polyneuropathy, vitamin B12 deficiency, hypothyroidism and uremia.

Pathophysiology

The occurrence of neuropathic symptoms depends on many factors such as hyperglycemia, hypertension, dyslipidemia, increased weight, smoking and

exposure to neurotoxic agents such as ethanol. Some biochemical mechanisms such as the polyol pathway, advanced glycylation end products (AGEs) and oxidative stress are important in the development of the symmetrical forms of diabetic poly-neuropathies.

The accumulation of sorbitol and fructose inside the cells decreases the activity of Na/K-ATPase, increases cell osmolality, decreases nerve myo-inositol and impairs axonal transport leading to propagation of an abnormal action potential. Al-dose reductase inhibitors may be clinically used in the future to improve nerve conduction. In chronic hyperglycemia, excess glucose may interact with amino acids, nucleotides or proteins in the circulation or tissues by a non-enzymatic reaction involving formation of advanced glycosylation products (AGEs). Vascular injury occurs by increase in vascular permeability and monocyte influx.

Hyperglycemia may increase the production of oxidative stress and reactive oxygen species and reduce antioxidant defense. As a result, peripheral nerve damage occurs leading to nerve ischaemia and facilitation of AGE reactions. Thus, the use of antioxidant alpha-lipoic acid may hold promise for improving neuropathic symptoms.

Another factor is the disruption of the hexosamine pathway. Excess glucose in patients with hyperglycemia may bypass the glycolytic intermediates into the hexosamine pathway and enhance the formation of uridine diphosphate-N-acetyl glucosamine (UDPGlcNAc) leading to cellular damage and enhanced oxidative stress. Studies have shown that oral benfotiamine may reduce both oxidative stress and hexosamine-modified proteins and is a potential therapy in men with type 1 diabetes.

The conversion of the excess glucose to diacylglycerol leads to the activation of protein kinase C (PKC), which is responsible for vasoconstriction and nerve hypoxia. The disturbance of the PKC pathway potentiates neurovascular alterations that predispose to DPN. Animal studies indicate that inhibitors of PKC activation enhance nerve conduction and correct the reduction of the nerve blood flow in diabetic rats.

Furthermore, high glucose may stimulate activation of the nuclear enzyme poly ADP-ribose polymerase (PARP). The activation of the PARP pathway may lead to development of DPN. The use of PARP inhibitors showed significant improvements in neuropathic symptoms and can be used in the future.

Ischemia has metabolic consequences that may be aggravated by insulin deficiency and hyperglycemia. Autopsy samples of diabetic patients with advanced polyneuropathy showed thick endoneural blood vessel walls or vascular occlusions. Retrospective studies showed that impairment of anti-thrombotic mechanisms plays a role in the development of DPN. This is confirmed by the low levels of thrombomodulin and tissue plasminogen activator in peripheral nerve microvessels of diabetic patients.

Hyperglycemia is responsible for the loss of the neurotrophic peptides that physiologically mediate nerve repair, regeneration and tonic conservation, leading to the impairment of peripheral nerve repair mechanisms. Insulin is a neurotrophic factor for peripheral neurons, and therefore insulin deficiency in type1 diabetic patients may compromise nerve integrity and impair the maintenance of peripheral nerve fibers.

The variation of gene expression may alter cellular phenotypes. There will be changes in cell physiology and reduction in neurotrophins. Clinical trials of the neurotrophin human recombinant nerve growth factor, were inconclusive.

Prevention therapies

For the prevention of DPN, optimal glucose control is necessary. Glucose control enhances the improvements in surrogate measures of neuropathy, including nerve conduction velocity and vibration perception thresholds. In addition, clinical experience has suggested that vigorous glycaemic control is associated with improvement in symptoms for patients who develop acute painful DPN after a period of extreme hyperglycaemia such as diabetic ketoacidosis (DKA).[10]

Regular foot examination is essential to prevent ulceration and infection and avoid the need for amputation.[11] Maintaining normal blood pressure, exercising regularly and smoking avoidance/cessation are also recommended.[12] Limiting the amount of alcohol intake, maintaining a healthy weight by eating a suitable diet and avoiding high levels of lipids in the blood, and regular follow-up by health care providers is also important.

Pharmacological treatment strategies for painful DPN

Sometimes the pain may resolve spontaneously.[13] A previously silent nerve may recover by improving glucose level, leading to spontaneous firing and the perception of pain. Remission is suspected if the symptoms start after a sudden metabolic change, including episode of DKA or occasionally an improvement in glycaemic control, when the duration of diabetes was relatively short, or when marked weight loss preceded the onset of pain.[14]

Therapeutic classes

Treatments for painful DPN include a number of anti-depressants, capsaicin cream and anti-convulsants. Other treatments include lidocaine patch, alpha-lipoic acid and isosorbide dinitrate topical spray.[15]

Tricyclic antidepressants

Tricyclic antidepressants, such as amitriptyline and desipramine, reduce neuropathic symptoms in patients with painful DPN by inhibiting re-uptake of serotonin and norepinephrine by presynaptic neuronal cells and increasing the synaptic concentration in the CNS. The therapeutic effect occurs within two weeks and continues to increase at six weeks, and at lower doses compared to that given for treatment of depression.[16] Desipramine is an alternative for amitriptyline due to its fewer anticholinergic side effects compared to amitriptyline.

Dual serotonin and norepinephrine reuptake inhibitor anti-depressant (SNRIs)

SNRIs are anti-depressant drugs effective for treating pain in DPN.[17] Since all the studies that have shown the effectiveness of duloxetine or venlafaxine were of short duration, long-term effectiveness and safety are uncertain.[18] Comparative trials indicate that amitriptyline could be as effective as duloxetine for treatment of painful DPN, and is less expensive. Venlafaxine is another drug that belongs to the SNRI family.[19]

Anti-convulsants

Both newer anti-convulsants, such as pregabalin, and classic ones such as valproate, are used for treating painful DPN. Pregabalin is a second generation FDA approved first line anti-convulsant for treatment of pain described as dysesthetic, such as burning or pins and needles.[20] Pregabalin binds to the alpha2-delta subunit of voltage-gated calcium channels. Pregabalin is structurally similar to gabapentin except for the activity at GABA or benzodiazepine receptors.[21] Another second generation anti-convulsant is gabapentin. It increases the brain GABA levels, binds to the alpha2-delta subunit of voltage gated calcium channels and inhibits branched chain amino acid transferase. Two small placebo-controlled trials showed that valproic acid may reduce pain in DPN; however, there is insufficient evidence to support its use as a first-line treatment for DPN.[22] Carbamazepine has not been evaluated in recent randomised trials for the treatment of painful DPN.[23]

Capsaicin

Capsaicin is a natural product extracted from plants of *Solanaceae* family that causes analgesia by local depletion of substance P, preventing its accumulation in peripheral sensory neurons, since substance P is a chemomediator of pain transmission from the periphery to the CNS. It is available for topical applications : cream, gel, liquid, lotion and patch. Capsaicin cream can be given for patients with symptomatic painful DPN who are refractory to or intolerant to anti-depressants or anti-convulsants.[24]

Anaesthetic drugs

A systematic review published in 2011 found that the evidence for the effectiveness of anaesthetic drugs such as mexiletine is controversial. The highest-quality trial reported no significant advantage of mexiletine over placebo. On the other hand, other studies showed beneficial effects, especially if a local effect is required.[25]

Isosorbide dinitrate

A placebo-controlled pilot trial of isosorbide dinitrate topical spray in 22 diabetic patients showed a remarkable reduction in overall neuropathic pain and burning sensation in the treatment group.[26]

Opioids

Several studies support efficacy of opioids such as dextromethorphan, tramadol, morphine sulphate and oxycodone CR. Dextromethorphan, a weak sigma opioid receptor agonist and an N-methyl-D-aspartate (NMDA) receptor antagonist, was moderately effective compared with placebo, according to two small trials, for reducing pain in patients with DPN. Several low-quality randomised controlled trials suggest that controlled-release oxycodone may be effective for treatment of painful DPN. However, these trials lacked evidence of long-term effectiveness because of the potential for abuse, addiction and overdose, and other potential sources of bias. Some experts have opposed the use of opioids for treatment of painful DPN.[24]

Acute painful neuropathy

For a patient with acute painful neuropathy, simple analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) can manage the pain. They can be used as first line treatment in painful DPN; however, in chronic painful DPN, they are not effective and need to be managed with treatment with off-label medications. Ibuprofen and naproxen are NSAIDs that control pain by decreasing the inflammation caused by DPN by reduction of cyclooxygenase (COX) activity, which lowers prostaglandin (PG) synthesis. Moreover, NSAIDs are beneficial in patients with musculo-skeletal or joint deformities due to long-standing neuropathy; the joint abnormalities may actually be the main source of pain.[20]

Table 1. Summary of the pharmacological treatment of diabetic peripheral neuropathy

Medication	FDA approved	Dosage	Side effects	Comments
Amitriptyline	No	25-100 mg at bedtime	Dry mouth, urinary retention, sedation, vertigo, constipation	Inferior to Duloxetine or Venlafaxine Contraindication: Patients older than 60y old
Desipramine	No	10-25mg titrated to 100-150 mg at bedtime	Dry mouth, sedation, dizziness, confusion, constipation, urinary retention, blurred vision, weight gain, arrhythmias.	Superior to Amitriptyline (lower anti-cholinergic SE, less sedation) Preferred for elderly patients
Duloxetine	Yes	60mg/day	Nausea, somnolence, hyperhidrosis, anorexia, vomiting, constipation, fatigue, dry mouth	First drug approved for treatment of DPN Avoid use in hepatic impairment ml/min**30** Avoid use if CrCl >
Venlafaxine	No	75-225 mg/ day	Nausea, somnolence, ECG changes	May be added to gabapentin for better response
Carbamazepine	No	600mg/day (200 mg TID) to 800 mg daily (200 mg QID)	Agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus, aplastic anemia	Observe for excessive sedation
Gabapentin	No	900-3600 mg/ day in 3 divided doses	Dizziness, somnolence, diarrhea, fatigue, GI upset, peripheral edema	Reduce dosage if GFR < 60 ml/min
Pregabalin	Yes	150mg/day (50 mg TID) to 300mg/day (100 mg TID)	Somnolence, dizziness, peripheral edema, weight gain	Second agent approved for treatment of DPN. May lead to physical or psychological dependence
Valproate sodium	No	500-1200 mg/ day in 2 or 3 doses	Elevated liver enzymes, nausea	-
Morphine sulfate	No	15-30 mg every 12 - 24 h	Constipation, Somnolence, dizziness, nausea, vomiting, itchiness	Chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia. Data are insufficient to recommend this drug over oxycodone, dextromethorphan, or tramadol
Oxycodone CR	No	Max dosage: 120 mg/day in 2 doses of CR formulation	Constipation, Somnolence, dizziness, nausea, vomiting, itchiness	Chronic use may lead to tolerance, frequent dose escalation, hyperalgesia. Data insufficient to recommend this drug over oxycodone, dextromethorphan or tramadol
Dextro methorphan	No	400 mg/day in 4 divided doses	Sedation (at recommended doses)	Dissociative anesthetic with powerful psychedelic effects at higher doses. Data insufficient to recommend this drug over oxycodone, dextromethorphan or tramadol
Tramadol	No	210 mg/day in 2 or 4 divided doses	Nausea, sedation, constipation, headache, dry mouth, urinary retention confusion, tremor, seizures	Data insufficient to recommend this drug over oxycodone or dextromethorphan
Capsaicin cream	No	0.075% TID or QID	Stinging, burning, itching, coughing, sneezing, rash	May be used as adjunct to oral medications
Lidocaine patch	No	Applied once up to 12 h within 24 h period	Application site reactions (blisters, bruising, burning sensation, de-pigmentation, dermatitis)	May be used as adjunct to oral medications

Combination treatment

The benefit of combination treatment was small but statistically significant. Gabapentin combined with morphine was more effective than either drug alone for reducing the intensity of pain during week four of treatment at the maximum tolerated daily dose.[27]

The combination of nortriptyline with gabapentin was more effective than either agent alone for reducing the mean intensity of daily pain during week four of treatment at the maximum tolerated daily dose (nortriptyline 50 mg and gabapentin 2180 mg in combination). Another study stated that the most common side effects of the combination therapy were constipation, sedation and dry mouth.[28]

Diabetic neuropathy complications

Bladder hypocontractility

Bethanecol hydrochloride may be used in patients with DPN who suffer from bladder hypo-contractility since it acts to produce contraction to initiate micturition and empty the bladder; however, it is rarely used due to difficulty in timing effect and gastrointestinal stimulation.[29]

Orthostatic hypotension

Some patients with DPN may experience orthostatic hypotension, if the table salt and pressure stockings fail to control the condition. Fludrocortisone acetate can be used to increase the standing blood pressure by increasing the sodium retention and expanding the plasma volume.[30]

Digestive problems

For occasional constipation due to DPN, isotonic polyethylene glycol may be used since it is not absorbed and continues to hold water by osmotic action through the small bowel and colon, resulting in mechanical cleansing. Isotonic polyethylene glycol has lower chance of dehydration and electrolyte imbalance compared with hypertonic sugar solution.[31]

Sexual dysfunction

Patients with DPN may suffer from erectile dysfunction, a difficult condition to treat. Once the diagnosis is confirmed, sildenafil or any other related phosphodiesterase type 5 inhibitor (PDE5 inhibitors) is recommended. Other classic methods including vacuum devices or intra-cavernosal papaverine injections may be useful.[32]

Gustatory sweating

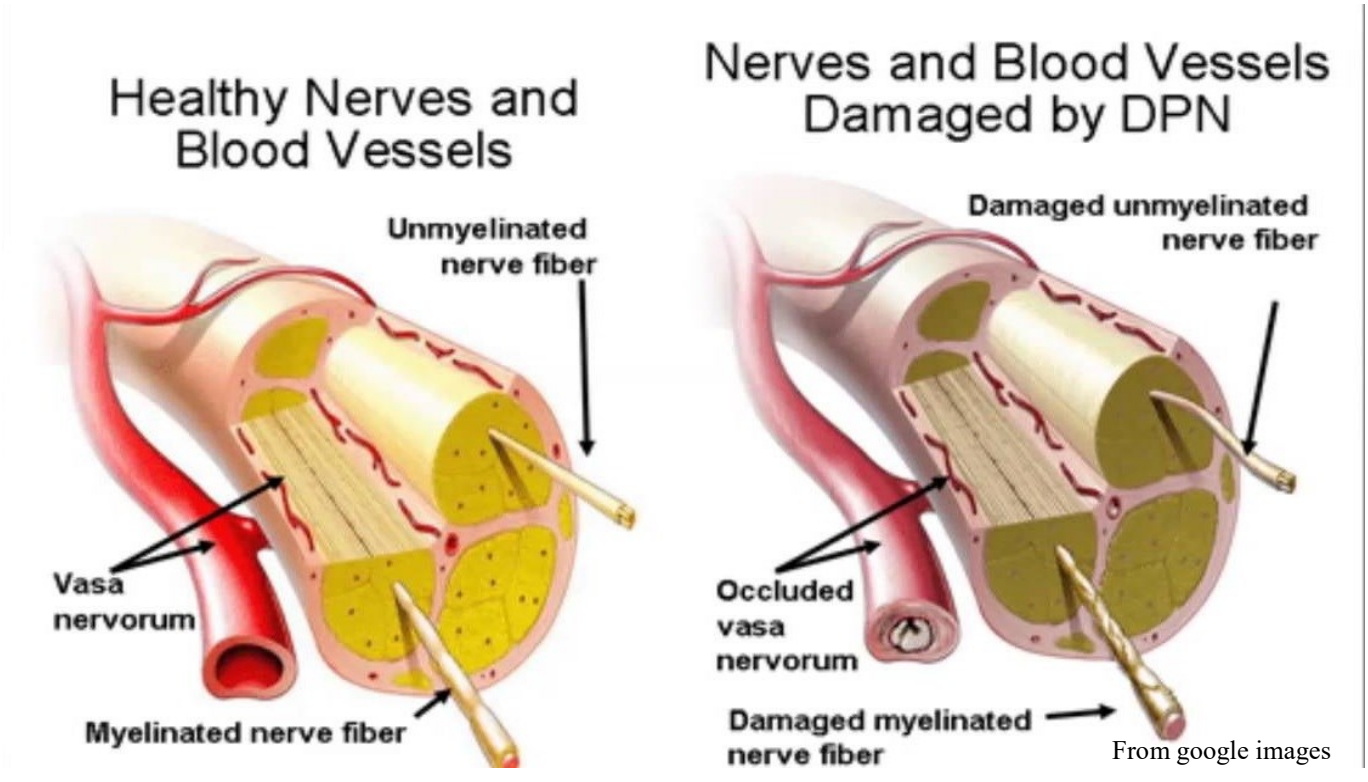
Patients with gustatory sweating can use glycopyrrolate, an anti-muscarinic compound.[33]

Non-pharmacological treatments of painful DPN

Transcutaneous electrical nerve stimulation (TENS)

Several forms of electrical stimulation have been utilised to manage pain in DPN, including TENS, percutaneous electrical nerve stimulation (PENS) and frequency-modulated electromagnetic neural stimulation (FREMS).[20]

Although data on the use of electrical nerve stimulation are limited, in 2010 the American Academy of Neurology (AAN) issued a statement supporting the



From google images

use of TENS for pain in neurologic disorders and concluded that TENS is probably effective in reducing pain from DPN. An updated 2011 guideline from the AAN, evaluating the treatment of painful DPN in three small trials, concluded that PENS is probably effective.

Spinal cord stimulation (SCS)
SCS is another invasive method, which includes implantable electrodes that transport electrical stimulation to the dorsal columns of the spinal cord. Although some data from a small open-label trial suggest that SCS reduces pain for patients with refractory painful DPN affecting the legs, further trials are needed. On the other hand, complementary therapies such as acupuncture are under investigation.[34]

Pancreas transplantation
Pancreas transplantation is considered to maintain insulin secretion. The reversal of neuropathy takes around 10 years after transplantation.[35] However, another study concluded that pancreas transplantation improves the motor and sensory function but not the conduction velocity or the autonomic function.[36]

Dietary supplements
More investigations are necessary regarding the benefit of dietary supplements. Some studies show that zinc sulfide improves the glycaemic level. Additionally, vitamin B complex may reduce the parasthaesia. 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.[37]

Potential future therapeutic options

Antioxidants
Since increased oxidative stress is one of the mechanisms implicated in the pathogenesis of DPN, antioxidants have been investigated for their ability to diminish oxidative stress, improve the underlying pathophysiology of neuropathy, and reduce pain. Alpha-lipoic acid (ALA), a strong antioxidant, has been associated with improved symptoms of DPN in several prospective, placebo-controlled studies.[38] The SYDNEY 2 trail concluded that the optimal dose of ALA was 600 mg once daily, as higher doses were limited by increasing adverse events including nausea, vomiting and vertigo, without increasing efficacy.[39] However, the strength of these findings is limited by the short duration of the trial.

Acetyl-L-carnitine (ALC)


Two randomised controlled trials found that ALC 1000 mg three times daily, compared with placebo, was associated with remarkable improvement in pain. The benefit of ALC needs confirmation, particularly since significant improvement was not found with lower dose of ALC.[40]

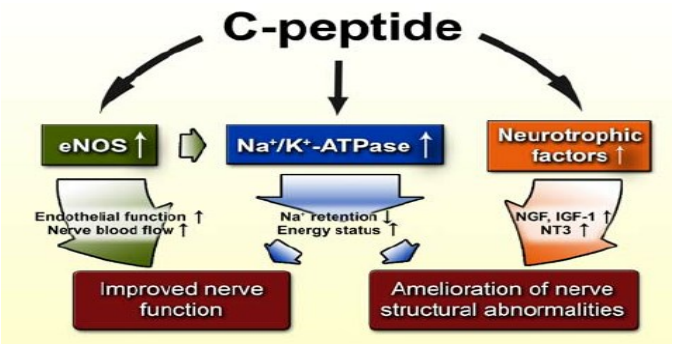
Aldose reductase inhibitors
Aldose reductase inhibitors are experimental therapies that inhibit the rate-limiting enzyme in the polyol pathway that is activated in hyperglycemia. Many studies that include aldose reductase inhibitors, such as alrestatin, epralrestat and sorbinil, had problems due to the poor study design. None of these medications is approved for use in the USA; epralrestat is the only medication that is marketed in Japan; it works by decreasing the intracellular sorbitol accumulation. Epralrestat 150mg daily for 3 months has been shown to improve sensory and motor nerve conduction velocity and vibration threshold such as pain, numbness and hyperaesthesia, coldness in the extremities, muscular weakness, dizziness and orthostatic fainting in metabolically stable patients with symptomatic DPN.[41]

Botulinum toxin type A
Botulinum toxin type A may reduce neuropathic pain and improvement in sleep quality in DM through its modulatory effects on the firing afferent sensory fiber; however, the results of these studies need to be confirmed in a larger population with longer periods of time.[42]

Actovegin
Actovegin is a highly filtered extract, derived from calf blood, which enhances the absorption of glucose and oxygen uptake in tissue and improves physical performance and stamina. It has been reported that 1800 mg sequential intravenous actovegin and oral actovegin over 160 days reduced neuropathic symptoms and improved vibration perception threshold, sensory function and quality of life in type 2 diabetic patients with symptomatic DPN.[43]

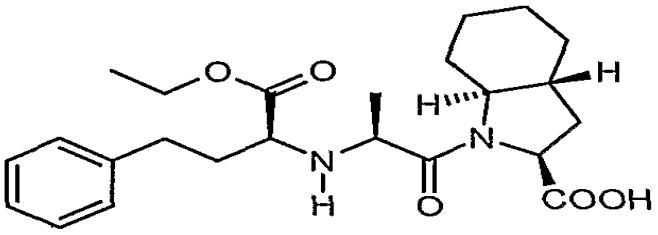
C-peptide

C-peptide, a 31-amino acid component of pro-insulin, improved sensory function in patients with type 1 DM and mild neuropathy. C peptide does so by activating of Na^+/K^+ ATPase and stimulating various transcription factors. Thus, it reverses the structural and functional changes due to DM in rats and humans.[44]



Angiotensin-converting enzyme (ACE) inhibitors

Studies on trandolapril, concluded that its use by normotensive diabetic patients reduced the occurrence of neuropathy at 12 months. Another study concluded that a combination of manidipine, a calcium channel blocker and delapril, an ACE inhibitor, or delapril on its own, remarkably decreased occurrence of neuropathy.[45]



Conclusions

Many advances have been established in the management of DPN due to improved knowledge of the disease mechanism, manifestations and diagnosis. Advances in DPN therapy involve the use of antioxidants, acetyl-L-carnitine, aldose reductase inhibitors and actovegin, as well as C-peptide and trandolapril. Transcutaneous electrical nerve stimulation is one of the non-pharmacological therapies to manage pain in diabetic neuropathy. Pancreas transplantation may be used to maintain insulin secretion. Spinal cord stimulators implants and acupuncture need further study to be recognised for the management of neuropathic pain.

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TEST YOUR KNOWLEDGE

Answers on back page

1) Which of the following is a SNRI, effective for treating pain in DPN?

a) Venlafaxine
b) Amitriptyline
c) Pregabalin
d) Capsaicin

2) ***Which of the following is a second generation anticonvulsant that increases brain GABA levels?***

a) Desipramine
b) Gabapentin
c) Duloxetine
d) Oxycodone

3) ***Which of the following drugs is available as a patch for DPN?***

a) Tramadol
b) Dextromethorphan
c) Valproate
d) Lidocaine

Is there a problem?

An adult patient is given the below prescription to treat his musculoskeletal pain. Is there any major error with the prescription?

KJB HOSPITAL

Patient Name: Hussein Ali Age: 35 years
Address: Street No: 879

Rx

Diclofenac 25mg tablet
1 tablet two times a day x 5 days

Dr. Fahad
Signature Date: 15/2/18

Answer (Prescription Exercise)

The dose is wrong. For musculoskeletal pain in an adult, the dose is 75-150mg daily in 2-3 divided doses.

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Promotion of E-cigs to help smokers quit: benefits vs risks

According to Britain's Royal College of Physicians (RCP), E-cigarettes are likely to bring benefits for public health and should be widely promoted to smokers to help them quit tobacco. In a report likely to further fuel a debate over electronic cigarettes, the influential British doctors group stressed that tobacco smoking is both addictive and lethal, and concluded that e-cigarettes are "much safer than smoking".

E-cigarettes are not a gateway to smoking, and do not lead to the normalization of the habit - two issues often cited by critics who fear the devices can lure children and young people into smoking habits. E-cigarettes, which heat nicotine-laced liquid into vapor, have rapidly grown into a global market for "vaping" (heating a liquid to generate an aerosol) products that was estimated at around $7 billion in 2015.

Tobacco smoking kills half of all smokers, plus at least another 600,000 people a year who are non-smokers via second-hand smoke. This makes it the world's biggest preventable killer, with a predicted death toll of a billion by the end of the century, according to the World Health Organisation (WHO).

As we gain clearer knowledge of the effects of cigarette- and VNP-oriented policies, a long-term

https://www.rand.org/blog/2014/03/where-theres-vapor-is-there-fire-we-need-evidence-on.html

view that reduces the use of the most toxic combusted tobacco nicotine delivery products will become a more realistic goal.

To those ends, and to help formulate tobacco control policy, experts devised a series of frameworks for assessing the possible impact of both short-term and long-term use of e-cigarettes in never-smokers, current smokers, and former smokers. The lead author David Levy of Georgetown University in Washington DC, states that "there is no magic way to regulate" and that this is a "complex problem" and that he and his colleagues tried "to provide a framework for analysing that problem, looking at the potential harms as well as the potential benefits." They expect the regulators to move in the right direction if they use the framework or something similar.

The authors noted that dual use of e-cigarettes and conventional cigarettes may lead to substantial reductions in the quantity and duration of cigarettes smoked, thus decreasing the risk for lung cancer and chronic obstructive pulmonary disease.

Starting to use e-cigarettes before smoking conventional cigarettes may also, delay or prevent smoking initiation in those who would otherwise have smoked. They noted that if, VNP use encourages the long-term use of cigarettes, or VNPs are used by those who would not have otherwise smoked, the net societal benefit would be diminished and VNPs could incur population-level harm.

In 2014, the US Food and Drug Administration (FDA) proposed a law that would extend the agency's authority to regulate additional products that meet the legal definition of a tobacco product, such as e-cigarettes. However, the authors note that before imposing regulations, the FDA "must consider scientific evidence" on the individual- and population-level benefits and harms of the devices.

Although the notion of e-cigarettes being safe and thus becoming normalised, could have unintended consequences, cigarettes are likely to be much more dangerous than e-cigarettes.

So if one can get people to quit smoking cigarettes and switch to e-cigarettes, on balance, there'll be a public health gain. Measures affecting the availability of both e-cigarettes and conventional cigarettes are needed to achieve that. It's going to be important to monitor e-cigarette use at younger ages and implement policies to discourage that use, such as not allowing their sale below a certain age. But even more important is to raise the age for cigarettes. If the age for e-cigarettes is raised but not for cigarettes, then smoking is encouraged.

Further regulation of the advertising of tobacco products is required, including banning advertisements at the point of sale, placing strong health warnings on cigarette packages, and continuing to increase taxes on tobacco products.

Opposition from the tobacco industry could pose a hurdle to implementing those measures. Experts recommend that cigarette companies should not gain control of the e-cigarette market. Regulations are needed to allow some degree of competition in that industry so it's not dominated by the cigarette manufacturers.

References

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2. *Levy DT, et al. 2016. Addiction. DOI: 10.1111/add.13394*

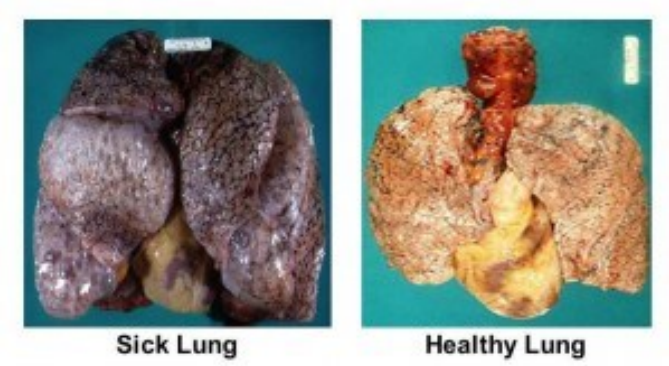
Statins confer benefits in patients with COPD

Chronic obstructive pulmonary disease (COPD), includes progressive lung diseases such as emphysema and chronic bronchitis. Symptoms include increasing breathlessness, tightness in the chest, coughing and wheezing. The most common causes for these conditions include smoking and exposure to secondhand smoke. Workplace exposure to chemicals and fumes and genetics may also contribute to COPD. It is the third leading cause of death in the United States, according to the U.S. National Heart, Lung and Blood Institute.

Statins are well known for their use in the control

of LDL cholesterol levels but they may have benefits beyond this application. A new study suggests people with chronic lung disease who take these drugs may extend their survival. Authors of the new study noted that it's long been known that people with COPD have inflammation in their lungs. However, it's also possible that people with COPD, or at least some of them, may have inflammation throughout their body.

The study from Canada included nearly 40,000 people with COPD. The participants were age 50y and older from British Columbia. The researchers identified people as having COPD if they had received at least three prescriptions for COPD



http://www.ikomed.com/technology/treatment-for-copd/

medications in a 12-month period. The study team then looked to see who was also taking a statin within a year of being labeled as having COPD. Almost 20% had received at least one statin prescription. The researchers adjusted the data to account for a number of factors including age, sex, income and place of residence.

There were 39,678 patients with COPD that met the study inclusion criteria. Of them, 7,775 (19.6%) had received at least one statin drug dispensed in the exposure ascertainment window. There were 1,446 all-cause deaths recorded in the cohort in the 1y period after exposure ascertainment. In multivariate analysis, the estimated hazard ratio (HR) for statin drug exposure was 0.79 (95% CI, 0.68-0.92; *P* =.0016), suggesting a 21% reduction in the risk from statin drug use on all -cause mortality. For lung-related mortality, there was also a considerable reduction in the risk for all-cause mortality from statin drug use (HR, 0.55; 95% CI, 0.32-0.93; *P* = .0254). The authors concluded that their findings, in conjunction with previously reported evidence, suggest that statin drug use may benefit a specific subtype of patients with COPD. The findings were published Sept. 7 in the journal Chest.

Some experts noted that people with COPD have cardiovascular disease, and treating co-morbid conditions can really help. The survival benefit observed in the study may not be unique to COPD, but it was a very significant survival benefit for people with COPD. According to Dr. Len Horovitz, a pulmonary specialist at Lenox Hill Hospital in New York City, there might be a subset of COPD patients who might benefit from statin use who don't need a statin for cardiovascular reasons, but the heart and lungs are intertwined, and it's hard to "tease out" someone with COPD who doesn't have risk factors for cardiovascular disease. Because most people with COPD are smokers or former smokers, most also have cardiovascular disease. And that cardiovascular disease is usually reason enough to prescribe the statin.

References:

1) Statins May Help People With COPD Live Longer. https:// www.drugs.com/news/statins-may-help-copd-live-longer-66947 . html ?utm _ sourc e= ddc &utm _medium =email& utm _ campaign=Newsletter+Vol+157+-+September+2017

2) Raymakers. et al.. CHEST 152(3) , 486 – 493.

Which medication is right for seasonal allergies?

Seasonal allergies are real diseases that can interfere with work, school or recreation. Allergies can also trigger or worsen asthma and lead to other health problems such as sinus infection (sinusitis) and ear infections in children.

An allergy is the body's reaction to a substance that it has identified as an invader. If one has allergies and encounters a trigger- called an "allergen"- the immune system reacts to it by releasing histamines by degranulation of mast cells. Histamines cause undesired symptoms such as repetitive sneezing and itchy watery eyes. Seasonal allergies are usually caused by plant pollen which can come from trees, weeds and grasses in the spring, and by ragweed and other weeds in late summer and early fall. Since a person can't always stay indoors when pollen counts are high, the health care provider may recommend prescription or over-the-counter (OTC) medications to relieve symptoms.

The U.S. Food and Drug Administration (FDA) regulates a number of medications that offer allergy relief. Anti-histamines reduce or block symptom-causing histamines and are available in many forms, including tablets and liquids. Many oral

anti-histamines are available OTC and in generic form. When choosing an OTC anti-histamine, patients should read the Drug Facts label closely and follow dosing instructions. Some anti-histamines can cause drowsiness and interfere with the ability to drive or operate heavy machines like a car. There are other anti-histamines that do not have this side effect; they are non-sedating. Some non-sedating anti-histamines are available by prescription.

Nasal corticosteroids are typically sprayed into the nose once or twice a day to treat inflammation. Side effects may include stinging in the nose.

Decongestants are drugs available both by prescription and OTC and come in oral and nasal spray forms. They are sometimes recommended in combination with anti-histamines, which used alone do not have an effect on nasal congestion.

Drugs that contain pseudoephedrine are available without a prescription but are kept behind the pharmacy counter to prevent their use in making methamphetamine -a powerful, highly addictive stimulant often produced illegally in home laboratories. In the United States, a pharmacist may need to be consulted and the patient's identification has to be shown to purchase drugs that contain pseudoephedrine.

Using decongestant nose sprays and drops for more than a few days may give a "rebound" effect -where the nasal congestion could get worse. These drugs are more useful for short-term use to relieve nasal congestion.

Immunotherapy may help if other medications don't relieve symptoms. One form of allergen immunotherapy is allergy shots in which the body responds to injected amounts of a particular allergen, given in gradually increasing doses, by developing immunity or tolerance to that allergen. Patients can receive injections from a health care provider; a common course of treatment would begin with weekly injections for two to three months until the maximum dose is reached. After that, treatment could continue monthly for 3-5y.

Another form of allergen immunotherapy involves administering the allergens in a tablet form under the tongue (sublingual) and are intended for daily use, before and during the pollen season. These medications have the potential for reducing the immune response to allergens and are not meant for immediate symptom relief. Sublingual therapy should start three to four months before the allergy season. Although they are intended for at-home use, these are prescription medications, and the first doses are to be taken in the presence of a health care provider.

The product label should be carefully read before buying an OTC product for children. Some products can be used in children as young as 2y of age, but others are not appropriate for children of any age.

Reference

https://www.drugs.com/fda-consumer/seasonal-allergies-which-medication-is-right-for-you-304.html

The "MSG" syndrome

Growing interest in nutrition and good health has led to increased concern regarding the consumption of processed foods and what they contain. While freezing and canning foods has increased their availability and diversity, as well as being less seasonal dependant, this has come at the cost of having to add chemicals generally as preservatives but often also to add flavours not present in the actual food. These may have long term harmful effects as well as causing often quite severe allergic reactions.

One common food additive that is widely used is Monosodium Glutamate (MSG) which was first marketed as a flavour enhancer in Japan in 1909. It carries the designation E-621 and is sold in the form of a white crystalline powder with the appearance of fine sugar or table salt.

MSG is the sodium salt of glutamic acid, an abundant naturally occurring non-essential amino acid that occurs in virtually all foods and is particularly rich in vegetables such as mushrooms and broccoli, as well as several types of meat. It is utilised in the brain and is essential for healthy brain function as an excitatory neurotransmitter. Although there is no chemical difference between glutamate in MSG and glutamate in natural foods, the glutamate in MSG may be easier for the body to access, because it is not bound inside big protein molecules that need to be metabolised.

The sodium salt of the glutamic acid has an effect on the umami taste (the fifth basic taste, along with sweetness, sourness, bitterness and saltiness). Umami has been used to describe the taste of meat; it is sensed through taste receptors that typically respond to glutamate.

MSG can reportedly "change almost any food from bland to tasty". This has alarmed many, as rancid tastes of expired food could be masked by tricking the brain into thinking that the food consumed is nutritious. Also, because MSG creates an illusion of protein taste in food, less "real food" may be added to a food product by manufacturers; for example, chicken soup may contain less of the usual portion of chicken with added MSG and still taste as good. This would benefit industries in terms of reduced cost. In addition, the salt is believed to stimulate the pancreas to produce insulin, even when no carbohydrates and protein are present. This is a type of "anti-appetite suppressant" effect, which leads to an increase in the consumer's appetite after they just had a meal due to the increased insulin levels. Again this benefits the food suppliers as customers come back for more food! MSG is commonly added to canned vegetables, soups, processed meats, and is very commonly found in many East Asian and most especially in Chinese food, being responsible for the "Chinese food syndrome".

Some individuals may experience allergic reactions when eating foods that contain the additive, which leads to a headache, excessive sweating, skin flushing, muscle tightness and numbness or burning in the mouth and throat. Nausea and chest pain are also experienced during the allergic reaction, according to the Mayo Clinic.

Although the US FDA has labelled MSG as safe, the European Union classifies it as a food additive that is permitted in certain foods and is subject to quantitative limits.

Sources

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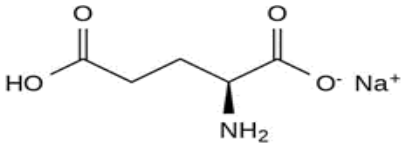

Article by Ajwan Bebehani

IN THE NEWS

Does propranolol improve progression-free survival in patients with thick melanoma?

Preclinical and retrospective studies showed that β -blockers inhibit angiogenesis and disrupt migration of melanoma cells via inhibition of noradrenaline-dependent responses.

53 patients with melanoma were treated with propranolol for off-label use. Patients with histologically confirmed stage IB to IIIA cutaneous melanoma and no evidence of metastasis were

eligible for the study. At the time of diagnosis, they were asked to take propranolol (80 mg daily) as an off-label adjuvant treatment. Use of propranolol at the time of diagnosis was significantly inversely associated with recurrence of melanoma with approximately an 80% risk reduction for propranolol users. The primary outcome was progression-free survival. Disease progression was assessed by evaluating the presence of lymphatic, in-transit, or visceral metastases, and the cause of death was recorded.

In the absence of randomized, double-blind, placebo-controlled clinical trials, this study is the first off-label study of propranolol for melanoma treatment. These results confirm recent observation that β-blockers protect patients with thick cutaneous melanoma from disease recurrence.

This study is in accordance with the present policy of "drug re-purposing" in oncology. Re-purposing the vast arsenal of approved drugs with a nononcology primary purpose may prove an attractive and inexpensive strategy for offering more effective treatment options to patients with cancer.

Adapted from: https://jamanetwork.com/journals/jamaoncology/article-abstract/2655005

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved in September and October 2016

Amri-K Ampoule Solution for Injection, Phytomenadione (Vitamin K1)10.0mg/ml, Amriya Pharm. Ind./ Egypt, Gulf Nawras Medicine & Medical Supplies.

Aracenac Film Coated Tablets 100mg, Aceclofenac 100mg, Arafarm Group S.A./Spain, Mercury for Drugs & Medical Supply.

Aralevo Film Coated Tablets, Levocetirizine Dihydrochloride 5mg, Arafarma Group S.A./Spain Manufacturing Co./Saudi Arabia, Mercury for Drugs & Medical Supply

Arxia Film Coated Tablets 60, 90 and 120mg, Etoricoxib 60, 90, 120mg, Laboratorios Cinfa, S.A./Spain, Ali Abdulwahab

Bels Sterile Suspension 27mg/ml, 3 and 5ml vials, Phospholipid 27mg (Bovine Lipid Extract Surfactant), Bles Biochemicals Inc./Canada, Ali Abdulwahab

Cefaks Film Coated Tablets 250mg, Cefuroxime axetil 250mg, Deva Holding A.S./Turkey, Golden Care

Chelaton Tablets for Oral Suspension 125mg, Deferasirox 125mg, Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia, Ali Abdulwahab

Chelaton Tablets for Oral Suspension 250 and 500mg, Deferasirox 250, 500mg, Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia, Ali Abdulwahab

Desirett Film Coated Tablets, Desogestrel 75 µg (mcg), Exeltis Germany GmbH/Germany, Warba

Epclusa Film Coated Tablets, Sofosbuvir 400mg Velpatasvir 100mg, Gilead Sciences Int. Ltd./UK, Warba

Esmo Delayed Release Tablets 20 and 40mg, Esomeprazole (as Magnesium) 20, 40mg, Apotex Inc./ Canada, Alghanim Healthcare.

Fluxar Solution for IV Infusion, Fluconazole 2mg/ml, PT. Novell Pharmaceutical Laboratories/ Indonesia, Palestine Pharmacy

Gaviscon Peppermint Liquid Relief Oral Suspension, Sodium Alginate 500mg Sodium Bicarbonate 267mg Calcium Carbonate 160mg, Reckitt Benckiser healthcare (UK) Limited/UK, Al-Wazzan

Grani-Denk 1mg/ml and 3mg/ml Concentrate for Solution for Injection or Infusion, Granisetron (as Hydrochloride) 1mg/ml and 3mg/3ml, Denk Pharma GmbH & Co. KG/Germany, Al-Wazzan

Hepavir Film Coated Tablets 0.5mg, Entecavir (as monohydrate) 0.5mg, Spimaco/Saudi Arabia, Warba

Hepavir Film Coated Tablets 1mg, Entecavir (as monohydrate) 1mg, Spimaco/Saudi Arabia, Warba

Hyrocortison VUAB Powder for Solution for Injection 100mg, Hydrocortisone (as hydrogen succinate) 100mg, VUAB Pharma a.s./Czech Republic, Al-Rwani

L-Cet Oral Solution 0.5mg/ml, Levocetirizine dihydrochloride 0.5mg/ml, Oman Phar. Products Co. LLC/ Sultanate of Oman, Al-Hafez

Lidocaine Injection B.P. 1 and 2%, Lidocaine Hydrochloride Anhydrous (as hydrochloride monohydrate) 10mg, KSPICO/Kuwait, KSPICO
Lukra Chewable Tablets 4 and 5mg, Montelukast (as sodium) 4, 5mg, Neopharma/UAE, Al-Wazzan
Lukra Film Coated Tablets 10mg, Montelukast (as sodium) 10mg, Neopharma/UAE, Al-Wazzan
Montapine Tablets 10mg, Memantine HCl 10mg, Apotex Inc./Canada, Ali Abdulwahab
Ocrevus Concentrate for Solution for Infusion, Ocrelizumab (rDNA) 300mg/10ml, F. Hoffmann La Roche Ltd./Switzerland, Ali Abdulwahab
Plegridy Solution for Injection in Prefilled pen [(63mcg+94mcg) Initiation Pack], Peginterferon beta-1a (rDNA), Biogen Idec Ltd./UK, Al-Homaizi
Plegridy Solution for Injection in Prefilled pen 125mcg, Peginterferon beta-1a(rDNA), Biogen Idec Ltd./ UK, Al-Homaizi
Pravia CR Tablets 300mg, Sodium Valproate 199.9mg Valproic acid 87.0mg (equivalent to 300mg Sodium Valproate), The United Pharmaceutical Manufacturing Co. Ltd./Jordan, Al-Hajery
Pravia CR Tablets 500mg, Sodium Valproate 333mg Valproic acid 145mg (equivalent to 500mg Sodium Valproate), The United Pharmaceutical Manufacturing Co. Ltd./Jordan, Al-Hajery
Protoheal New Ointment, Lidocaine Hydrochloride 20mgFluocinolone Acetonide 0.1mg, Dar Al Dawa Development & Investment Co. Ltd./Jordan, Safwan
Protoheal New Suppositories, Lidocaine Hydrochloride 20mg Fluocinolone Acetonide – 0.1mg, Denk Pharma GmbH & Co. KG/Germany, Safwan
Regaine for Men Cutaneous Foam 5%, Minoxidil 50mg/gm, Mcneil Products Limited/UK, Al-Wazzan
Saxenda Solution for Injection 6mg/ml, Liraglutide (rDNA) 6mg/ml, Novo Nordisk A/S/Denmark, Safwan
Sitralix Film Coated Tablet 10 and 20mg, Escitalopram (as Oxalate) 10, 20mg, KSPICO/Kuwait, KSPICO
Sodium Chloride Intravenous Infusion BP- NS 0.9% w/v, Sodium Chloride 0.9%, Claris Lifesciences Limited/India, Advanced Technology Co. (ATC)
Tyra Film Coated Tablets 20mg, Tadalafil 20mg, Dar Al Dawa Development and Investment Co. Ltd./ Jordan, Dar Al Maali
Unidil Tablets 3.125, 6.25, 12.5 and 25mg, Carvedilol 3.125, 6.25, 12.5, 25mg, United Pharmaceutical Manufacturing Co. Ltd./Jordan, Al-Hajery
Venclexta Tablets 10, 50 and 100mg, Venetoclax 10, 50, 100mg, AbbVie Inc./USA, Al-Mojil
Vivazac Tablet 150mg, Irbesatran 150mg, The United Pharmaceutical manufacturing Co. Ltd./Jordan, Al-Hajery
Vivazac Tablet 300mg, Irbesatran 300mg, The United Pharmaceutical manufacturing Co. Ltd./Jordan, Al-Hajery
Xalafil Tablets 20mg, Tadalafil 20mg, KSPICO/Kuwait, KSPICO
Xeljanz XR Extended Release Tablets, Tofacitinin (as citrate) 11mg, Pfizer Inc./USA, Al-Homaizi
Zepatier Tablets, Elbasvir 500mg Grazoprevir 100mg, Merck Canada Inc./Canada, Al-Homaizi

Answers to: Test your knowledge

Correct answers:
1-A; 2-B; 3-D

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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