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Management of cluster headaches

Headache, which is known as cephalgia, is a very common disorder. About 95% of the population suffers from at least one episode in their lifetime. According to the International Classification of Headache Disorders, they are classified into primary and secondary headaches (1). Primary headaches are sub-classified into migraine, tension-type headache and trigeminal autonomic cephalgias (Figure 1).

Trigeminal autonomic cephalgias include hemicrania continua, cluster headaches (CH), paroxysmal hemicranias etc. Each of these headaches differ in duration and frequency. Cluster headache, which is unilateral head pain that is centred over one eye or one temple, has the longest duration and lower frequency of up to eight attacks per day in comparison with others and is also associated with autonomic symptoms which include lacrimation and congestion. Secondary headaches are caused by underlying medical conditions such as intracranial neoplasm, head or neck trauma, ear, eye and sinus infections.

Epidemiology and genetics

Life time incidence of cluster headache has been found to be 124 per 100,000, while one year incidence was found to be 53 per 100,000. On the other hand, the mean prevalence of cluster headaches in the general population is 0.1% and it has been shown that cluster headache is more common in males than females (3).The relation of genetics to cluster headache is not clear, but it is likely to be an autosomal dominant gene that is present in 3-4% of males and 7-10% of females. First degree relatives of patients with cluster headache are 14-48 times more likely to get cluster headache in comparison to the general population (4).

Description and clinical features

The phrase cluster headache arises from the tendency of attacks to cluster together into bouts that last several weeks. Cluster headaches are characterised by circadian rhythm of painful attacks, which commonly awaken the patient at night and are more common in the spring and fall seasons.

The headache strikes one side of the head often behind or around one eye. The affected side of the face during attack may get red, swollen and teary (Figure 2). To diagnose patients with cluster headache, they should fulfill certain criteria. First, the patient should have at least one of the signs and symptoms ipsilateral to the headache, which include conjunctival infection, nasal congestion and eyelid edema. In addition, the patient may also experience miosis, sensation of fullness in the ear, ptosis and forehead and facial sweating. Second, the patient should have at least five attacks. And these attacks are characterised by sudden, severe or very severe unilateral orbital, supraorbital or temporal pain, which lasts from 15-180 min if not treated. Peak intensity of the attack is usually rapid and lasts for three min, but may last up to nine or 10 min.

Cluster headaches are classified into episodic cluster and chronic cluster headaches. In episodic cluster headache, the patient should have at least two cluster periods, which last from seven days to one year if left untreated; and these periods are separated by pain free remission periods of one month or more. In contrast to episodic cluster headache (ECH), chronic cluster headache (CCH) attacks occur without a remission period, or with remissions that last less than one month, for at least one year.

Patients with cluster headache may suffer from specific symptoms that may occur min to days before pain onset. These symptoms are called local predromes, which include autonomic signs with or

In this issue

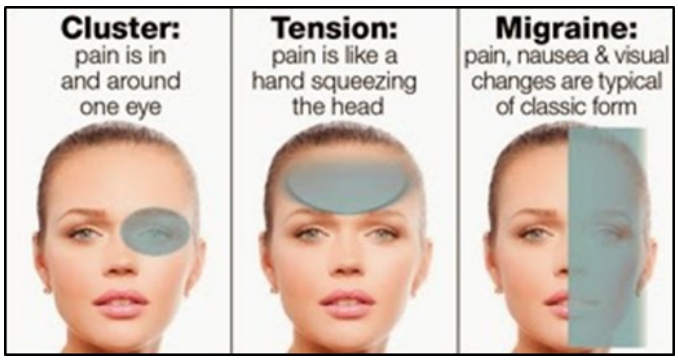

Figure 1. Types of headaches. (Adapted from pain-

without pain, blurred vision, dyspepsia, irritability and sensitivity to smells.

These premonitory symptoms can predict cluster attacks in 40% of headache cases. Although most of cluster attacks are spontaneous, they may be triggered by volatile substances such as solvents and oil based paints. In addition, even a small amount of alcohol may precipitate cluster attack during an active period.

Pathophysiology

The pathophysiology of the trigeminal autonomic cephalgias is not well understood but there are theories that may explain pathogenesis of cluster headaches. There are three main features that characterise a cluster headache, which include trigeminal distribution of the pain, ipsilateral autonomic features and the episodic and circadian rhythm of cluster headache. In order to explain these features many studies proposed three main theories, which include vascular theory, trigeminal autonomic reflex, and hypothalamic activation (5). These theories may be interrelated and involve many central and peripheral neuro-modulatory pathways (3).

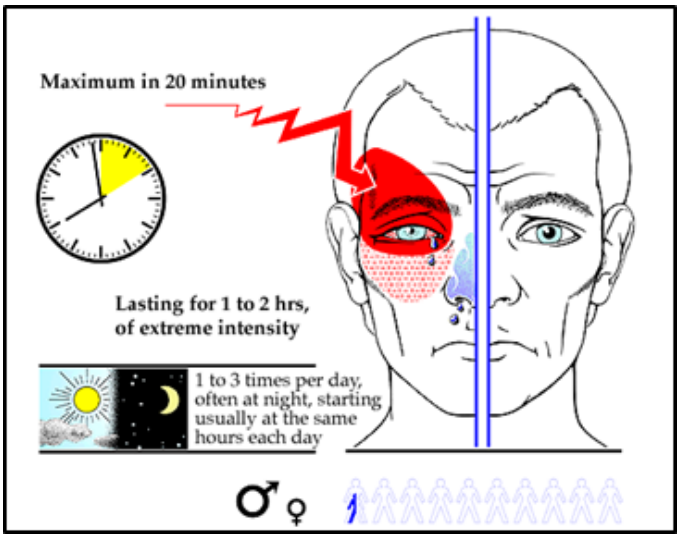

Figure 2. Depiction of cluster headache showing unilateral nature of headache and prevalence in males. Adapted from painmanagementlasvegas.com (2)

Neurovascular theory

Cluster headache is known to be a neurovascular headache because there is vasodilation of the ipsilateral ophthalmic artery during attack. Vasodilation results in increased corneal indentation pulse amplitude, intraocular pressure, and skin temperature around the eyes. It was suggested that during cluster attack there is an inflammatory process involving walls of the cavernous sinus, which is called venous vasculitis. As a result of inflammation, the venous outflow from the cavernous sinus is impaired and leads to vascular congestion within the atrial and venous circulation, which leads to pain and injury of traversing sympathetic fibers in the carotid artery.

Trigeminal autonomic reflex

Trigemino-cerebrovascular system consists of trigeminal neurons and cerebral blood vessels they innervate. This system has a sole sensory afferent role in the innervation of the cerebral blood vessels and has efferent pathway. Cell bodies in the trigeminal ganglion contain vasodilator peptides, such as calcitonin gene-related peptide (CGRP), substance P and neurokinin A. Stimulation of these nerve fibers that innervate cranial blood vessels can cause release of neuropeptides both peripherally and centrally, which results in pain and pain signals.

The activation of trigeminal nerve can explain pain associated with cluster attack and may initiate an autonomic manifestation called trigeminal autonomic reflex. The cerebral blood vessels are also innervated by sympathetic and parasympathetic nerves. Once the trigeminal nerve is stimulated, it will cause cerebral vasodilation and increase brain blood flow; this effect is mediated through mechanisms which include stimulation of parasympathetic outflow and antidromic activation of trigeminal afferents with the release of CGRP.

Hypothalamus theory

Cluster headache attacks are characterised by circadian rhythm and periodicity because they occur in one to eight times a day with a clock-like regularity. These attacks occur often at the same time each year and the onset has been found to be related to photoperiod duration, especially in July and January. This periodicity suggests that there is biological clock or

pacemaker that control and regulate these attacks. This biological clock is the located in the suprachiasmatic nucleus in the gray matter of the hypothalamus. The hypothalamus plays a major role in modulating the neuroendocrine system by regulating the production and secretion of hypophyseal hormones and maintain melatonin homeostasis levels (6).

Melatonin is the most sensitive marker of hypothalamic activity because it is strongly related to the circadian rhythm and chrono-regulatory functions (5). The 24 h production of melatonin is decreased and the nocturnal peak in the concentration is blunted in patients with cluster headache; this cannot be explained by pain induced stress because normally the levels of melatonin are high due to the release of endogenous norepinephrine (5). Low levels of melatonin can be explained by reduced availability of serotonin, which is needed for the synthesis during cluster headache. This is because the serotonergic system is impaired during CH.

Neuroendocrine changes were also noticed in cluster headache patients due to changes in hypothalamo-hypophyseal-adrenal (HPA) axis. During an attack there was alteration in secretory circadian rhythms of luteinizing hormone (LH), cortisol and prolactin. The concentration of cortisol and prolactin were high during active periods of attack compared to between attacks. In contrast to cortisol, concentration of the testosterone was lowered in men during the attacks. This provided the first evidence of involvement of hypothalamus in cluster headache attacks.

Role of nitric oxide

Several studies have been shown that plasma concentration of nitric oxide (NO), which vasodilates intracranial arteries, is increased during cluster headache attack (7). In the trigeminal ganglion, CGRP and NOS co-localize in many neurons, thus it has been suggested that NO causes release of CGRP by activation of the trigeminovascular system (3). It has also been found that CGRP may induce release of NO (8). One theory is that the hypothalamus is involved in pathogenesis of cluster headache by producing large amounts of NO as the hypothalamus contains large numbers of NOS containing neurons (9)

Tyrosine metabolism

Tyrosine is a precursor for the synthesis of catecholamines and elusive amines such as tyramine. Giovanni et al (10) found that patients with CH had abnormal tyrosine metabolism, which resulted in high levels of dopamine, tyramine and noradrenaline,

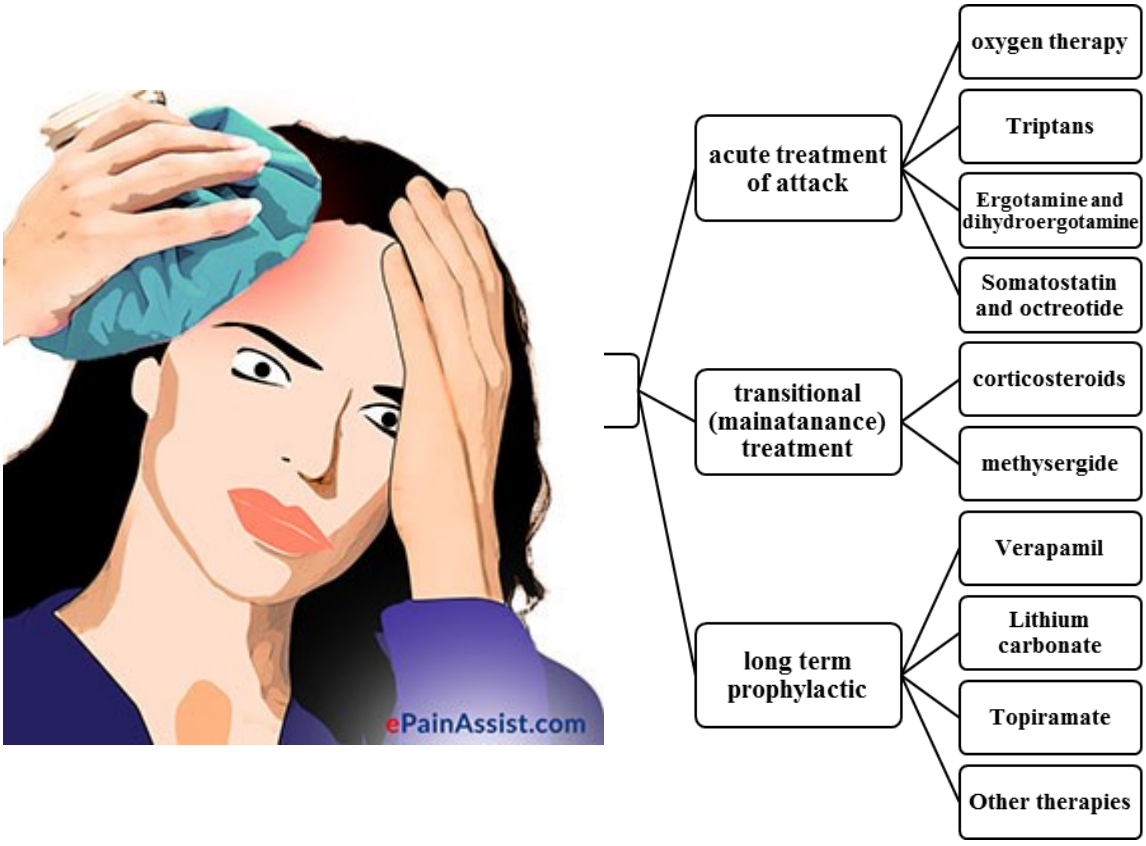

Figure 3. Drugs are used for acute treatment of an attack, transitional and long term prophylactic therapy

while the levels of octopamine and synephrine were low. In addition, high levels of tyramine and dopamine may result in abnormal functionality of trace amino acid receptors (TAAR), which are located abundantly in the hypothalamus. Thus, the dysregulation of TAAR will result in high noradrenaline levels, which might contribute to chronic cluster headache.

Treatment of cluster headache

The management of CH is classified into three categories, which are acute treatment to abort an occurring attack, transitional to induce a rapid prevention of cluster attacks and long term prophylactic therapy (Figure 3).

Acute treatment

Oxygen therapy

Oxygen is considered to be the first line treatment in the management of an acute setting in cluster headache. Oxygen has a direct inhibitory effect on the cranial parasympathetic nerve fibers. Oxygen acts as a neuro-modulator acting on the neurotransmitter levels and deactivating the trigeminal autonomic reflex arch. To assess the efficacy of oxygen, Kudrow et al (11) conducted a study on 52 patients with acute cluster attack. They administered oxygen through a facial mask at a rate of 7 L/min for 15 min and found that patients younger than 50 y with episodic cluster headache had the best response.

Another study was conducted to assess efficacy of oxygen therapy in patients with acute attack in a double blinded crossover study. They treated 19 patients with either oxygen or air inhalation at a rate of 6 L/min, and found that the average pain relief score were higher with oxygen in comparison to air (12). In conclusion, it has been found that oxygen therapy is effective in the treatment of cluster attacks for many years because of no adverse effects. However, many patients with cluster attacks do not use oxygen because O2 devices are relatively expensive, bulky and unpractical.

Triptans

Triptans, which are 5-$HT_{1B/1D}$ agonists, are the drugs of choice for the treatment of acute cluster attacks. They are available in formulation for intranasal administration and subcutaneous injections. A study was conducted to assess the efficacy of subcutaneously administered sumatriptan to cluster patients in acute attacks. Hardebo (13)found that subcutaneous sumatriptan is more effective than intranasal sumatriptan. Oral zolmitriptan was also evaluated in acute treatment of cluster headache, where oral zolmitriptan was found to be superior to placebo in episodic but not chronic cluster headache s (14). Intranasal zolmitriptan had similar effectiveness when compared to intranasal sumatriptan in the treatment of cluster headache, however oral zolmitriptan had limited efficacy (15).

Ergotamine and dihydroergotamine

The efficacy of ergotamine derivatives in CH have not been evaluated in controlled studies. Reports are based on small open label studies and on case reports. A study conducted by Kudrow (11)to compare the efficacy of sublingual ergotamine with oxygen, concluded that the response rate of ergotamine was 70% in comparison to 82% for oxygen. Ergotamine was more convenient in comparison to oxygen, however it was less effective.

Lidocaine

The effect of intranasal lidocaine was examined in 30 men with episodic cluster headaches. The results were modest in patients treated with lidocaine for 2 consecutive cluster attacks, with 27% reporting a moderate relief and 27% mild relief and 46% no relief. Lidocaine should not be used as a first line therapy in patients with acute cluster attack, however it may be used as adjunctive therapy in patients that do not respond to other therapies (15).

Somatostatin and octreotide

The efficacy of intravenous somatostatin was examined in 72 attacks experienced in 8 men in comparison to placebo. Somatostatin infusion was superior to placebo in relieving cluster pain and was comparable with intramuscular ergotamine (16). Subcutaneous octreotide, which is a somatostatin analog, was evaluated for its efficacy in relieving pain in cluster attacks. It was significantly superior to placebo with regard to headache response rate (17). The main advantage of somatostatin and octreotide is that they lack vasoconstrictive effect, which makes them an option for patients who cannot use triptans because of vascular disease.

Short term preventative therapy (transitional prophylaxis)

Patients with cluster headache may suffer from many cluster attacks per day, as a result acute treatment alone is not sufficient. In addition, many patients do

Table 1. Long term maintenance prophylactic therapy for cluster headache.

Therapy	Level of Evidence (EFNS Guidelines)*	Target Dose per Day	Monitoring	More Common AEs
Verapamil	A	200-900 mg	EKG	Hypotension, constipation, peripheral edema
Lithium carbonate	B	600-900 mg	Lithium levels, renal function, thyroid function	Diarrhea, tremor, polyuria
Topiramate	B	50-200 mg	Serum bicarbonate	Paresthesias, weight loss, cognitive dysfunction, fatigue, dizziness, taste alteration
Valproic acid	C	500-2000 mg	CBC, liver function	Weight gain, fatigue, tremor, hair loss, nausea
Melatonin	C	10 mg	None	Fatigue, sedation
Baclofen	C	15-30 mg	None	Drowsiness, dizziness, ataxia, muscle weakness
Botulinum toxin	Not rated	50 units	None	Muscle weakness, injection site pain
Gabapentin	Not rated	800-3600 mg	CBC	Somnolence, fatigue, dizziness, weight gain, peripheral edema, ataxia
Clonidine	Not rated	0.2-0.3 mg	None	Fatigue, hypotension

*See Appendix for detailed guidelines.
AEs = adverse effects; CBC = complete blood count; EFNS = European Federation of Neurological Societies; EKG = electrocardiogram.

Adapted from American Headache Society (15).

not tolerate or have some contraindication for using acute treatment. If these patients with frequent attacks are treated continuously, this will lead to over use of medications and adverse events. As a result, prevention is a critical step for therapeutic management of all cluster headache patients.

To obtain cluster control at initiation of maintenance prophylactic therapy, corticosteroids or methysergide are often given concurrently with maintenance drugs. However, the efficacy of these drugs is based on case studies and open label studies.

Methysergide is semisynthetic ergot alkaloid used for the prophylaxis of cluster headache attack for many years. Based on open studies, the percentage of patients that benefited from methysergide range from 20- 73%, and it was found that the drug was more effective in episodic cluster headache (18).

Long term (maintenance) prophylaxis

Verapamil

Verapamil has been used as a first line for long term prevention of cluster headaches; due to its efficacy, safety profile, and ability to co-administer it with other symptomatic and transitional therapies with less drug interactions when compared to lithium bicarbonate. It has been introduced off label as a prophylaxis.

Lithium carbonate

Lithium carbonate is widely used as an alternative to verapamil, however its pharmacological action in cluster headache is not known. Despite its effectiveness, lithium carbonate is used as a second line treatment because of its potential adverse effects and narrow therapeutic window.

Topiramate

Topiramate is considered a second line therapy for cluster headache prophylaxis and it has many mechanisms of action (18). However, it is not known whether these mechanisms contribute to the prevention of cluster headache. Topiramate has been shown to have an inhibitory effect on trigeminovascular nociceptive neurons, activated by stimulation of the superior sagittal sinus in rats (18). Topiramate has been investigated in open studies only and was found to be effective in decreasing the frequency of cluster attacks.

Other therapies

Valproic acid has been evaluated for the treatment of cluster headache. A double blinded placebo study

was done to assess the effectiveness of valproic acid in the treatment of cluster headache attacks. There was no difference between placebo and valproic acid administration and the response rate was high for both groups (19).

The plasma levels of melatonin decrease at night in patients with cluster headache suggesting that low levels of melatonin may play a role in the promotion of attacks. Leone et al. (20) conducted a double blinded placebo controlled trial on 20 patients; 18 had episodic cluster headache whereas 2 had chronic cluster headache. Five of 10 patients with episodic cluster headache who received melatonin had cluster remission within 5 days, while none of the 10 patients who received placebo responded. Patients with chronic cluster headache did not benefit from melatonin.

Gabapentin is a well-tolerated medicine widely used in the treatment of neuropathic pain, as a result it was trialed in patients with CH. An open trial of gabapentin was conducted on 12 patients; all reported freedom from pain after 8 days of treatment (21). Although gabapentin is well tolerated drug, in clinical practice the rapid onset of action has not been noticed.

Capsaicin, a known neuropeptide depletor, causes the release of neuropeptides from the primary sensory neuron and eventually depleting the nerve terminal from substance P and CGRP. Intranasal capsaicin was shown to be in the beginning effective in reducing frequency of attacks, however the attacks invariably recurred (22).

Botulinum toxin type A was also investigated in an open label study as an add-on therapy in 3 episodic cluster headache and 9 chronic cluster headache patients. A total of 50 units were injected ipsilateral to the headache in all 12 patients. A reduction in the attack frequency was seen in 2 patients, and one case reported remission from cluster headache. However, the rest of patients did not benefit from the treatment (23).

Neuro-stimulation and interventional approaches

Invasive procedures are available for patients who are refractory to pharmacological treatments. These procedures include peripheral nerve block, neuro-stimulation and as a last option ablative surgery.

Neuro-stimulation

Peripheral nerve stimulation, which is also called occipital nerve stimulation (ONS), is a non-destructive surgical approach for refractory cases of cluster headache. The procedure involves implantation of a battery-powered pulse generator with a wire, both are placed under the skin, the wire connects the device to the occipital nerve.

Since the hypothalamus is involved in the pathophysiology of cluster headache, hypothalamic deep brain stimulation (DBS) is considered to be the most promising form of neurostimulation. Leone et al. (24) reported that attacks improved significantly after DBS in a patient with chronic cluster headache that was not responsive to drug therapy.

Peripheral nerve block

Peripheral nerve blocks (PNBs) have been employed in the treatment of refractory cluster headache. Usually injection targets the greater occipital nerve (GON) because it could interrupt the trigeminal autonomic reflex pathway. Peres et al assessed the effectiveness of GON as transitional therapy in 14 patients with cluster headache. GON block was administered ipsilateral to head pain using lidocaine 1% and triamcinolone 40 mg and they evaluated the patients 1 week before and 1 week after GON block. The procedure was well tolerated; 9 out of 14 patients had a good or moderate response (25).

Surgery

The role of ablative surgeries has declined, with the development of other treatment options. Usually surgery is kept as a last-resort in the treatment of drug resistant patients who have chronically intractable and strictly unilateral side locked cluster headache. In comparison to chronic cluster headache,

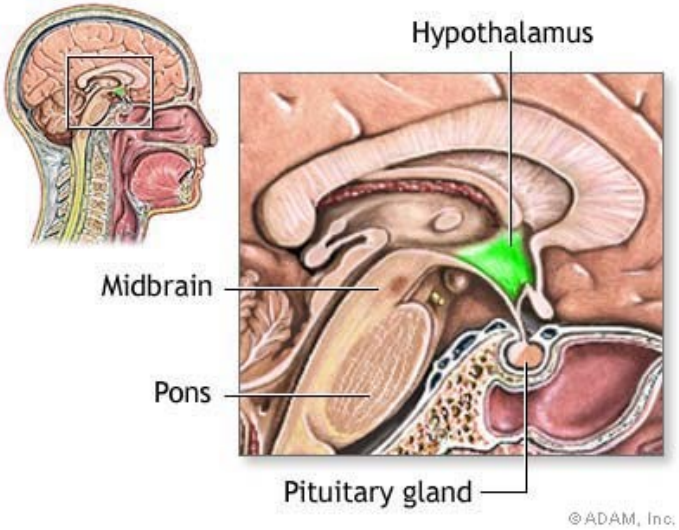

Table 2. Other therapies available for the treatment of cluster headache

Drug	Comments
Symptomatic therapy	
Ergotamine and dihydroergotamine	Lacks clinical trials and studies and its efficacy is based on clinical experience. It should not be used in patients with coronary, cerebral, vascular disease.
Lidocaine	Used as adjunctive therapy in patients that do not respond to other therapies.
Somatostatin and octreotide	They lack vasoconstrictive effect, making them viable treatment for patient with vascular disease.
Transitional therapy	
Methysergide	Lack placebo-controlled trails, it was found to be more effective in episodic cluster headache. Not to be used in more than 6 months.
Prophylactic treatment	
Topiramate	May be used as second-line option, however it has only been investigated in open label studies and it is associated with adverse events, which limit its use
Valproic acid	Associated with potential risk of hepatic failure
Gabapentin	Clinical practice did not observe their rapid onset of action
Melatonin	Contradictory findings

patients with episodic cluster headache rarely need surgical treatment as remission occurs. A number of procedures are available for refractory cases, such as radiofrequency ablation of the trigeminal ganglion, trigeminal sensory rhizotomy, gamma knife surgery, and microvascular trigeminal nerve decompression (15).

Current treatments

Treatment of cluster headache is essential because of the frequency of attacks and disability during a cluster period. Usually cluster headache management is divided into 3 categories, which include acute, transitional and prophylactic treatment. To alleviate the intense pain in acute setting of cluster attack, currently the first-line management includes 100% oxygen therapy, sumatriptan and zolmitriptan (18).

Acute symptomatic treatment is not sufficient alone, therefore, in order to control attacks, bridging with a transitional therapy is needed before starting long term prophylaxis. Currently, corticosteroids have been found to be highly effective and most rapid acting of the transitional preventive therapy.

Long term preventive therapy is used to maintain remission in cluster headache patients and prevent relapse. Verapamil is used as first line therapy for both episodic and chronic cluster headache patients due to its effectiveness and safety profile (15). An alternative available second-line is lithium carbonate; used if verapamil is not effective, however it has a narrow therapeutic window that is more associated with side effects (15) (Table 2).

Other therapies

Other therapies have been introduced because 10% to 20% of patients with cluster headache are resistant or develop resistance to conventional treatment. In addition, there are drugs with limited potential such as clonidine that was assessed in two studies (3). Despite that the first conducted study showed that the drug has positive outcome, the second one did not confirm these results. As a result

more studies are needed to assess its effectiveness. Since nocturnal plasma levels of melatonin are decreased in patients with cluster attacks, melatonin may be used as a therapeutic agent but there are contradictory findings, thus there is a need for further trials.

Several neuropeptides are released during cluster attack, such as substance P and CGRP. Civamide (*zucapsaicin)*, which is a cis-isomer of capsaicin, is a transient receptor potential vanilloid receptor modulator that depletes neuropeptides. Civamide is under active investigation because it selectively depresses activity in type-C nociceptive pathway and causes release and subsequently depletion of neuropeptides, which are involved in the pathophysiology of cluster attack. Intranasal civamide was compared to placebo and it was concluded that it produced more that 50% reduction in the frequency of cluster attacks (26). However, more studies are needed to ascertain its usefulness in acute treatment.

CGRP levels are elevated during cluster attack due to activation of trigeminal system and initiation of trigemino-vascular autonomic reflex that causes vasodilation and intense pain. The central role of CGRP in pathophysiology of cluster headache has made it a potential target for the treatment of cluster attack.

Conclusion

Cluster headache is characterised by severe unilateral pain and autonomic symptoms. There are no curative treatments. Pharmacological management is divided into 3 main categories. Acute treatment, which includes triptans and oxygen, is effective to alleviate pain during attack. Corticosteroids are the most widely used transitional therapy. For long term prevention, first line treatment is verapamil due to its safety and efficacy profile. Better understanding of the pathophysiology of cluster headache will be useful for developing new treatments.

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TEST YOUR KNOWLEDGE

1. Which of the following is a triptan used in the treatment of cluster headache?

A. Ergotamine
B. Sumatriptan
C. Verapamil
D. Methysergide
E. Lidocaine

2. ***A cis-isomer of capsaicin that is a vanilloid receptor modulator is***

A. Civamide
B. Melatonin
C. Dihydroergotamine
D. Valproic acid
E. Gabapentin

3. ***Which of the following is a somatostatin analog?***

A. Methysergide
B. Lidocaine
C. Octreotide
D. Topiramate
E. Lithium

Answers on back page

Is there a problem?

A 40 year old male patient was given the following prescription for his dyslipidemia. Is there any major error with the prescription?

BMX HOSPITAL

Patient Name: Mr. Ali Ahmad Age: 40 years
Address: Street No.1

Rx

Atorvastatin 20mg tablet
1 tablet twice daily
Send one pack

Dr. Tony
Signature Date: 4/12/16

Answer (Prescription Exercise)

The frequency is incorrect. Atorvastatin should be given once daily.
Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

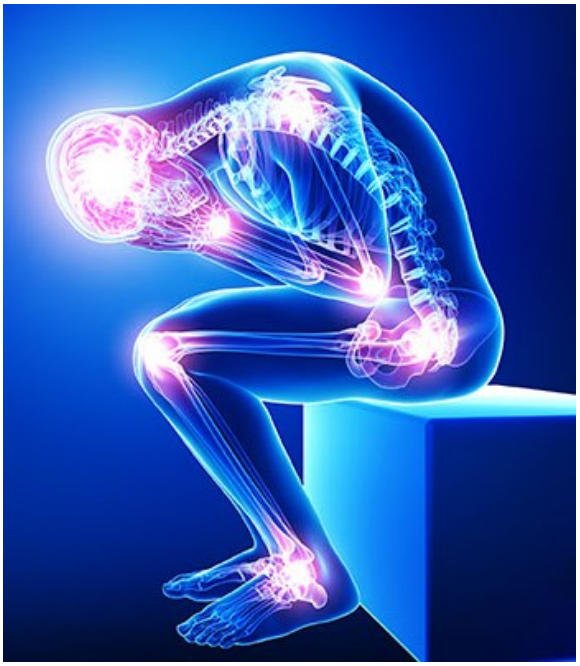
Chronic pain relieved by blocking a stress-related gene

A group from University College London (UCL) and their colleagues have found that through glucocorticoid signaling, the protein FKBP51 can regulate the perception of chronic but not acute pain in mice. Stress and chronic pain can go hand in hand, yet much of how stress and chronic pain–related signaling are connected remains a mystery. Previously shown to be involved in responses to stress in humans and rodents, FKBP51 now appears to be a factor common to both processes. The results, published in Science Translational Medicine, point to FKBP51 as a potential therapeutic target to alleviate long-term, persistent pain. The authors also confirm quite well that the mechanisms underlying acute pain versus chronic pain are distinct.

The study suggests that changes in the glucocorticoid system and FKBP51 in the neurons of the spinal cord contribute to the switch from analgesia to hyperalgesia, or hypersensitivity to pain, and to the development of chronic pain.

The glucocorticoid receptor is an important regulator of stress and inflammatory responses and FKBP51, an intracellular protein, is known to negatively regulate glucocorticoid signaling. Other groups, including McLean and colleagues, had previously shown that genetic variants of FKBP51 in humans result in higher levels of the protein, which can increase individuals' vulnerability to pain after a trauma; these variants have also been associated with major depression and post-traumatic stress disorder (PTSD). FKBP51 levels increase in the brain when the glucocorticoid receptor is activated, when cortisol binds the receptor, which can prolong the stress response. During chronic pain, FKBP51 also appears to promote inflammation and pain sensitivity by regulating glucocorticoid receptor function.

The UCL group started with the observation that FKBP51 expression and protein levels increase in the dorsal horn of the spinal cord, where pain sensory neurons are clustered, when inflammation is induced in the ankle joint of mice or rats, a model of arthritic pain. They wanted to test whether



FKBP51 more than just correlated with a pain state but could actually regulate the development of chronic pain.

Using FKBP51 knockout mice, the team found that these animals could cope better with the long-term pain induced by arthritic joints and nerve damage compared to their wild-type counterparts. The researchers also knocked down FKBP51 with small interfering RNA (siRNA) in the spinal cord, several days before or after inducing the ankle inflammation. As with the knockout mice, knockdown animals also showed reduced pain sensitivity. In a third test, an inhibitor of FKBP51 called SAFit2, injected into the spinal canal, led to a similar reduction in pain sensitivity.

In each case, initial, early pain signaling in the spinal cord was not affected by the absence of FKBP51; FKBP51-knockout mice were also still able to perceive acute pain in the form of hot, cold, or mechanical stimuli, the researchers reported.

After confirming that FKBP51 and the glucocorticoid receptor are both expressed in the same neurons within the spinal cord, the researchers used a drug antagonist of glucocorticoid receptor to test whether FKBP51 regulates glucocorticoid-mediated pain sensitivity in both injured and control mice. In

uninjured wild-type or knockout mice, glucocorticoid receptor signaling served an anti-inflammatory role. But when the wild-type animals were injured, GR [glucocorticoid receptor] signaling switched to a pro-inflammatory function, which did not happen in the knockout mice. According to experts, without FKBP51, the switch of the glucocorticoid receptor signaling from an anti-inflammatory to a pro-inflammatory role doesn't happen, so the knockout mice feel less pain.

Stress hormones, including glucocorticoids, are released after an injury or trauma, serving to dampen inflammation. But when the injury or stress is persistent and the release of the hormones is prolonged, this can have negative effects for the body, and these data support that idea.

FKBP51 could be a potentially promising target for treating chronic pain in patients, particularly in those that have had some sort of physical trauma or injury, similar to the mouse model. Given the terrible sometimes devastating side effects of opiate drugs, it is necessary to consider additional avenues for treatment of chronic pain and this study makes a very strong case for FKBP51 as one of those targets.

Source:
http://www.the-scientist.com/?articles.view/articleNo/45305/title/Blocking-a-Stress-Related-Gene-Relieves-Chronic-Pain/

Chemicals that change the way DNA is packaged could improve the effects of current antipsychotics

While antipsychotic drugs alleviate the symptoms of many people with schizophrenia, around a third of patients resist such treatments. A study, led by Javier Gonzalez-Maeso of the Mount Sinai School of Medicine, suggests that this frustrating intractability depends on how DNA is packaged. He and his colleagues found that antipsychotic drugs can suppress the expression of glutamate receptors in the brain, stunting their effectiveness as treatments for schizophrenia. But the researchers also found a way of boosting the effects of antipsychotic, by pairing them with drugs that block the gene suppression pathway.

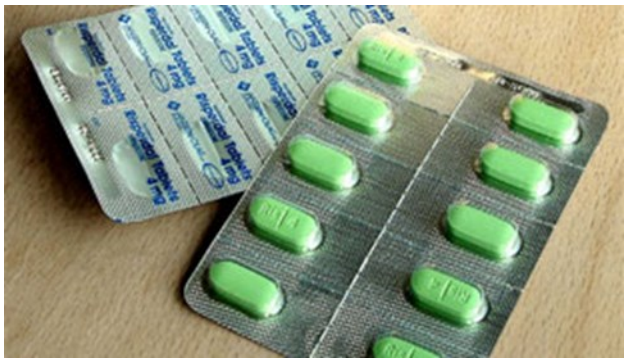
Second-generation antipsychotic drugs target the receptors for two brain signaling chemicals, dopamine and serotonin. In 2008, they had shown that serotonin and glutamate receptors interact antagonistically, with serotonin receptors linked to psychotic behaviors, and glutamate receptors linked to suppression of those symptoms. Now, the team has shown that long-term doses of antipsychotics suppress both pathways in a mouse's frontal cortex, an area of the brain involved in thought and perception. Thus, while the drugs may reduce psychotic episodes caused by the over-activation of serotonin receptors, they also hinder the helpful effects of the glutamate ones.

The reason for this, it turns out, is because the drugs change the structure of DNA in a way that inhibits the expression of mGlu2, the glutamate receptor gene. The genome's long strands of DNA wrap around proteins called histones to fit neatly inside the cell nucleus.

The Mount Sinai team found that clozapine, a second-generation antipsychotic drug, can alter the histones near a mouse's mGlu2 gene after just 3 weeks of treatment. The drug increases the levels of an enzyme called HDAC2, which alters the histones ahead of mGlu2 so they pack DNA more tightly. This silences the gene, and prevents glutamate receptors from being made.

The result is worse psychotic symptoms. When they loaded mouse brains with extra copies of HDAC2, the rodents produced fewer glutamate receptors and developed more schizophrenia-like behaviours, such as head twitches, hyperactivity, and poorer performance on memory tasks.

But by injecting the rodents with SAHA, a drug



that inhibits HDAC2, the researchers were able to reverse these effects. Glutamate receptor levels went up and behavioral tics fell away. SAHA even boosted the antipsychotic effects of clozapine. For example, clozapine on its own slashed the frequency of head twitches in the mice by two thirds, but the addition of SAHA cut that frequency even further.

It is hoped that these results will encourage other scientists to develop drugs that block HDAC2 as ways of treating schizophrenia, in conjunction with antipsychotics. But HDAC inhibitors have not improved the effects of antipsychotics in clinical trials. Other researchers noted that the HDAC inhibitor valproate has been tested with very mixed results. However valproate is a very broad-ranging inhibitor, and drugs which target HDAC2 more specifically could show stronger effects. Indeed, drugs that target mGlu2 receptors directly have already shown some promise in clinical trials as ways of controlling psychotic symptoms.

Adapted from: http://the-scientist.com/2012/08/05/boosting-antipsychotic-drugs/

MicroRNA mixture turns skin cells into neurones

Unique microRNA molecules, plus a mixture of transcription factors, can convert human fibroblasts directly into striatal medium spiny neurones.

Researchers at Washington University School of Medicine in Saint Louis have successfully turned human fibroblasts into striatal medium spiny neurones, the type of brain cells affected in Huntington's disease.

The team had used specific microRNA molecules known to play roles in brain development- called miR-9 and miR-124 -to turn fibroblasts into neural precursor cells. But the researchers wanted to direct the fate of the cells even further- to make them specifically become medium spiny neurones (MSNs).

These microRNAs control chromatin remodeling by promoting the switching of the subunits of the chromatin remodeling complex. By doing that, they somehow provide this cellular state that responds better to transcription factors.

In addition to the microRNAs, the team added different combinations of transcription factors to fibroblasts. A combination of four factors, BCL11B, DLX1, DLX2, and MYT1L, all found naturally at high levels in the developing brain, ended up being the winning mixture.

Not only did the new MSNs express all the cellular markers indicative of the cell type, they also survived for months in the brains of mice, where they grew in normal patterns and showed the expected activity. In fact, the cells more closely resembled MSNs than scientists have previously achieved using induced pluripotent stem cells -where fibroblasts or other adult cells are first coaxed into stem cells before being directed down the path to become neurones.

The team plans to continue working on using the direct conversion protocol to study Huntington's disease. They're already using skin cells from Huntington's patients to try to generate MSNs for therapeutic use, but the group also wants to fine tune their method to create other neuronal cell types as well.

Reference:
Victor, M.B., Richner, M., Hermanstyne, T.O. et al (2014) Generation of Human Striatal Neurons by MicroRNA-Dependent Direct Conversion of Fibroblasts. Neuron 84: 311-323

NEWS from the FDA

"Farmaceutical" drug from transgenic chickens

The FDA approval in December, 2015, of Alexion Pharmaceuticals' Kanuma (sebelipase alfa) is only the fourth for a recombinant protein drug produced in an unconventional expression system. It is purified from the egg white of transgenic hens (*Gallus gallus*), a production method chosen because of the glycosylation pattern of the resulting protein. It is approved for treating two forms of lysosomal acid lipase (LAL) deficiency: a fatal, early-onset form called Wolman disease and cholesteryl

Advice from Centre for Disease Control

Deep vein thrombosis (blood clots)

Deep vein thrombosis (DVT) is often an underdiagnosed and serious, but preventable medical condition. It occurs when a blood clot forms in a deep vein. These clots usually develop in the lower leg, thigh, or pelvis, but they can also occur in the arm. Another type of blood clot, called pulmonary embolism (PE), can form when part of a blood clot breaks off and travels to the lungs.

It is important to know about DVT and PE because they can happen to anyone and can cause serious illness, disability, and in some cases, death. The good news is that blood clots are preventable and treatable if discovered early.

Symptoms

About half of people with DVT have no symptoms at all. The following are the most common symptoms that occur in the affected part of the body:

- swelling
- pain
- tenderness
- redness of the skin

PE can occur without any symptoms of a DVT. Signs and symptoms of a PE include:

- difficulty in breathing
- faster than normal or irregular heartbeat
- anxiety
- coughing up blood
- very low blood pressure, lightheadedness, or fainting

Steps for self protection

The following tips can help prevent blood clots:

- moving around as soon as possible after being on bed rest, such as after surgery, illness, or injury
- if at risk for blood clots, consider:
  - ♦ graduated compression stockings (sometimes called "medical compression stockings")
  - ♦ medication (anticoagulants) to prevent blood clots.
- when sitting for long periods of time, such as when traveling for more than 4h, consider:
  - ♦ getting up and walking around every 2-3 h
  - ♦ exercising legs while sitting by:
    raising and lowering heels while keeping toes on the floor
    raising and lowering toes while keeping heels on the floor
  - ♦ tightening and releasing leg muscles
- ♦ wearing loose-fitting clothes

ester storage disease, a less severe form that can cause liver fibrosis, cirrhosis and eventually liver failure.

Despite its undoubted potential from a cost and performance perspective, molecular 'farming' has remained a minority pursuit in the decade following the first such approval, that of ATryn, a recombinant anti-thrombin produced in the milk of transgenic goats.

In terms of volume, biologics produced in unconventional systems represent a tiny fraction of the industry's total output. Kanuma could mark a turning point in the development of the sector, given the blockbuster ambitions that Alexion, of Cheshire, Connecticut, has attached to the product. Last June, Alexion paid $8.4 billion in cash and shares to ac-

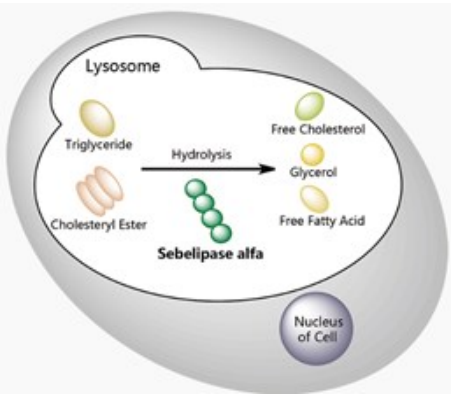
quire its developer, Lexington, Massachusetts-based Synageva BioPharma (formerly AviGenics).

The original AviGenics organization was formed in Athens, Georgia, in 1996 to employ a retroviral approach to generating transgenic chickens for the production of recombinant proteins. The chick egg production system has certain advantages. Chick egg whites lack proteases in the cell lysate that plague other production systems. These give rise to breakdown products that can cause immunogenicity problems. The chick egg does not have any proteases but protease inhibitors. Even so, severe hypersensitivity reactions occurred in 21 of 106 patients who received Kanuma during clinical trials, three of whom developed anaphylaxis. The issue necessitates strict medical supervision during administration of the drug. But the scaling flexibility and cost profile of the production system are both favorable.

In parallel with transgenic animals, plant-based production systems are emerging. Improving yields have eliminated the once controversial prospect of growing genetically modified crops to produce pharmaceuticals in open field systems. Contained greenhouse facilities, as well as newer bioreactor vessels for culturing transgenic plant cells, are now sufficient.

Protracted manufacturing problems that emerged at a Genzyme CHO facility in Allston, Massachusetts, in 2009 created an opportunity for Protalix Biotherapeutics, of Carmiel, Israel, to win approval for its ERT for Gaucher disease, Elelyso (taliglucerase alfa), which is produced in a closed plant cell–based system, contained within disposable plastic chambers. New York-based Pfizer's move to in-license and subsequently acquire rights to this product outside of Israel and Brazil (where Protalix has entered a technology transfer and supply agreement with the country's health ministry) shows big pharma is at least open to the technology, even if it not yet getting involved in early-stage development. All of a sudden plant antibodies became known around the world.

Glycosylation patterns in plant-produced proteins



can differ from those obtained in mammalian culture systems. They tend to be homogeneous however, whereas mammalian cell production systems generate a wider distribution of glycosylation variants. Greenovation Biotech, of Freiburg, Germany, has engineered the glycosylation machinery of its producing strain of moss, *Physcomitrella patens*, in order to eliminate plant specific α-1,3-fucose and β-1,2-xylose residues and maximize the numbers of proteins with N-terminal mannose residues, so as to favor uptake by kidney cells. The company recently obtained clearance to conduct the first trial of a therapeutic produced from this system, α-galactosidase A, in patients with Fabry disease. The company, which, like Protalix, also uses a closed, disposable cell culture system, is scaling up production from 300 liters to 5,000 liters. That would be sufficient to cover the world's entire population of patients with Fabry disease.

Production systems based on mammalian cell culture continue to set the standard, and alternative systems have failed to keep pace with them over the past two decades. But they are filling niches that conventional systems have failed to address adequately, and the next two decades are unlikely to be a repeat of the last two. As the case of Synageva shows, the opportunity exists, and it's all about getting products out onto the market.

Source: http://www.nature.com/nbt/journal/v34/n2/full/nbt0216-117.html

Ipilimumab for earlier stage melanoma

Ipilimumab (Yervoy, Bristol Myers Squibb) is now approved by the FDA as an adjuvant therapy for stage III melanoma patients. In this setting, the immunotherapy is used following surgery to lower risk of relapse. Ipilimumab is already approved for treatment of metastatic stage IV melanoma.

The monoclonal antibody, first approved in 2011, blocks the cytotoxic T-lymphocyte antigen 4

(CTLA-4) which can slow down a patient's immune system against cancer. Ipilimumab blocks this antigen, facilitating the immune system's ability to recognize melanoma cells as foreign.

Ipilimumab was the first immune checkpoint antibody to be approved for melanoma.

Approval of Yervoy extends its use to patients at high risk of recurrence of melanoma after surgery.

According to a statement by the Melanoma Research Foundation, the approval is the first by the FDA in 20 years for an adjuvant melanoma therapy. Another available adjvuvant option for stage III patients is interferon.

The FDA approval is based on the EORTC 18071 phase III randomized, double blind clinical trial of 951 patients with high-risk stage III melanoma. All patients had complete lymph node dissection prior to starting the trial. Patients were randomized to either 10 mg/kg ipilimumab or placebo infusions every 3 weeks for 4 doses, and then every 3 months for up to 3 years or to placebo (*The Lancet Oncology* 16(5):522-30: 2015.

The most common reported side effects were rash, diarrhea, fatigue, itching, headache, weight loss, and nausea. The most common high-grade immune-related adverse events were gastrointestinal, hepatic and endocrine. Adverse events resulted in 52% of patients discontinuing treatment. Five patients (1%) died due to a drug-related adverse event in the ipilimumab treatment arm. Three patients died from colitis (two with gastrointestinal perforation), one patient because of myocarditis, and one patient from multi-organ failure due to Guillain-Barré syndrome.

The median recurrence-free survival was 26 months in the ipilimumab study arm compared to 17 in the placebo arm. The 3-year recurrence-free survival was 47% in the ipilimumab arm compared to 35% in the placebo arm.

Adjuvant ipilimumab significantly improved recurrence-free survival for patients with completely resected high-risk stage III melanoma. The adverse event profile was consistent with that observed in advanced melanoma, but at higher incidences in particular for endocrinopathies. The risk-benefit ratio of adjuvant ipilimumab at this dose and schedule requires additional assessment based on distant metastasis-free survival and overall survival endpoints to define its definitive value.

Source: http://www.oncotherapynetwork.com/

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved in September and October 2016

Actilor Syrup; Desloratadine -2.5mg/5ml;Neopharma/UAE
Adwiflam Ampoules75mg/3ml; Diclofenac Potassium – 75mg; ADWIA/Egypt
Atorvastatin Azevedos Tablets 10,20,40,80mg; Atorvastatin (as calcium) – 10,20,40,80mg; Laboratorios Azevedos-Industria Farmaceutica S.A./Portugal
Azitro Tablets 250mg; Azithromycin (as dehydrate) – 250mg; Deva Holding A.S./Turkey
Betacal Injection; Calcipotriol (as monohydrate) – 0.005% Betamethasone (as dipropionate) – 0.05%; Jerash Pharmaceuticals Ltd./Amman
Blincyto Powder for Solution for I.V. Infusion 35mcg;Blinatumomab (rDNA) – 35mcg; Amgen Inc./USA
Danset Injection 8mg; Onolansetron (as Hydrochloride Dihydrate) – 8mg; ADWIA/Egypt
Dapamix Sustained Release Film-Coated Tablets;Indapamide – 1.5mg; A-Taqaddom Pharmaceutical Industries/Jordan
Ferriprox Oral Solution; Deferiprone – 100mg; Apotex Inc./Canada
Gordex Powder for Solution for IV Injection/Infusion; Esomeprazole Sodium – 42.60 (equivalent to Esomeprazole 40mg); Gulf Pharmaceutical Industries (Julphar)/UAE
G-Pride Tablets; Glimepiride –1,2,3,4,mg; Oman Pharmaceutical Products Co. L.L.C./Sultanate of Oman
Hepatab Tablets 0.5, 1mg; Entecavir (as monohydrate) – 0.5, 1mg; Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia

Joswe Flamex Capsules 200, 400mg; Celecoxib – 200, 400mg; Jordan Sweden Medical & Sterilization Co. (Jose Medical)/Jordan
K-Flam Powder for oral Solution; Diclofenac Potassium – 50mg/sachet; Neopharma/UAE
Levetiracetam Normon Tablets 1000mg; Levetiracetam – 1000mg; Laboratories Normon S.A/Spain
Locoid Ointment; Hydrocortisone Butyrate – 1mg/gm; Astellas Pharma Europe B.V./The Netherlands
Magnacef Capsules 400mg; Cefixime (as trihydrate) – 400mg; Ram Pharmaceutical Industries Co. Ltd./ Jordan
Moldamine Powder for Suspension for Injection 1200000 IU; Benzathine Benzylpenicillin – 1200000; S.C. Antibiotice S.A/ Romania
Normosang Concentrate for Solution for Infusion; Human hemin – 25mg/ml; Orphan Europe SARL/ France
OxyNorm Hard Capsules; Oxycodone Hydrochloride – 5,10,20mg; NAPP Pharmaceuticals/UK
Peyona Solution for Infusion/Oral Solution; Caffeine citrate 20mg equivalent to caffeine – 10mg; Chiesi Farmaceutici S.p.A./Italy
Praxabind Solution for Injection/Infusion 50mg/ml; Idarucizumab (rDNA) – 50mg; Boehringer Ingelheim International GmbH/Germany
Renacol Effervescent Granules; Sodium Bicarbonate – 1.76g/sachet, Tartaric Acid – 0.89g/sachet, Anhydrous Citric Acid – 0.72g/sachet; Anhydrous Sodium Citrate – 0.63g/sachet; Neopharma/UAE
Roxicef Powder for IM/IV Injection or Infusion; Cefuroxime (as sodium) – 750mg; KSPICO/Kuwait
Simbrinza Eye Drops, Suspension; Brinzolamide – 10mg; Brimonidine tartrate – 2mg; Alcon Laboratories (UK) Ltd./U.K.
Surgicaine Injection 1:200,000; Bupivacaine Hydrochloride Anhydrous – 5mg; Epinephrine (Bitartrate) – 0.005mg; Novocol Pharmaceutical of Canada Inc./Canada
Suxamethonium Chloride VUAB Powder for Solution for Infusion 100mg; Suxamethonium Chloride (as dihydrate) – 100mg; VUAB Pharma a.s./Czech Republic
Taltz Injection; Ixekizumab (rDNA) – 80mg/ml; Eli Lilly Company/USA
Uripan Syrup; Oxybutynin – 5mg; ADWIA/Egypt
Vancomycin Sandoz Powder for Solution for Infusion 500, 1000mg; Vancomycin (as HCl) – 500, 1000mg; Lek Pharmaceuticals/Solvenia
Vargatef Sof t Capsules 100, 150mg; Nintedanib (as esilate) – 100, 150mg; Boehringer Ingelheim International GmbH/Germany

Answers to: Test your knowledge

Correct answers:
1-b; 2-a; 3-c

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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