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Targeting the endocannabinoid system for the management of neuropathic pain

Diabetic neuropathy from uncontrolled hyperglycemia, posttherpetic neuralgia, trigeminal neuralgia, HIV-related peripheral neuropathy and cancer-related neuropathy are examples of neuropathic pain syndromes. Signs and symptoms include paresthesia, numbness, burning or cold and shock-like sensation. Central neuropathic pain is caused by a lesion or disease of the central somatosensory nervous system. This includes changes in the spinal cord neurons, the descending pain-controlling systems and abnormal brain plasticity. Peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system; changes in the excitability of the peripheral nerve and the dorsal root ganglion. A common feature of these syndromes is co-existence of negative and positive symptoms which reflect, respectively, loss- and gain-of-function of the somatosensory system. Some patients describe it as burning or cold and shock-like spontaneous pain, paresthesia and numbness. The pain affects quality of life and may cause mood or sleep disturbances. It is difficult to diagnose and hard to achieve a satisfactory treatment response.

Types of neuropathic pain

Diabetic neuropathic pain is caused by nerve damage or disorders associated with microvascular complications that occur in a patient with diabetes mellitus due to uncontrolled hyperglycaemia [1]. Symptoms usually include numbness, tingling, pain and weakness. Dizziness with postural changes can be seen with autonomic neuropathy.

In case of posttherpetic neuralgia, it is defined as severe pain in the area of distribution of a herpes zoster eruption, persisting more than 30 days after the onset of rash or after cutaneous healing. The pain is usually described as a continuous deep aching, burning, stabbing and shooting sensation; allodynia, a type of evoked pain that is provoked by a non-noxious stimulation, is frequent.

Trigeminal neuralgia is a chronic neuropathic pain condition, affecting one or more branches of the trigeminal nerve. It is characterised by unilateral, sudden, shock-like and brief (fractions of a second to minutes) painful attacks, which follow the distribution of trigeminal nerve branches, and with no other sensorimotor or autonomic signs and symptoms. Each one of the syndromes differs in diagnosis, prognosis and treatment [2].

Peripheral neuropathy is a common neurological complication in type-1 HIV infection. There are six major clinical types of HIV-associated neuropathies. Distal sensory polyneuropathy (DSP), the most common one can be caused by infectious, metabolic, inflammatory, nutritional and toxic factors [1, 3]. Direct neurotoxicity of the virus and its products and neurotoxicity of combination anti- retroviral therapy (cART) are two distinct pathophysiologic processes which may contribute to the development of HIV DSP, but the actual pathogenesis is incompletely understood. Neuropathy in HIV is mainly distal, symmetric, sensory neuropathy characterised by a variety of clinical symptoms. The most frequently encountered ones are decreased or absent ankle jerks and decreased pinprick and vibration sensation involving the distal lower extremities. HIV DSP can be asymptomatic, but many patients experience numbness, tingling, or pain in a stocking-glove distribution [4].

Cancer-related neuropathic pain is chronic with acute exacerbations, peaking several times a day. It can be disease related, caused by released inflammatory cytokines that sensitise neurones leading to PNS or CNS damage, or related to the acute or chronic effects of cancer treatment. These exacerbations can be either triggered or spontaneous.

Such spontaneous and evoked types of pain are perceived in areas of sensory abnormality (hyposensitivity, hypersensitivity, or both). Spontaneous pain may be ongoing, with a constant or fluctuating pain intensity, or dominated by pain paroxysms of short duration with pain-free intervals or a less intense background pain. Other sensations, such as paraesthesia and dysesthesia (unpleasant abnormal sensation) may be present spontaneously or occur only when evoked by a stimulus. Dynamic mechanical allodynia (or touch-evoked allodynia) is the most common form in cancer patients [5].

In this issue

Endocannabinoid system

The endocannabinoid system has become an interesting therapeutic target for treating and managing neuropathic pain. This is composed of endocannabinoids, their receptors and enzymes involved in their synthesis and degradation. Several diseases or disorders like emesis, pain, inflammation, multiple sclerosis, anorexia, epilepsy, glaucoma, schizophrenia, cardiovascular disorders, cancer, obesity, metabolic syndrome related diseases, Parkinson's disease, Huntington's disease, Alzheimer's disease and Tourette's syndrome could possibly be treated by drugs modulating the endocannabinoid system. Cannabinoids are either exogenous or endogenous. Exogenous cannabinoids known as phytocannabinoids for example cannabidiol (CBD) and tetrahydrocannabinol (THC) are derived from actual cannabis plants. The other exogenous cannabinoids are synthetic, for example nabilone and dronabinol derived from THC [6]. Endogenous cannabinoids are anandamide (N-arachidonoylethanolamide (AEA) and 2-arachidonyl glycerol (2-AG) [7,8]. Anandamide binds to CB1 receptor and acts as mood enhancer and stimulates sensation of joy and happiness acting on the same receptors as THC.

Cannabinoid receptors

The main receptor targets for eCBs are type-1 (CB1) and type-2 (CB2) G protein-coupled cannabinoid receptors that are coupled to adenylate cyclase [9]. Tetrahydrocannabinol, the psychoactive constituent of cannabis, exerts its effect on the brain and body through activation of CB receptors [10]. CB1 is mainly localised in the brain (hippocampus, cerebellum and cerebrum), whereas CB2 is localised mainly in the periphery (spleen, tonsillar and immune cells). The two main endocannabinoids are anandamide and 2-AG, which are CB receptor ligands made from phospholipids that are integral to mental function and stress management. They help in maintaining homeostasis. They are produced as needed and then rapidly degraded to inactive substances. They differ from other neurotransmitters in that they act with retro- grade suppression, so they work on presynaptic neurones. Cannabinoids act at CB1 receptors to inhibit neurotransmitter release, by decreasing glutamate release from primary afferent terminals

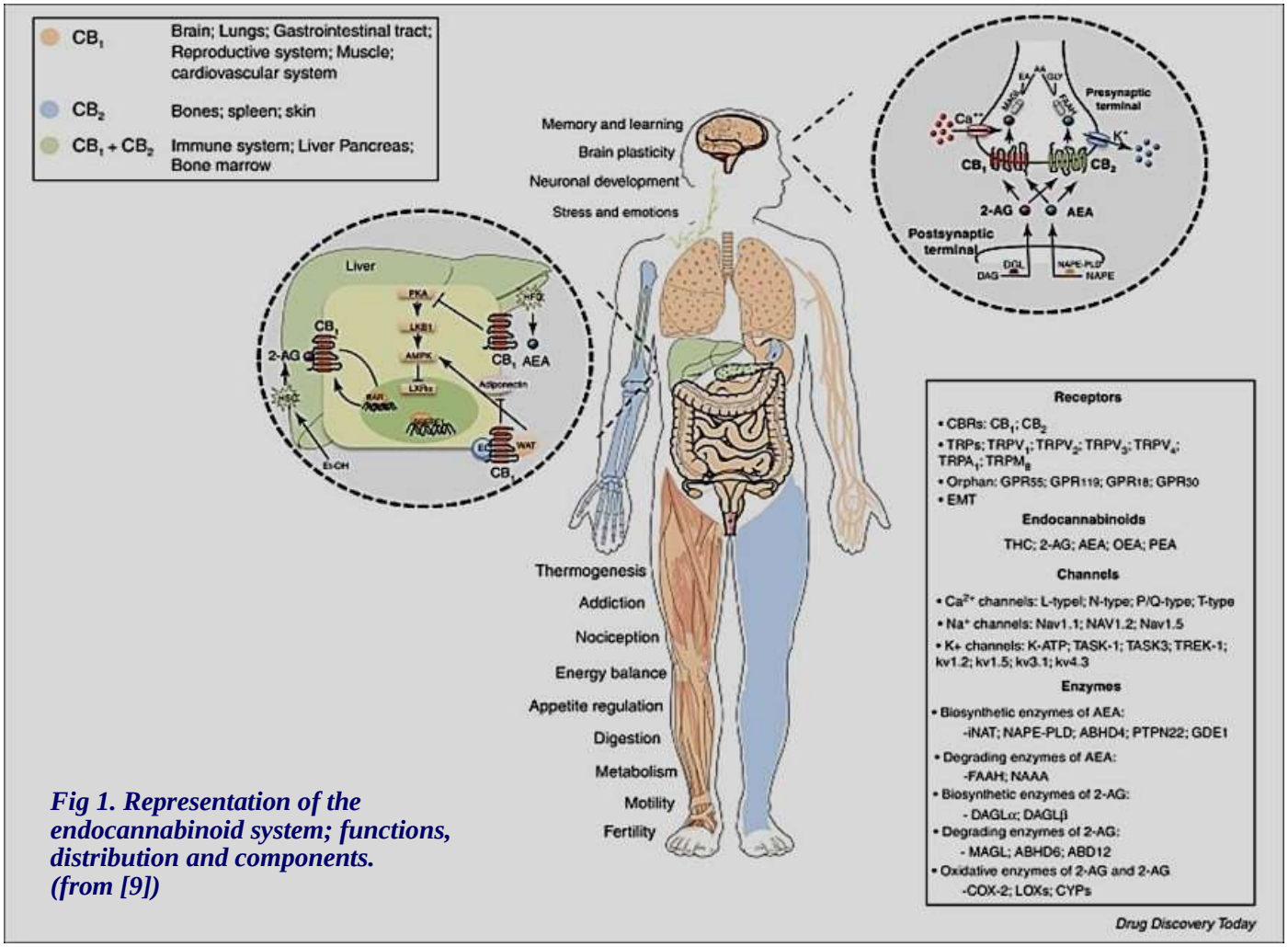

Fig 1. Representation of the endocannabinoid system; functions, distribution and components. (from [9])

and inhibiting C fibers leading to antinociception through inhibition of neural transmission in the spinal cord [11] (Fig 2).

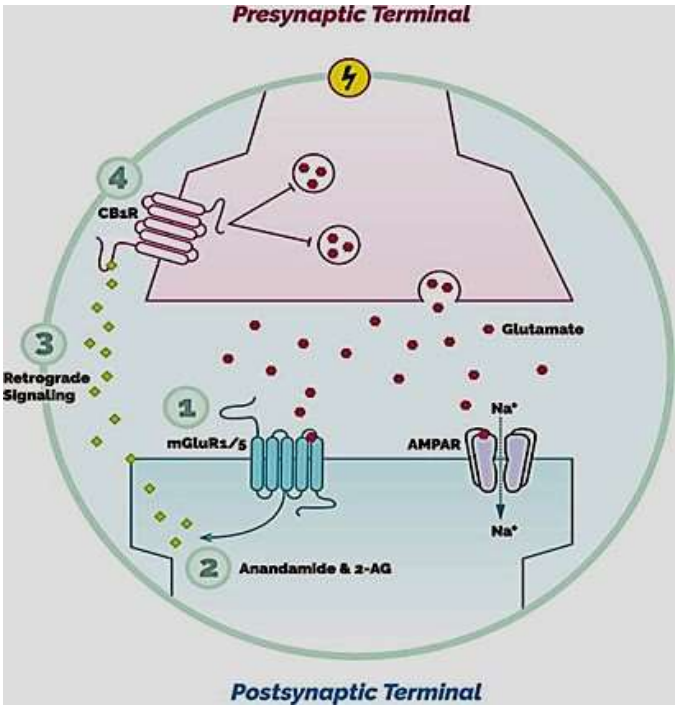

Fig 2. Endocannabinoid synthesis a & signaling [12]

A schematic representation of the endocannabinoid inactivating pathways is illustrated in Fig 3.

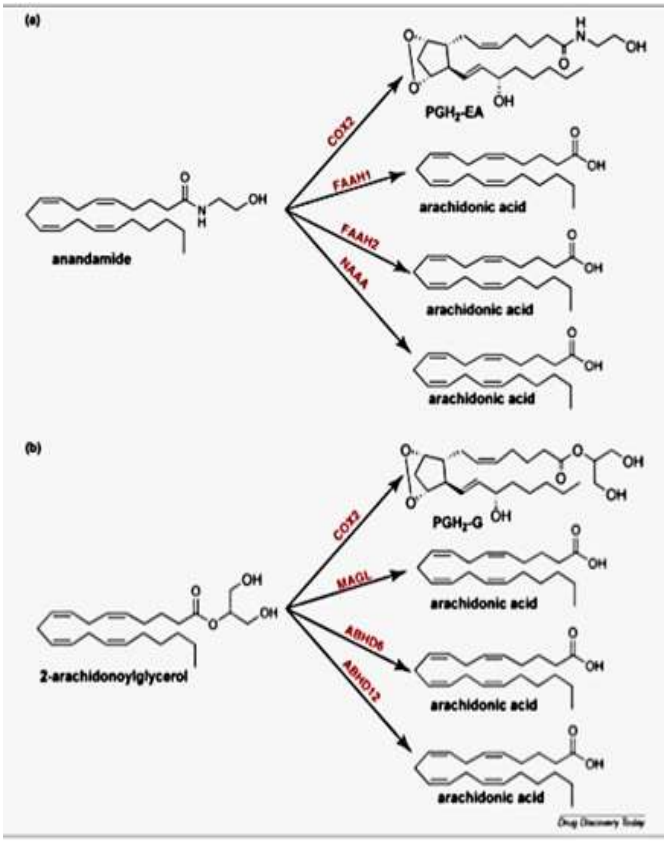

Fig 3. Endocannabinoid inactivating pathways [13]

Preclinical studies

The pathophysiology of neuropathic pain is complex due to functional alterations of the CNS and PNS, in addition to neuro-immune interactions. Deletion of CB1 receptor in peripheral nociceptors leads to enhanced pain behaviour and decreased antinociceptive effects of cannabinoid receptor agonists, indicating an important role of peripheral CB1 receptors in neuropathic pain [2]. CB2 receptor deletion also leads to varying effects on neuropathic pain. CB2 (−/−) mice show exacerbated pain behaviour, while CB2 over-expression in the CNS attenuates neuropathic pain [2]. Both CB1 and CB2 receptor agonists give antinociceptive effects in laboratory animal models of neuropathic pain.

Most preclinical studies on animal models of neuropathic pain using streptozocin (STZ) to induce diabetes, 2′,3′-dideoxycytidine (ddC, zalcitabine), an anti-retroviral to induce HIV-related thermal hyperalgesia and cisplatin or paclitaxel to induce chemotherapy-related neuropathic pain, found decreased anandamide and 2-arachidonyl glycerol levels. Cannabinoid receptor agonists, inhibitor of fatty acid amide hydrolase (FAAH), the enzyme which degrades anandamide, inhibitors of monoacylglycerol lipase (MAGL), the enzyme which degrades 2-arachidonyl glycerol, as well as cannabis and its extracts managed to either prevent the development of or to reduce signs of neuropathic pain such as allodynia and hyperalgesia in animal models. The results also showed that using CB2 selective agonists would overcome the CNS side effects, tolerance and physical withdrawal associated with CB1 selective agonists [14].

Decreased endocannabinoids (AEA and 2-AG) levels were shown in two of the three animal models of neuropathic pain: diabetic neuropathic pain and cancer-related neuropathic pain. No studies were found that studied the expression of AEA in HIV-related neuropathic pain, although there were changes in the expression of FAAH and MAGL [15-17].

Small-fibre (C and Aδ) neuropathy is responsible for the early hyperalgesia and allodynia, and the late hypoalgesia, impairment of warm thermal perception and skin blood flow in diabetic patients. Most of these small diameter nociceptive neurones constitutively express vanilloid receptors (TRPV1) and cannabinoid CB_1 receptors, which mediate pro- and anti-nociceptive actions, respectively. There appears to be a differential regulation of CB1 versus TRPV1 expression and/or function in diabetes. While up-regulation and sensitization of the TRPV1 receptor protein occurs in response to hyperglycemia, leading to acute thermal hyperalgesia and allodynia

in diabetic animals and decreased neuronal expression of CB1 receptors in *in vitro* and *in vivo* models of diabetic neuropathy have also been reported [18]. In diabetic neuropathic pain models, CB agonists (e.g. ACEA, a highly selective CB1 receptor agonist and AEA, a non-selective CB agonist), an anandamide reuptake inhibitor (AM404), and a FAAH inhibitor (ST4070) reduced hyperalgesia and allodynia. Cannabinoid receptor agonists (e.g. WIN-55,212-2, a non-selective CB agonist, and L-759,656, a selective CB2 receptor agonist) had anti-hyperalgesic effects in streptozocin-induced diabetic mice [18].

In an animal study investigating the anti-hyperalgesic activities of endocannabinoids in a mouse model of antiretroviral-induced neuropathic pain, an antiretroviral 2′,3′-dideoxycytidine (ddC, zalcitabine) was administered to induce thermal hyperalgesia [16].

Treatment with ddC did not affect the expression of endocannabinoid-synthesizing enzymes in the brain or spinal cord. The expression of endocannabinoid-inactivating enzymes (FAAH and MAGL) in the spinal cord were not affected by ddC treatment. On the other hand, ddC treatment significantly decreased the transcripts of FAAH and MAGL in the brain and in the paw skin, respectively. The results of the study showed that ddC induces thermal hyperalgesia and dysregulation of the mRNA expression of endocannabinoid molecules, more importantly down-regulation of *MAGL* and *FAAH,* which are involved in the inactivation of the endocannabinoids AEA and 2-AG [16].

Treatment with 2-AG and AEA increased the reaction latency in mice with ddC-induced thermal hyperalgesia, whereas there was no significant change in the reaction latency to thermal stimuli in naïve mice. The anti-hyperalgesic activity of AEA was dependent on activation of both CB1 and CB2 receptors, whereas that of 2-AG was dependent on CB1 receptor and G-protein coupled receptor (GPR55), but not CB2 receptor. Since there was low expression of the degrading enzyme transcripts in mice with ddC-induced thermal hyperalgesia, AEA and 2-AG had anti-hyperalgesic activity but they did not show any activity in naïve mice [16].

It has also been observed that treatment with cannabinoid receptor agonists such as WIN 55,212-2 had anti-hyperalgesic activity in a rodent model of HIV-induced neuropathic pain. Two FAAH inhibitors, URB597 and PF-3845, were administered and significantly decreased cold and tactile allodynia with no significant decrease in mechanical hyperalgesia compared with vehicle treatment. AM251, a CB1 antagonist, and SR144528, a CB2 antagonist, blocked the tactile and cold anti-allodynic effect of URB597, but no effect was observed when AM251 or SR14452 were given alone. Administration of AM251 or SR144528 also significantly blocked the anti-allodynic effect of PF3854 [19]. To summarise, endocannabinoids (2-AG and AEA), cannabinoid receptor agonists (e.g. WIN-55,212-2) and FAAH inhibitors (e.g. URB597 and PF-3845) decreased mechanical hypersensitivity, cold and tactile allodynia in animal models of HIV-related neuropathic pain.

Endocannabinoids (2-AG and AEA), cannabinoid receptor agonists (e.g. WIN-55,212-2, a non-selective CB agonist and MDA19, a novel cannabinoid ligand and AM1241, a selective CB1 agonist, CB2 receptor-selective agonists such as AM1710 and LY2828360), FAAH inhibitors (e.g. ST4070, URB597 and URB937), MAGL inhibitors (e.g. JZL184) and cannabis extracts (e.g. THC) prevented or decreased mechanical allodynia and hyperalgesia in animal models of cancer or paclitaxel-induced neuropathic pain.

The studies that measured the expression of endocannabinoids in animal models of CINP suggest that there is a specific deficiency of endocannabinoids in the periphery during CINP [20].

Thus, increasing the levels of these endocannabinoids in the periphery by inhibiting either degradation or transportation may help in managing CINP [21]. Δ^9 tetrahydrocannabinol (THC), and WIN 55,212-2 prevented the development and attenuated established CINP symptoms mainly in a CB1 receptor dependent manner, because CB1 receptors are expressed at higher concentrations in the nervous system, while CB2 receptors are mainly expressed in the immune cells [20]. For the previous reasons, a CB1 receptor-selective agonist ACEA was used and resulted in prevention of the development of cisplatin-induced mechanical allodynia in rats, when administered either systemically or locally [22].

Unfortunately, it resulted in several problems such as physical dependence, tolerance and withdrawal adverse effects. Therefore, it would be better to use CB2 receptor-selective agonists to produce anti-allodynic effects and avoid the unwanted central effects associated with CB1 receptor-selective agonists. CB2 receptor-selective agonists such as AM1710 and LY2828360 reduced paclitaxel-induced mechanical and cold allodynia without producing tolerance and physical withdrawal [23, 24]. From these results it becomes clear that targeting the endocannabinoid system for prevention and treatment of CINP is a reasonable therapeutic option [20].

Clinical Studies

In clinical trials of diabetic neuropathic pain, cannabis was effective in reducing pain in two clinical trials, whereas Sativex and ASP8477, did not show any significant effect compared to placebo.

A randomized, double-blinded, placebo-controlled crossover study was conducted with sixteen patients with painful diabetic peripheral neuropathy (DPN) to study the effect of using inhaled cannabis on pain and hyperalgesia of DPN. The results were dose-dependent reduction in spontaneous and evoked pain [23].

Another randomized double-blind placebo-controlled crossover study was conducted to evaluate the analgesic efficacy of vaporized cannabis in neuropathic pain patients. They found that it reduced the daily pain scores and neuropathic pain scale score compared with placebo [24]. A randomized placebo-controlled double-blind clinical trial to assess efficacy of Sativex, a cannabis-based medicinal extract, in painful DPN found no significant difference in total pain score (TPS) between Sativex and placebo [25]. In another clinical trial (NCT00710424) Sativex was found to have beneficial effects [26].

Another randomized clinical trial to assess the efficacy of ASP8477, a FAAH inhibitor, in patients with painful DPN found no significant effect with ASP8477 compared to placebo [27].

In two clinical trials of HIV-associated neuropathic pain, smoked cannabis was found to be effective in managing and reducing daily pain compared to placebo. There is an ongoing clinical trial to study the effect of cannabis and its extracts on HIV-related neuropathic pain. In a randomised clinical trial study, smoked cannabis was found to be efficacious in the management of painful HIV-associated sensory neuropathy. It resulted in significant reduced daily pain and it also decreased experimentally induced hyperalgesia [28]. Another randomised crossover clinical trial to study the effect of smoked cannabis on painful HIV-associated sensory neuropathy found reduction in daily pain score and significant reduction in pain intensity [29]. An ongoing clinical trial to study the effect of cannabis and endocannabinoids on HIV- related neuropathic pain is due to complete by end of 2020 [30].

In a randomised placebo-controlled clinical trial of cancer-related neuropathic pain to study THC and THC:CBD extract effect on intractable-cancer related pain including neuropathic pain, it was shown that THC:CBD extract, but not THC alone, was effective in relieving pain [31]. Another double-blind placebo-controlled crossover pilot trial used an oral mucosal spray containing cannabinoid extract, known as nabiximols (an extract of cannabis) or Sativex, to treat CINP. This trial found that no significant difference in numeric rating scale for pain intensity (NRS-PI) between the treatment and the placebo groups [32] meaning that Sativex was not effective against chemotherapy induced neuropathic pain (CINP).

Current and potential uses of drugs that modulate the endocannabinoid system in management of neuropathic pain

Although animal studies and clinical trials have shown that use of drugs that act on the endocannabinoid system is effective in relieving diabetic, HIV-related, cancer-related neuropathic pain, none of these drugs are FDA approved for that purpose, and their use is off-label [33].

Cannabis sativa (hemp) resulted in significant efficacy in treating neuropathic pain in patients in general but the cannabis extract (Sativex) or FAAH inhibitor had no effect [34].

Cannabinoids are now recommended in Canada as third-line agents in treating neuropathic pain, including HIV patients and diabetic patients, after gabapentinoids, tricyclic antidepressants (TCAs), and serotonin-norepinephrine re-uptake inhibitors (SNRI) as first-line drugs, lidocaine, capsaicin, and tramadol as second-line drugs, strong opioids (morphine and oxycodone) and botulinum toxin-A (BTX-A) as third -line drugs [26, 35]. This recommendation is still weak due to potential of abuse, misuse, dependence, and adverse drug reactions. Currently, available cannabinoid formulations are dried cannabis, nabilone (Cesamet), Dronabinol, and nabiximols (Sativex) [35]. According to the randomised clinical trials, there are no cannabinoid treatments that are effective in treating chemotherapy-induced neuropathic pain [36].

According to pre-clinical and clinical data, potential effective drugs in treating neuropathic pain include non-selective CB receptor agonists, selective CB1 receptor agonists, selective CB2 receptor agonists, FAAH inhibitors, MAGL inhibitors, cannabis, and cannabis THC:CBD extract. Nevertheless, further investigation is needed. Several obstacles that need to be overcome, such as the regulations that restrict access to cannabis products [37]. The disadvantages that were observed with using selective CB1 receptor agonists were CNS side effects, physical withdrawal and tolerance.

In order to overcome these disadvantages, using CB2 selective agonists could be the solution [37]. In the future, cannabis, cannabis extracts and various drugs that act on the endocannabinoid system have potential to be used clinically to manage neuropathic pain.

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TEST YOUR KNOWLEDGE

Answers on back page

1) The CB2 receptors are mainly localised in the

A. Hippocampus
B. Spleen
C. Cerebellum
D. Cerebrum

2) Which enzyme is involved in the degradation of 2-AG into glycerol and arachidonic acid?

A. Monoglycerol lipase
B. NAPE-PLD
C. Phospholipase A
D. Glycerophosphodiesterase

3) Which of the following is a cannabis-based medicinal extract assessed in clinical trials for painful DPN?

A. B-vex
B. Vexarine
C. Effexor
D. Sativex

Is there a problem?

A patient is given the below prescription by his dentist to treat a dental infection. Is there any major error with the prescription?

KJB HOSPITAL

Patient Name: Hussein Ali Age: 32 years
Address: Street No: 56

Rx

Clindamycin 300mg capsule
1 capsule two times a day x 5 days

Dr. Fahad
Signature Date: 5/6/19

Answer (Prescription Exercise)

The frequency is wrong. For dental infection in an adult, the 300mg dose should be taken every 6 hours

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Plenity™ – a new prescription aid in weight management

Plenity is a new orally administered, non-stimulant, non-systemic aid in weight management based on proprietary hydrogel technology with a highly favorable safety and efficacy profile demonstrated in clinical studies.

A pivotal study reported that about 60% of adults treated with Plenity were responders, losing on average 10% of their weight (22 pounds) and 3.5 inches from their waists within 6 months. Gelesis, a biotechnology company developing first -in-class hydrogel therapeutics to treat obesity and other chronic diseases related to the gastrointestinal (GI) tract, announced on April 14 2019 that the US FDA has cleared the Company's lead product candidate, Plenity (Gelesis100), as an aid in weight management in adults with a Body Mass Index (BMI) of 25–40 kg/m^2, when used in conjunction with diet and exercise. A BMI of 25 kg/m^2 and over is the accepted definition of overweight; a BMI of 30 kg/m^2 and above commonly defines obesity. The safety and efficacy profile of Plenity makes it well-suited for these individuals. It is the only prescription weight management product to be cleared for use by overweight adults with a BMI as low as 25 kg/m^2, with and also without co- morbidities such as hypertension, type 2 diabetes or dyslipidemia. There is no restriction on how long Plenity can be used to assist in weight management.

Plenity, a superabsorbent hydrogel is administered in the form of capsules taken with water before lunch and dinner. Plenity is made by cross-linking two naturally-derived building blocks- cellulose and citric acid- to create a three-dimensional

Image from Gelesis

hydrogel matrix. Plenity particles rapidly absorb water in the stomach and homogenously mix with ingested foods. Rather than forming one large mass, the capsules release thousands of non-aggregating particles that rapidly absorb water in the stomach, creating small individual gel pieces with the elasticity (firmness) of plant-based foods (e.g., vegetables) without caloric value. The gel pieces increase the volume and elasticity of the stomach and small intestine contents, contributing to a feeling of fullness and satiety and inducing weight loss. Once it arrives in the large intestine, the hydrogel is partially broken down by enzymes and loses its three-dimensional structure along with most of its absorption capacity. The released water is reabsorbed in the large intestine, and the remaining cellulosic material is expelled in the faeces.

Plenity is considered a medical device because it achieves its primary intended purpose through mechanical modes of action consistent with mechanobiology constructs.

The company reports that this novel, non-stimulant and non-systemic treatment has been shown in clinical studies to be effective, safe and well-tolerated. It had a unique combination of effectiveness combined with a highly favourable safety and tolerability profile. About 26% of the adults who completed the treatment with Plenity were "super-responders," defined as achieving at least 10% weight loss. These super-responders achieved an average of about 14% weight loss or approximately 30 pounds. The overall incidence of adverse events (AEs) in the Plenity treatment group was no different than placebo. The most common ones were gastrointestinal disorders.

* Plenity is contraindicated in patients who are pregnant or are allergic to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium oxide
* Plenity may alter the absorption of medications.
* Its use should be avoided in patients with the following conditions: esophageal anatomic anomalies, including webs, diverticuli, and rings; suspected strictures (such as patients with Crohn's disease); or complications from prior gastrointestinal (GI) surgery that could affect GI transit and motility.
* It should be used with caution in patients with active GI conditions such as gastro-esophageal reflux disease (GERD), ulcers or heartburn.
* Overall, the most common treatment related adverse events (TRAEs) were GI-related TRAEs with 38% of adults in the Plenity group and 28% of adults in the placebo group experiencing a GI-related TRAE. Plenity will be broadly available by prescription in the U.S. in 2020.

The preliminary studies on Plenity do show promising results, but long-term data are always the key for any and all weight loss products or plans.

Gelesis is developing its second candidate, Gelesis200, a hydrogel optimised for weight loss and glycemic control in patients with type 2 diabetes and pre-diabetes.

Adapted from Gelesis.com and myplenity.com

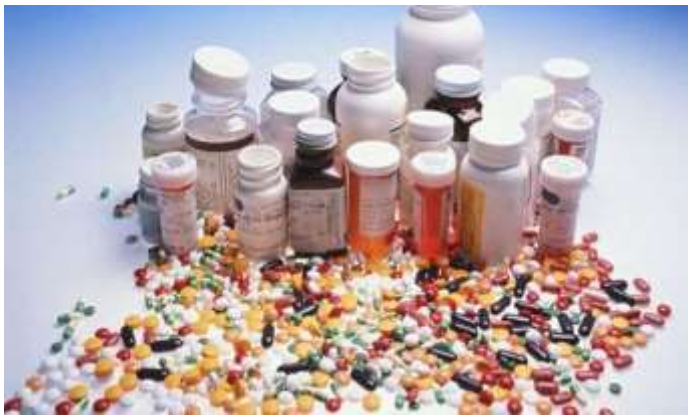
Triple whammy effect of polypharmacy

Polypharmacy has become a medical burden, a cause of concern for the medical field, the patients involved as well as the caregivers. Whilst pharmaceutical companies may benefit from polypharmacy, it may be rather bad news for the individual patient. Polypharmacy refers to the concurrent use of multiple medications by a patient, commonly considered to be the use of five or more. It is, not surprisingly, most common in the elderly, affecting about 40% of older adults living in their own homes. Elderly people are at a greater risk for adverse drug reactions (ADRs) because of the metabolic changes and reduced drug clearance associated with ageing; this risk is exacerbated by increasing the number of drugs used.

One of many pharmaceutical errors has been given a nickname- the "triple whammy effect". This effect describes the unfavorable outcomes when combining an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-II receptor block-

er (ARB) with a diuretic and a non-steroidal anti-inflammatory drug (NSAID). This combination is used in the treatment of hypertension and heart failure. All these drug classes have one thing in common - the potential to decrease renal function. When prescribed all at once, the chances of the patient developing an acute kidney injury (AKI) increases.

To have a clearer understanding of the topic, the mechanism of action of each drug must be observed. By reducing the plasma volume, diuretics reduce renal blood flow, leading to an increase in serum creatinine concentrations. Automatically, the body tries to compensate via the renin-angiotensin system by constricting the efferent renal arteriole to increase glomerular filtration pressure, favoring water and sodium retention. However, this mechanism is blocked by ACEI, or ARB, lowering the glomerular filtration pressure further. NSAIDs inhibit prostaglandins and bradykinin, leading to the vasoconstriction of the afferent renal arterioles, thus reducing the kidney's ability to regulate glomerular blood flow. Clearly the combination of these 3 drugs cause



stress upon the kidneys, causing elevated serum creatinine levels as one of the detectable clinical out- come.

Managing patients receiving these three drugs in combination chronically should be done with caution. Patients should be monitored for altered blood pressure and serum creatinine, particularly during the first few months of the therapy.

Article contributed by Ajwan Behbehani

A parasitic fish could help fight brain cancer and stroke

Researchers turn to an ancient species of fish called lampreys in a bid to find a better way of delivering therapeutic drugs into the brain to treat conditions and events ranging from cancer to stroke.

Lampreys are one of the oldest surviving species of eel-like jawless fish. They populate both rivers and coastal sea waters in temperate regions around the world. These strange-looking fish are rendered particularly uncanny by their boneless, tooth-lined mouth. They are also parasitic, feeding on the blood of other fish. New research suggests that these aquatic-dwellers may provide an adaptable vehicle for drugs that treat the biological effects of conditions or health events affecting the brain.

A recent study, conducted by a team of scientists from University of Wisconsin-Madison and the University of Texas at Austin, has looked at a type of molecule from the immune system of lampreys, called "variable lymphocyte receptors" (VLRs). The researchers explain that what makes VLRs interesting is their ability to target the extracellular matrix (ECM), a network of macromolecules that provide structure to the cells they surround. This network makes up a large part of the central nervous system, so the research team believes that VLRs can help carry drugs to the brain, boosting the effectiveness of treatments for brain cancer, brain trauma, or stroke.

Normally, drugs will not easily penetrate the brain due to the blood-brain barrier, which stops potentially harmful agents leaking into the brain. However, this barrier also prevents medications from reaching their target. In the case of some health events that affect the brain, the blood-brain barrier becomes permeable, which can expose the brain to further problems but also allows drugs to get in.

Molecules like VLRs normally couldn't carry medications into the brain, but anywhere there is a disruption to the blood-brain barrier, they can deliver medications right to the site of pathology.

In the current research, the investigators were interested in testing the effectiveness of VLRs,

taking advantage of the disruption of the blood-brain barrier in the case of glioblastoma, an aggressive form of brain cancer. They tested their hypothesis on mouse models of aggressive brain cancer, and report their results in the journal *Science Advances*.

The research team worked with mouse models of glioblastoma, treating them with VLRs bound to doxorubicin, a drug used to treat this form of cancer in humans. They report that this approach was promising, prolonging survival in the rodents treated with this experimental combination.

The investigators note that binding VLRs to various drugs may have another important benefit- it could allow delivery of significantly higher doses of those drugs to the brain ECM.

The lamprey molecules will potentially accumulate much more of the drug in the abundant matrix compared to specific delivery to cells. And this binding property could help solve yet another problem. The researchers explain that brain cells discharge chemicals that reach them. However, since VLRs target the ECM that surrounds brain cells, this could allow the drugs to act on the cells for more extended periods. This could be a way to hold drugs in place that would not otherwise accumulate well in the brain, so they can be more effective.

Finally, the researchers note that the VLRs freely circulated through the body in the mouse models, but they did not accumulate in healthy tissue. This suggests that these molecules would not disrupt healthy, functioning organs.

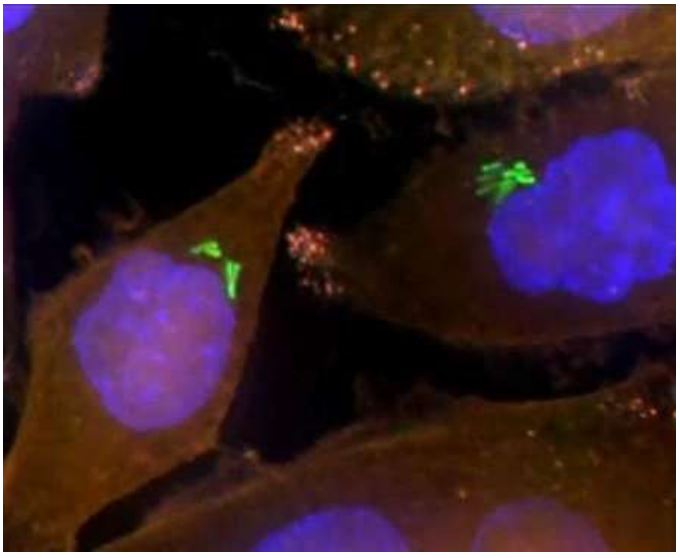
Going forward, the investigators want to try combining VLRs with other types of anti-cancer drugs, including those used in immunotherapy, to see how well the molecules would work with a more diverse array of therapies. Another possibility that the re- searchers would like to investigate is that of using VLRs to detect any disruptions of the blood-brain barrier, which might indicate the onset of a pathological event. They propose to do this by binding VLRs to sophisticated probes compatible with brain imaging technologies.

For the time being, however, researchers are excited about trying this strategy in different disease model systems and there are several disease processes that disrupt the blood-brain barrier and could conceive of delivering a variety of different therapies with these molecules.

Source:
https://www.medicalnewstoday.com/articles/325211.php

How bacteria might hinder chemotherapy

To the reasons that chemotherapy sometimes does not work, perhaps we can now add one more: bacteria. In a study published in *Science*, researchers describe findings that certain bacteria can be found inside human pancreatic tumours. The findings further showed that some of these bacteria contain an enzyme that inactivates a common drug used to treat various cancers, including pancreatic cancer. Working with mouse models of cancer, these researchers demonstrated how treatment with antibiotics in conjunction with chemotherapy may be significantly superior to treatment with just chemotherapy alone.



Bacteria (seen as green in photo above) inside human pancreatic cancer cells (AsPC-1 cells). The cells' nuclei are stained blue while their cytoplasm is stained

The bacteria the researchers found live within the tumours, and even within the tumour cells. They isolated bacteria from the tumours of pancreatic cancer patients and tested how they affect the sensitivity of pancreatic cancer cells to gemcitabine, a commonly used chemotherapy drug. Indeed, some of those bacteria kept the drug from working. Further investigation showed that these bacteria metabolize the drug, making it ineffective. The researchers were able to find the bacterial gene responsible for this was a gene called cytidine deaminase (CDD). They demonstrated that CDD comes in two forms- a long and a short form. Only bacteria with the long form of the CDD gene could inactivate gemcitabine. The drug had no apparent effect on the bacteria.

The group examined over 100 human pancreatic tumours to show that these particular bacteria with long CDD do live in the patient's pancreatic tumours. They also used multiple methods to visualise the bacteria inside human pancreatic tumours. This is crucial, since bacterial contamination is a real issue for lab studies.

Oddly enough, it was an earlier incidence of bacterial contamination that led this team to this study. While testing the effect of many normal, non-cancerous, human cells on the sensitivity of cancer cells to chemotherapy, they found a specific sample of normal human skin cells that rendered pancreatic cancer cells resistant to gemcitabine. Tracking down the cause led the team to bacteria that had accidently contaminated these skin cells. They showed that a bacterium called Mycoplasma hyorhinis had infected the skin cells. If they killed it off with antibiotics, the cells could no longer rescue cancers from chemotherapy. And if they added the bacterium to mice that were suffering from tumours, the rodents became resistant to gemcitabine. The team showed that 76% of the biopsies taken from the tumours of 113 pancreatic cancer patients contained traces of bacterial DNA, compared to only 15% of 20 healthy pancreases taken from organ donors.

While bacterial DNA could just have come from dead cells, the team also *saw* whole intact bacteria within the tumours. They treated the samples with fluorescent antibodies designed to target the bacterial molecules. After revealing how these bacteria degraded the drug, they began to wonder if other bacteria might have a similar mechanism for inactivating the drug, and whether such bacteria might be found inside human tumours.

In the present study, further experiments in mouse models of cancer were done with two groups of bacteria: those containing the long form of the CDD gene and those in which the gene had been knocked out. Only the group with the CDD gene intact exhibited resistance when the drug was given to the mice. After treatment with antibiotics, this group also responded to the chemotherapy drug.

Reference

Leore T. Geller et al. Science, 2017; 357 (6356): 1156.

Underuse of buprenorphine for opioid addiction

Despite being at the front lines in the battle against opioid addiction as the first to treat chronic pain and opioid overuse, few primary care and family physicians use the one drug available to them to treat addiction, buprenorphine. In the US, sublingual buprenorphine is the only treatment for opioid addiction that can be provided by primary care providers [PCPs], yet it's rarely used by them although the demand for it is enormous. Primary care is an ideal place for this drug to be used, with PCPs being the ones treating most of the chronic pain.

To prescribe buprenorphine for opioid addiction, physicians are required to obtain waivers from the Drug Enforcement Administration (DEA), but the number of primary care physicians with the certification is low. A study published in the Annals of Family Medicine, indicated that as few as 3% of PCPs were listed on the July 2012 DEA Drug Addiction Treatment Act (DATA) Waivered Physician List. In fact, only 2.2% of all US physicians had the waiver, the study showed. Among those, 46% were psychiatrists, 37% were PCPs, and 27% were in other specialties. Another study, published in Rural Remote Health, underscored the imbalance of need vs access to buprenorphine maintenance treatment in the primary care setting.

Google images

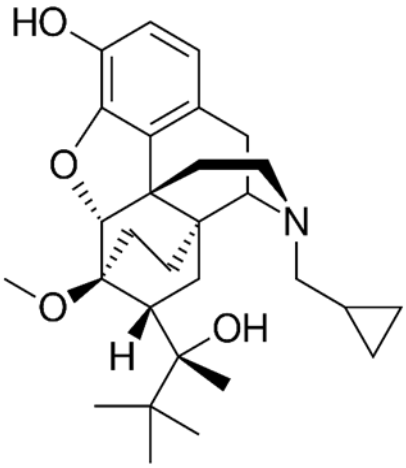
In a survey of 108 family physicians in Vermont and New Hampshire, the authors from the Geisel

School of Medicine at Dartmouth College in New Hampshire found that more than 80% of respondents reported regularly seeing patients addicted to opiates, while 70% said they felt as family physicians the responsibility to treat opiate addiction. Yet only 10% were buprenorphine prescribers.

Key factors reported in the study as potential barriers to adoption of buprenorphine included inadequately trained staff (88%), insufficient time (80%), inadequate office space (49%), and cumbersome regulations (37%).

Some experts advise physicians to seek input from experienced prescribers such as through the online web-based resource called the Providers' Clinical Support System– Medication Assisted Treatment (http://www.pcssmat.org).

The DATA waiver is not required to prescribe buprenorphine for pain- it is needed only for addiction. But US insurance will usually not pay for the drug when it's prescribed for pain. This is because of a technicality. Prescribing the high-dose sublingual form -which is FDA approved to treat addiction- is not FDA-approved to treat pain. Availability to patients would be much better if nurse practitioners and physician assistants were able to prescribe the drug.



Though an opioid itself, buprenorphine, a partial agonist, has a high binding affinity at the μ-opioid receptors, allowing the drug to counter the effects of full agonist opioids such as morphine, blocking the euphoria and having a significantly lower risk for respiratory depression or overdose.

Buprenorphine wipes out withdrawal and craving, it reverses sedation and actually turns it into activation, making people want to get out and become active.

Patients who are ideal candidates for buprenorphine include those being treated with long-term opiates who are showing the red flags of problematic behaviour and possible addiction.

Patients need to be educated about the spectrum of symptoms that are more the result of opioid overuse than the chronic pain that the opioids are being used to treat. Hyperalgesia, described as an increased sensitivity to pain, is typical in patients on high-dose opioids. The key to converting patients to buprenorphine is to educate them that they are treating withdrawal and not pain. They need to know that much of what they are feeling is not pain but a drug- induced withdrawal syndrome, and if the circular behaviour of the opioid overuse can be broken, their pain would be significantly improved. One has to be careful transitioning patients from methadone. It is necessary to wait 5 half-lives for the opioid to be eliminated from the body.

Pain and withdrawal symptoms decrease as the week continues, and those who really want to get better tend to do just fine.

Source:

http://www.medscape.com/viewarticle/863638?nlid=105468_1842&src=WNL_mdplsfeat_160524mscpedit_wir&uac=118197BN&spon=17&impID=1107363&faf=1

NEWS from the FDA

FDA approves first cannabis-based drug

In June 2018 the US FDA approved a cannabis-based drug for the first time.

Epidiolex was recommended for approval by an advisory committee and the agency had made a decision.

The twice-daily oral solution is approved for use in patients 2 years of age and older to treat two types of epileptic syndromes: Dravet syndrome, a rare genetic dysfunction of the brain that begins in the first year of life, and Lennox-Gastaut syndrome, a form of epilepsy with multiple

types of seizures that begin in early child-hood, usually between ages of 3 and 5.

Because of the adequate and well- controlled clinical studies that supported this approval, prescribers can have confidence in the drug's uniform strength and consistent delivery.

The drug is the first pharmaceutical formulation of highly-purified, plant-based cannabidiol (CBD), a cannabinoid lacking the "high" associated with tetrahydrocannabinol (THC) in marijuana, and the first in a new category of anti-epileptic drugs, according to GW Pharmaceuticals, the UK- based biopharmaceutical company that makes Epidiolex.

Cannabidiol is one of more than 80 active cannabinoid chemicals, yet unlike THC, it does not produce a "high".

The FDA has approved synthetic versions of some cannabinoid chemicals found in the marijuana plant for other purposes, including cancer pain relief.

The drug offers families "the first and only FDA-approved cannabidiol medicine to treat two severe, childhood-onset epilepsies". "These patients deserve and will soon have access to a cannabinoid medicine that has been thoroughly studied in clinical trials, manufactured to assure quality and consistency, and available by prescription under a physician's care," GW CEO said.

Epidiolex was due to become available in fall 2018. No information about cost is available yet, knowing that it will be discussed with insurance companies and announced later.

Epidiolex is an option for those patients who have not responded to other treatments to control seizures. According to the Epilepsy Foundation, up to one-third of Americans who have epilepsy have found no therapies that will control their seizures.

Shauna Garris, a pharmacist, pharmacy clinical specialist and adjunct assistant professor at the University of North Carolina's Eshelman School of Pharmacy, said the drug is effective and works somewhere between "fairly" and "very well." She has not used Epidiolex in her own clinical practice

and was not involved in the development of the drug but said she's not sure it will live up to "all of the hype" that has surrounded it. There are side effects, the most common being sleepiness. But many of them occur when it is taken with other medications, which is a concern because most patients are on other medications.

There are likely to be drug interactions and this could affect the effectiveness of the medication.

The European Medical Society is also considering approval of Epidiolex.

A phase three clinical trial is underway for a third seizure-related condition called tuberous sclerosis complex, which begins in infancy and causes a sudden stiffening of the body, arms and legs, with the head bent forward. if the results are positive, GW chemicals will apply for supplemental approval for this condition.

In the meantime, it is possible that once on the market, Epidiolex could be prescribed for off-label use.

As part of the FDA's review of the medication, the potential for abuse was assessed and found to be low to negative.

Adapted from: https://edition.cnn.com/2018/06/25/health/fda-approves-first-cannabis-drug-bn

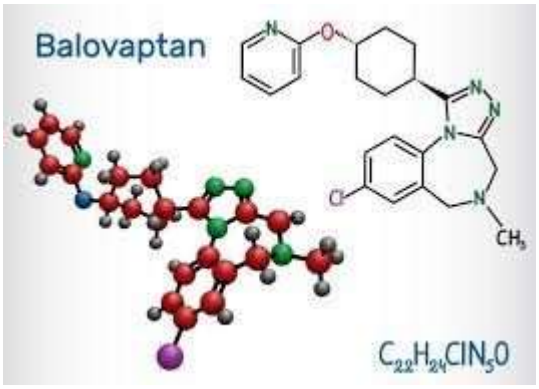
FDA grants 'breakthrough therapy' status to potential autism drug

The WHO estimates that global prevalence of autism spectrum disorder (ASD) is around one in every 160 people; in the EU, prevalence estimates range from 57 to 67 per 10,000 children.

Clinical trial evidence implicates the V1a receptor in mediating and modulating key social behaviours- such as repetitive behaviours, restrictive interests and communication issues- that are challenging for individuals with ASD and for which no pharmacological treatments currently exist.

On January 30th 2018 Roche said it had received a designation from the FDA to help expedite what could be the first drug to treat the core symptoms of autism. Roche said that the FDA has granted its breakthrough therapy designation for the development of balovaptan, a vasopressin 1a (V1a) receptor antagonist, with the potential to improve "core social interaction and communication" in those with autism.

There are only two drugs - risperidone and aripripazole- with FDA approval to treat irritability related to autism. No drugs are currently approved to address core symptoms of the condition. Results from a clinical trial in adults with autism released last year indicate that balovaptan was successful in helping mediate challenging social behaviours and was safe and well tolerated. Another trial looking at children and adolescents on the spectrum is underway and additional studies are in the works.



The FDA uses the breakthrough therapy designation to speed the development of promising medications for serious conditions. It offers drug makers added assistance and priority from the federal agency as they work to get a new treatment to market.

Source:
https://www.roche.com/investors/updates/inv-update-2018-01-29.htm

Midazolam nasal spray (Nayzilam) for seizure clusters

The US FDA has approved midazolam nasal spray (*Nayzilam*, UCB) for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in epilepsy patients aged 12 y or older.

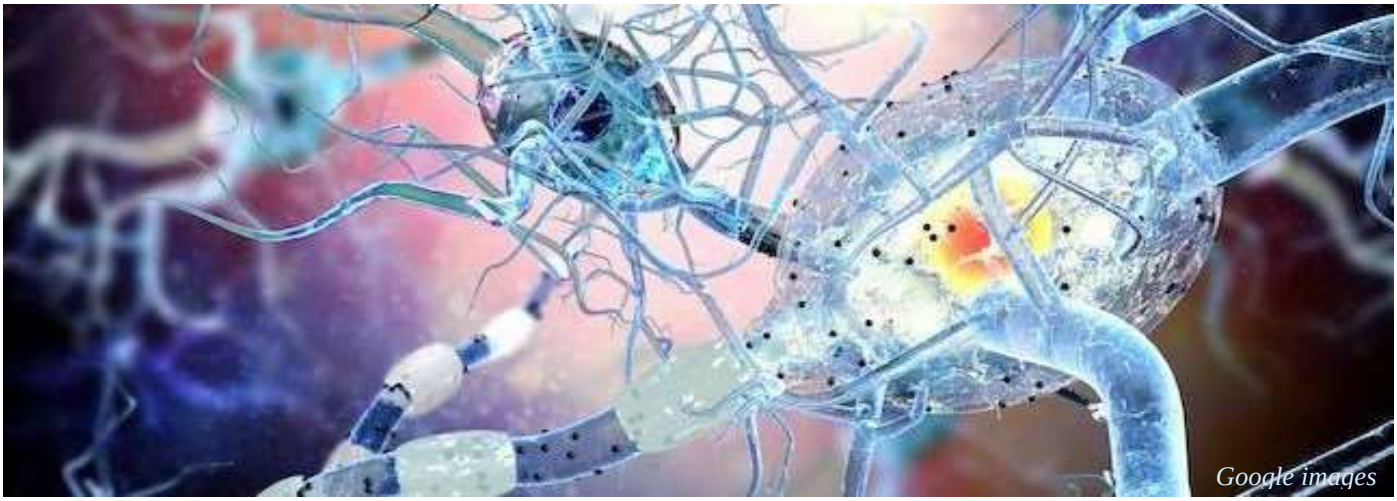
It is estimated that more than 150,000 people in the USA with uncontrolled epilepsy experience seizure clusters, which can increase the risk for physical injury, neurologic damage, prolonged seizures, and status epilepticus if left untreated.

Midazolam nasal spray is the first and only FDA-approved nasal option for treating seizure clusters; packaged as a single-use treatment that can be carried with a patient and administered by persons who are not healthcare professionals.

The availability of a new treatment option, such as Nayzilam, has potential to help improve the lives of patients and their families by providing another option for rescue care.

The effectiveness of midazolam nasal spray for the acute treatment of seizure clusters was established in a two-phase, randomized, double-blind, placebo-controlled trial. An open-label test-dose phase was followed by a comparative phase.

In the test-dose phase, tolerability was assessed in 292 patients who, in the absence of a seizure, received two 5-mg doses of midazolam nasal spray (10 mg total dosage) 10 min apart. Patients were excluded from participating in the comparative phase if they failed to meet pre-defined criteria



regarding blood pressure, heart rate, sedation electrocardiographic status and peripheral oxygen saturation.

In the comparative phase, 201 patients underwent treatment for a single seizure cluster episode in an outpatient setting with either a blinded dose of midazolam nasal spray 5 mg (134 patients) or placebo (67 patients).

If seizure activity persisted or recurred, patients in both groups had the option to receive a subsequent un-blinded dose of midazolam nasal spray 5 mg, to be used between 10 min and 6 h after ad- ministration of the initial blinded dose of study drug.

A statistically significantly higher percentage of patients who were treated with midazolam nasal spray met the primary efficacy endpoint of treatment success, defined as termination of seizures within 10 min after the initial blinded dose of the medication and the absence of a recurrence of seizures within 6 h of the initial blinded dose of the medication.

Numerical differences in favour of midazolam nasal spray were observed on each of the components of the treatment success responder definition: termination of seizure(s) within 10 min after initial dose of the drug (80.6% vs 70.1%), and the absence of seizure recurrence between 10 minutes and 6 hours after the initial dose (58.2% vs 37.3%).

The study also evaluated the occurrence and time to next seizure after receiving the initial blinded dose of the drug. A smaller proportion of patients who were treated with midazolam nasal spray experienced the next seizure within 24 h after the initial blinded dose (37.3% vs 46.3%). There was a statistically longer time to next seizure with midazolam nasal spray than with placebo.

The most common adverse reactions (≥5% in any midazolam nasal spray treatment group) were somnolence, headache, nasal discomfort, throat irritation, and rhinorrhea.

Midazolam nasal spray is contraindicated in patients with acute narrow-angle glaucoma. Concomitant use of benzodiazepines, including midazolam nasal spray, and opioids may result in profound sedation, respiratory depression, coma, and death.

Answers to: Test your knowledge

Correct answers
1-B; 2-A; 3-E

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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