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CAPSAICIN - POTENTIAL SOLUTION FOR CHRONIC PAIN TREATMENT

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SUMMARY

Chronic pain is a painful condition defined by its duration where pain persists three months or more. Pain is connected with the high price of health care, work inability and disability. Moreover, it has significant consequences for patients and their families, working organizations and the society as a whole. The prevalence of chronic pain can range between 11.0% and 51.3% in general population. Pain is usually coherent with distress and a range of psychological symptoms such as depression, anxiety, altered attention and cognition manifesting as fear. Comprehensive pain management should always include the treatment of associated psychological symptoms. Multidisciplinary approach in treating chronic pain and its comorbidities and proper education of primary care physicians and different specialists involved in the management of chronic pain are crucial for better clinical outcomes. Topical capsaicin acts as a highly selective agonist of transient receptor potential vanilloid 1 of C and Aδ nociceptors. Repeated applications or high concentrations give rise to a long-lasting effect termed defunctionalisation. In addition, the reduction of central sensitization through reduced C-nociceptor input contributes to capsaicin's indirect mechanism of action. Capsaicin provides effective durable pain relief and reduction of intensity and area of pain in adult patients with chronic pain with a faster onset of analgesia and considerably fewer systemic adverse effects than the conventional treatment. While offering high levels of pain relief, additional improvements in sleep, fatigue, depression and quality of life have been noticed. Topical administration avoids dangerous systemic adverse effects and enables the combination with other drugs and analgesics with limited drug-drug interactions. Adding capsaicin to the standard chronic pain treatment might improve, fasten and ease the challenging path of managing chronic pain consequently providing the patient and their society with better quality of life.

Key words: *capsaicin - pain - therapeutics - TRPV cation channels*

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INTRODUCTION

Chronic pain

Pain is „the subject's conscious perception of modulated nociceptive impulses that generate an unpleasant sensory and emotional experiences associated with actual or potential tissue damage or described in terms of such damage“ (Okeson 2013). The perception of pain is individual and complex because it depends upon a person's age, gender, earlier experiences, and psychological, sociocultural and neurophysiological characteristics.

Nociception is the process of interaction of noxious stimulus with a receptor, transduction, transmission and processing pain-related signals in the peripheral and central nervous system. Neuropeptides released from nociceptors are producing sterile inflammation response that enhances nociception, which results in pain hypersensitivity or peripheral sensitization. Nociceptive stimulus travels through peripheral C and Aδ nerve fibres to posterior horn of the spinal cord. Central sensitization processes at this level may lower the nociceptor threshold and promote development of chronic pain. The nociceptive pain pathway continues through spinothalamic tract and spinoreticular tract towards the brain, into the reticular formation, thalamus, limbic system and somatosensory cortex (Ropper & Brown 2005, Bosnar-Puretić & Demarin 2012). Nociceptive pain, depending on its origin, can be either cutaneous, somatic or visceral. Cutaneous pain originates from nociceptors in skin and subcutaneous tissue and somatic pain originates from muscle, bone or joint nociceptors. They are both typically well localized. On the contrary, referred pain is a phenomenon usually associated with visceral pain. Nociceptors in the hollow organs and smooth muscles are the origin of visceral pain. Neuropathic or neurogenic pain alludes the damage of a part of nerve tissue responsible for depolarization or transmission of pain and should not be used as a synonym for all types of pain. Possible causes are as follows: (1) direct damage of the nerve (i.e., multiple sclerosis, nerve injury), (2) amputation (phantom limb pain), (3) complication of systemic diseases (diabetes mellitus, herpes zoster infection). Patients with neuropathic pain commonly describe it as burning, stinging or tearing sensation with or without itching, numbness and hypersensitivity in affected area. Most cases of chronic non-malignant pain are neuropathic. Regardless of the cause, chronic pain is today considered a disease of the central nervous system (Balon et al. 2018).

Chronic pain is a painful condition defined by its duration where pain persists three months or more (Katz et al. 2015). As opposed to acute pain, chronic pain rarely has a protective function. This term includes a number of clinical entities that can be a result of the following: (1) serious progressive illness (i.e., malignancy), (2) static medical condition (i.e., amputation, herpes zoster infection), (3) disturbance in neural functioning or complex combination of neural disturbances and psychological disturbances of unknown aetiology (i.e., fibromyalgia, chronic pelvic pain of unknown aetiology, chronic tension type headache) (Demarin et al. 2008, Bašić-Kes et al. 2009, Varrassi et al. 2010).

Most people experience one or more pain disorders during their life. Pain is connected with the high price of health care (direct and indirect), work inability and disability. Moreover, it has significant consequences for patients and their families, working organizations and the society as a whole (Buljan 2009). The prevalence of chronic pain can range between 11.0% and 51.3% in general population (Dahlhamer et al. 2018, Fayaz et al. 2016). It is most commonly found in older patients, with the prevalence of 62% in patients older than 75 years (Fayaz et al. 2016). However, the prevalence of chronic pain in young patients between 18 and 39 years old may be as high as 30% (Fayaz et al. 2016). The prevalence of moderate to severely disabling chronic pain or high impact pain can range from 4.8% to 19% in adult population (Breivik et al. 2006, Dahlhamer et al. 2018, Pitcher et al. 2019). Therefore, chronic pain is a major public health issue with great social impacts on the individual suffering from it.

Although studied at different levels, chronic pain is still not completely understood and its management still represents a great challenge in clinical practice. The aim of this review is to show the association of chronic pain and psychiatric disorders and the diversity of the ongoing search for new potential treatment options for chronic pain such as capsaicin.

The association of chronic pain and mental disorders

Recent studies have shown that chronic pain can negatively impact many aspects of patient's life and its quality, including sleep, occupational functioning and socialization (Velly & Mohit 2018). Moreover, chronic pain conditions increase health care usage, cost and mortality. Some psychiatric disorders are more common among patients with chronic pain and there is a possible contribution of mental disorders to increased prevalence of chronic pain (Velly & Mohit 2018). Pain is usually coherent with distress and a range of psychological symptoms such as depression, anxiety, altered attention and cognition manifesting as fear. Comprehensive pain management should always include the treatment of associated psychological symptoms (Balon et al. 2018). Pain without a present anatomical or neurophysiological underlying cause is often attributed to psychopathology. Dyspareunia, phantom limb pain, fibromyalgia, orofacial pain, pelvic pain and medically unexplained abdominal pain, chest pain and headache are only a few examples of pain syndromes with a proposed psychological dysfunction in their aetiology (Gagliese & Katz 2000, Nielson & Merskey 2001, Stoudemire & Sandhu 1987). Pain without a certain anatomical distribution, pain that is spreading to noninjured territory, pain that is disproportionate with the injury or felt in the absence of the injury can be explained by peripheral and central neurophysiological mechanisms, but in the past have been accounted for in a great measure by psychological disturbances (Mannion & Woolf 2000).

Psychosomatic medicine connects psychological conditions and psychiatric disorders, psychosocial stress, family and occupational factors and somatic disorders with pain. The diagnoses often used in these disorders caused by psychological factors belong to the group of somatic symptom disorders, or earlier called somatoform disorders (Table 1). Depression and psychotic disorder can sometimes manifest itself with pain. On the other hand, pain disorder as a somatic illness can cause anxiety, depression, social phobia and isolation. Every pain has a more or less expressed psychological component (Buljan 2009). It has been noticed that patients suffering from chronic pain had emotional difficulties and were psychosocially and biochemically sensitive (Balon et al. 2018). Chronic pain is frequently associated with various psychiatric conditions, including major depressive disorder, anxiety disorders, posttraumatic stress disorder (PTSD), sleep disorders, eating disorders and substance abuse (Balon et al. 2018). The studies have shown that patients suffering from chronic pain are 2.3 times more likely to have a 12-month DSM-IV anxiety disorder, 3.3 times more likely to have a 12-month DSM-IV mood disorder and 2.7 times more likely to have a 12-month DSM-IV mental disorder (Pereira et al. 2017). Some studies have shown a two-fold increased likelihood of comorbid depression in patients suffering from joint pain and neck or back pain and a three-fold increased likelihood among those with chest pain (Oladeji et al. 2011).

The association between pain and certain psychiatric conditions is well established. The prevalence of pain in patients without depression is 8% (Bair et al. 2003). By contrast, the prevalence of pain in patients with subsyndromal depression, a brief depressive episode and a depressive episode is 28%, 20% and 34%, respectively (Bair et al. 2003). Not only pain and depression, but also pain and anxiety share common biological pathways and neurotransmitters, which implies that those conditions can be treated concurrently (Bair et al. 2003). Screening for PTSD is recommended in patients with chronic pain, because the prevalence of PTSD among patients with chronic pain can be as high as 23% (Andersen et al. 2019). Altered sleep quality and fatigue

Table 1. DSM-V codes and categories with ICD-10 equivalents in diagnosis of psychosomatic pain (adapted from Mayou et al. 2005)

DSM-V		ICD-10	
Code	Category	Code	Category
300.82	Somatic symptom disorder	F45.0	Somatization disorder
300.81	Somatic symptom disorder	F45.1	Undifferentiated somatoform disorder
300.11	Conversion disorder (functional neurological symptom disorder)	F44	Dissociative (conversion) disorder
307.80	Somatic symptom disorder	F45.4	Persistent somatoform pain disorder
300.7	Illness anxiety disorder	F45.2	Hypochondriacal disorder
300.82	Other specified/unspecified somatic symptom and related disorder	F45.8	Other somatoform disorders
300.89		F45.9	Somatoform disorder unspecified
316	Psychological factors affecting other medical conditions	F54	Psychological and behavioural factors associaed with disorders or diseases classified elsewhere

Table 2. Management of chronic pain (adapted from Finnerup et al. 2010)

Multimodal approach								
Pharmacological management								
	First-line drugs			Second-line drugs			Third-line drugs	
	SNRIs	TCA	Pregabalin, gabapentin, enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	Botulinum toxin A
Q	+++	++	+++	++	+++	+	++	++
E	++	++	++	++	+	?	++	++
T	++	+/++	++/+++	+/++	++/+++	+++	+/++	+++
C	+/++	+	+/++	+	++/+++	++/+++	+/++	++/+++
S	+++	+++	+++	+	+	+	+	+
N	all	all	all	all	peripheral	peripheral	all	peripheral
Non-pharmacological management								
Transcutaneous electrical nerve stimulation				Magnetotherapy		Laser therapy		Ultrasound
Acupuncture				Nerve block injection		Physical therapy		Neuroablation
Psychosocial support for the patient and for the patient's family								

Abbreviations used: Q = quality of evidence; E = effect size; T = tolerability and safety; C = cost and resource allocation; S = strength of recommendation; N = neuropathic pain conditions; SNRIs = serotonin-norepinephrine reuptake inhibitors; TCA = triclyclic antidepressants

are often a consequence of pain, too. Medications used for treatment of chronic pain (i.e., opioids) may contribute to respiratory depression and exacerbation of sleep apnoea (Marshansky et al. 2018). The association of chronic pain and substance-related disorders is also well documented (Martel et al. 2018). In addition, chronic pain has been identified as an independent risk factor for suicide (Racine 2018).

The connection of chronic pain and psychiatric disorders exists in many observed aspects and might quite often influence the clinical course of the diseases the patient is suffering from. It is important to note that it can be explained by both psychological and physiological mechanisms.

MANAGEMENT OF CHRONIC PAIN

There is a wide range of treatment options used in chronic pain management (Table 2). Medications used can be divided by their place of action: (1) nociceptors' threshold (i.e., non-opioid analgesics or anti-inflammatory drugs), (2) transmission through structures of peripheral nervous system (i.e., local anaesthetics), (3) perception of pain in central nervous system (i.e., opioid analgesics), (4) reaction and behaviour associated with pain (i.e., anxiolytics, antidepressants, opioid analgesics). Nevertheless, none of them are completely effective in each case of chronic pain and multidisciplinary approach in treating chronic pain and its comorbidities and proper education of primary care physicians and different specialists involved in the management of chronic pain are crucial for better clinical outcomes.

Conventional treatment

A number of treatments used in psychiatry are also beneficial in the management of chronic pain. Some antidepressants (e.g., tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors) mitigate pain associated with neuropathy, headaches and fibromyalgia (Leo & Quinton 2011, Balon et al. 2018). They are obviously helpful with comorbid depression and anxiety, too. In the same manner, anticonvulsants such as carba-

mazepine, gabapentin and pregabalin are helpful in management of pain. U.S. Food and Drug Administration (FDA) approved carbamazepine in the treatment of trigeminal neuralgia and gabapentin in the treatment of postherpetic neuralgia (Leo & Quinton 2011). Benzodiazepines are usually used as adjunctive treatment for pain associated with muscle spasms (Reddy & Patt 1994), but their main limitation is related to the combined use of benzodiazepines and opioids. Other nonpharmacological methods of treatment, such as transcutaneous nerve stimulation, magnetotherapy, laser therapy, ultrasound, EMG or thermal biofeedback and acupuncture are potentially effective, as well (Tan et al. 2011). Standard physical therapy, local blocking or analgesic therapy are used in severe cases of chronic pain and when the somatic nature of the disease prevails. Current medications are not fully effective because of lacking selectivity and have common and significant adverse effects that may additionally lower the quality of life of a patient suffering from chronic pain. Thus, there is a need for better treatment options in chronic pain management.

Psychiatric approach

The role of psychiatry and the psychiatrists in pain management has grown throughout the years. The opioid epidemic, the evolution of palliative care and raising awareness of pain comorbid with mental illness contributed most to it (Balon et al. 2018).

When the psychological component to chronic pain is present and if the patient has acknowledged its psychological factor, treatment options can include: courses of stress management techniques, music therapy, physical exercise, psychotherapeutic approach (i.e., cognitive-behavioural therapy) (Buljan 2009). Cognitive-behavioural therapy modifies distressing thoughts and cognitive distortions associated with pain and enhances coping skills to deal effectively with the experience of pain (Ehde et al. 2014).

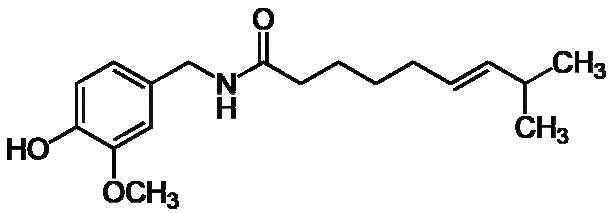

Figure 1. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide, $C_{18}H_{27}NO_3$). Chemical structure of capsaicin

Capsaicin

Capsaicin (Figure 1) is a compound of chili peppers responsible for their burning and irritant effect. This substance and its derivatives have been investigated for the treatment of pruritus, atopic dermatitis, rosacea, nonallergic and allergic rhinitis, chronic idiopathic cough, chronic obstructive pulmonary disease, obesity, dry eye syndrome and tumours, but recently their role in nociception has been studied (Basith et al. 2016). Capsaicin acts as a double-edged sword, displaying both pronociceptive and antinociceptive characteristics (Derry et al. 2017). Topical capsaicin acts as a highly selective agonist of transient receptor potential vanilloid 1 (TRPV1, Figure 2 and Figure 3) of C and Aδ nociceptors. TRPV1 controls movement of sodium and calcium ions across the cell membrane. Initially, capsaicin binding opens the ion channel causing depolarization, the release of vasoactive neuropeptides and the production of action potentials, which are usually perceived as itching, pricking, or burning sensations. Repeated applications or high concentrations give rise to a long-lasting effect termed defunctionalisation. In addition, the reduction of central sensitization through reduced C-nociceptor input contributes to capsaicin's indirect mechanism of action (Anand & Bley 2011). Capsaicin provides effective durable pain relief and reduction of intensity and area of pain in adult patients with chronic pain with a faster onset of analgesia and considerably fewer systemic adverse effects than the conventional treatment (Cruccu et al. 2017). While offering high levels of pain relief, additional improvements in sleep, fatigue, depression and quality of life have been noticed (Derry et al. 2017). The single application avoids noncompliance. Nevertheless, it must be applied under highly controlled conditions, after an injection of local anaesthetic, due to the initial intense burning sensation it causes. It is recommended to repeat the application after 12 weeks, because all the capsaicin effects on the TRPV1 are reversible (Derry et al. 2017). At this time, high-dose 8% capsaicin patch has been approved by the European Medicines Agency (EMA) for the treatment of pain associated with postherpetic neuralgia, HIV-associated distal sensory neuropathy and diabetic neuropathy. The intensity of pain significantly decreases after one, two or three weeks after capsaicin application, respectively (European Medicines Agency 2019). High-dose 8% capsaicin patch has recently been studied for treatment of pain associated with chemotherapy-induced neuropathy, neuropathic lumbosacral pain, phantom limb pain, posttraumatic and postoperative pain, peripheral neuropathic pain secondary to chronic inflammatory demyelination neuropathy and polyneuropathy of unknown aetiology (Table 3). Furthermore, low-dose capsaicin cream (0.025%, 0.075%) and patch (0.9%) have shown a beneficial effect on osteoarthritis, rheumatoid arthritis and fibromyalgia. Capsaicin can be used either as monotherapy, or in combination with other medications for chronic pain treatment. Therefore, we can assume that capsaicin can be a successful treatment option in psychiatric patients suffering from chronic pain. In spite of that, a careful analysis of obtainable data showed that there is no evidence of its efficacy in this group of patients to date.

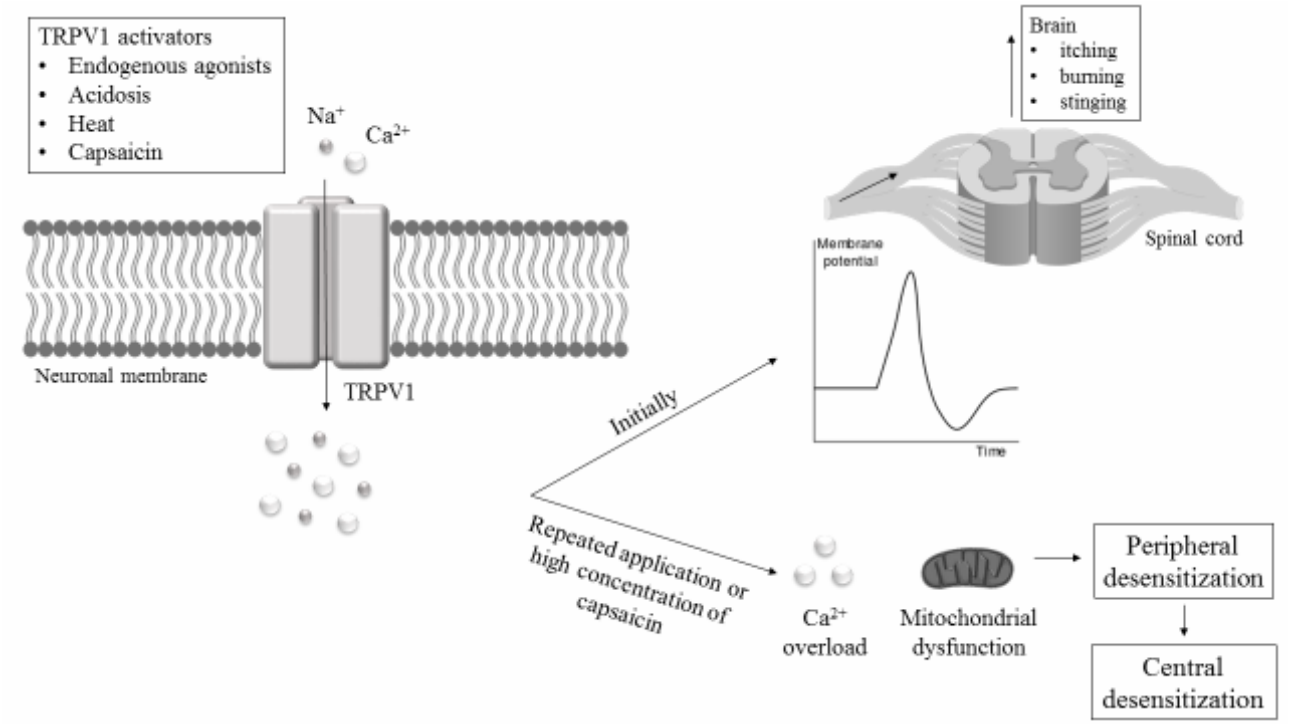

Figure 2. Capsaicin's mechanism of action. Capsaicin acts as a TRPV1 agonist on neuronal membrane. By activation of TRPV1, permeability for sodium and calcium cations increases causing depolarization of neuronal membrane. Initially, this leads to the formation of action potential, its transduction and transmission followed by perception of itching, burning and stinging. However, repeated application or high concentration of capsaicin leads to calcium overload and mitochondrial dysfunction. As a result, peripheral and central desensitization occur (Authors' work)

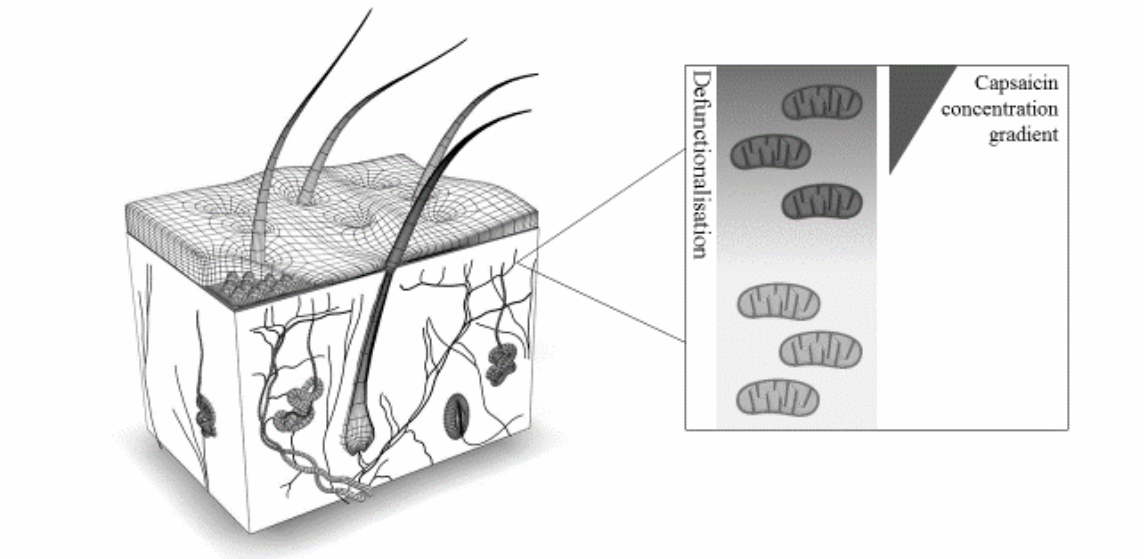

Figure 3. Capsaicin's effect. Concentration-dependent depth of defunctionalisation of nerve endings in skin where capsaicin patch is applied. (Authors' work)

In this review we are mainly concentrating on topical use of capsaicin because it is the only form approved by the FDA and the European Medicines Agency (EMA) so far. Dose of capsaicin treatment ranges from one to four cutaneous patches, which are usually applied for 30 minutes on feet (i.e., in patients with HIV-associated distal sensory polyneuropathy or diabetic peripheral neuropathy) or 60 minutes on other body sites (i.e., in patients with postherpetic neuralgia). Applying capsaicin on the face, above the edge of the scalp or near the mucous membranes should be strictly avoided. Better adherence in some anatomical localizations (i.e., foot) can be achieved by the use of conforming stretch gauze bandage or elastic compression socks. When the required time of application has elapsed, any residual of capsaicin needs to be removed with cleansing gel. If the pain persists or returns, reapplication is recommended after 90 days.

Table 3. Clinical status of capsaicinoids, capsinoids and other medications with a similar effect for the treatment of chronic pain (adapted from Basith et al. 2016)

Drug and type of action on TRPV1	Reference / Identifier	Administration	Indication	Clinical status
Capsaicin (different formulations: ALGRX-4975, NGX-1998, CNTX-4975-05, NGX-4010, CGS-200) agonist		Topical	PHN	FDA approved
		Topical	PHN, HIV-DSP, PNP	EMA approved
	NCT01200745	Topical	Chronic neck pain	Not applicable
	NCT03317613		PNP	Phase II
	NCT03899246		Sickle cell pain	Phase I
	NCT00008476, NCT00088686		Dental pain	Phase II completed
	NCT03464292		Fibromyalgia	Phase II
	NCT03660943		OA	
	NCT02854670		Provoked vestibulodynia	Phase III
	NCT03330639		Rhinogenic headache	Not applicable
Zucapsaicin (cis-capsaicin) agonist	NCT00845923	Topical	PHN	Phase II completed
	NCT00995306, NCT00077935	Topical	OA	Phase III completed
	NCT00069082, NCT00033839	Intranasal	Episodic cluster headache	Phase III completed
Resiniferatoxin agonist	NCT03542838, NCT00804154, NCT03226574, Iadarola & Gonella 2013, Fukushima et al. 2017	Topical and intraganglionic or intrathecal injection	Burns, Phantom limb pain, PNP, OA, Low back pain, Chronic gynaecological pain	Phase I
Capsazepine antagonist	NCT00008476	Topical	Facial pain	Phase II completed
	Walker et al. 2003, Kistner et al. 2016	Oral	Inflammatory pain, PNP	Preclinical
A-425619 antagonist	Honore et al. 2005, McDonald et al. 2008, McGaraughty et al. 2006	Oral	Inflammatory pain, PNP, OA	Preclinical
SB-705498 antagonist	NCT00281684	Oral	Dental pain	Phase II completed
ABT-102 antagonist	NCT00854659	Oral	Inflammatory pain, PNP, OA	Phase I completed
AZD-1386 antagonist	NCT00736658	Oral	Chronic pain	Phase I completed
	NCT00672646		Dental pain	Phase II completed
JNJ-39439335 antagonist	NCT01006304, NCT01343303, NCT00933582	Oral	Pain, OA	Phase I completed
JTS-653 antagonist	Kitagawa et al. 2013	Oral	PHN	Phase II
V-116517 antagonist	NCT01688947, NCT01688934	Oral	PHN, OA	Phase II completed
NEO-6860 antagonist	NCT02712957	Oral	OA	Phase II completed

Abbreviations used: FDA = Food and Drug Administration; EMA = European Medicines Agency; PHN = postherpetic neuralgia; HIV-DSP = HIV-associated distal sensory polyneuropathy; PNP = peripheral neuropathic pain; OA = osteoarthritis

Possible discomfort associated with patch application can be avoided by giving the patient an oral analgesic (i.e., tramadol 50 mg) or by applying a topical anaesthetic (i.e., 2.5-4% lidocaine or 2.5% prilocaine) to the area where capsaicin patch will later be placed and the surrounding area of 1-2 cm in width. The skin where the capsaicin will be applied needs to be undamaged, clean, dry and without visible irritation. Protection during the application and the removal of the patch is important and includes wearing nitrile gloves, protective glasses and a mask. Any contact with mucous membranes must be avoided. Otherwise, transient erythema, eye pain and irritation, cough or throat irritation may occur. Maximum plasma concentration

of capsaicin is assessed at the time of 60-minutes patch removal or 20 minutes after and measures up to 4.6 ng ml^{-1}. Systemic exposure to capsaicin is considered to be mild and transient and varies between different patient groups. In one-third of the patients with postherpetic neuralgia, 3% of the patients with diabetic peripheral neuropathy and none of the patients with HIV-associated distal sensory polyneuropathy systemic exposure of capsaicin has been proven. Population studies have shown that average elimination time is 130 minutes. The dose does not have to be adjusted in patients with renal and liver failure (European Medicines Agency 2019).

As any other drug, capsaicin can have several adverse effects. Common and very common adverse effects are localized application-site reactions, characterized by stinging or burning sensation, pruritus, papules and erythema, as well as mild and transient decrease in sensory function. They are generally mild to moderate intensity, self-limiting and transient. A small number of chemical burns associated with improper application have been described. Apart from this, several not so common adverse effects have been documented during administration of capsaicin: diarrhoea, nausea, vomiting, fatigue, infection, hypertension, coronary vasospasm, myocardial infarction and dizziness. Aforementioned systemic adverse effects occur in less than 5% of patients treated with capsaicin patch and can be avoided by reducing the stress of drug administration, the application of cold compresses and short-acting opioid premedication (European Medicines Agency 2019). Topical administration avoids dangerous systemic adverse effects and enables the combination with other drugs and analgesics with limited drug-drug interactions. Only insignificant transient decrease in systemic absorption of other medications has been noticed. The only known contraindication for capsaicin use is drug hypersensitivity. During pregnancy capsaicin patch should be applied with caution, because there is no data of capsaicin's effect on the intrauterine development. Capsaicin in doses higher than recommended has been proven to cause delayed skeletal ossification in a rat model. Moreover, capsaicin needs to be avoided during lactation, as its excretion into milk has been studied in animal studies. Furthermore, a decrease in sperm count and sperm mobility followed by a decrease in number of pregnancies have been observed in a rat model, but were statistically insignificant (European Medicines Agency 2019). Despite that, capsaicin's role on human fertility needs further investigation.

Capsaicin might be a promising drug for patients who suffer from several psychiatric disorders. Preclinical studies have shown that TRPV1 plays a key role in anxiety-related behaviour. Given the high degree of comorbidity between anxiety disorders and chronic pain and overlap in the TRPV-1-expressing neuroanatomical substrates involved in both anxiety and pain, it is likely that TRPV1 also plays an important role in anxiety-pain interactions. In addition, TRPV1 receptors antagonists administered systemically, have been shown to produce antidepressant-like effects in both rats and mice. Systemic administration of the TRPV1 antagonist capsazepine enhances antidepressant-activity in fluoxetine-treated mice. Intracerebroventricular injection of capsaicin causing desensitization of supraspinal TRPV1 has also been shown to produce an antidepressant-like effect. There is a suggested role of TRPV1 in schizophrenia, also. TRPV1 plays a role in brain development and schizophrenia is considered to be a complex neurodevelopmental disorder. Potential links between TRPV1 and schizophrenia include dopaminergic mechanisms and cannabinoid mechanisms (Finn & Leonard 2015). Further research in this area is warranted.

CONCLUSION

All things considered, chronic pain still represents a major treatment challenge, but capsaicin, although being apparently simple might be a potential solution. Despite the fact that there is evidence of positive effect of capsaicin, it is still rarely used in clinical practice. Adding capsaicin to the standard chronic pain treatment might improve, fasten and ease the challenging path of managing chronic pain consequently providing the patient and their society with better quality of life. It is hoped that this review will stimulate further investigation in this field.

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Contribution of individual authors:

Dora Gašparini & Rudolf Ljubičić were in charge of literature searches, figures design and writing of the manuscript, with input from all co-authors.

Jasenka Mršić-Pelčić designed the study.

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