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LEADING ARTICLE

# TRPV1-Targeted Drugs in Development for Human Pain Conditions

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**Abstract**
The transient receptor potential vanilloid-1 (TRPV1) is a non-specific cation channel known for its sensitivity to pungent vanilloid compound (i.e. capsaicin) and noxious stimuli, including heat, low pH or inflammatory mediators. TRPV1 is found in the somatosensory system, particularly primary afferent neurons that respond to damaging or potentially damaging stimuli (nociceptors). Stimulation of TRPV1 evokes a burning sensation, reflecting a central role of the channel in pain. Pharmacological and genetic studies have validated TRPV1 as a therapeutic target in several preclinical models of chronic pain, including cancer, neuropathic, postoperative and musculoskeletal pain. While antagonists of TRPV1 were found to be a valuable addition to the pain therapeutic toolbox, their clinical use has been limited by detrimental side effects, such as hyperthermia. In contrast, capsaicin induces a prolonged defunctionalisation of nociceptors and thus opened the door to the development of a new class of therapeutics with long-lasting pain-relieving effects. Here we review the list of TRPV1 agonists undergoing clinical trials for chronic pain management, and discuss new indications, formulations or combination therapies being explored for capsaicin. While the analgesic pharmacopeia for chronic pain patients is ancient and poorly effective, modern TRPV1-targeted drugs could rapidly become available as the next generation of analgesics for a broad spectrum of pain conditions.

## 1 Introduction

Acute pain is a protective physiological response against harmful stimuli, such as extreme temperature, chemical irritants or tissue damage caused by injury or chronic inflammatory diseases [1]. Noxious or potentially noxious stimuli are transduced into nerve impulses by primary afferent neurons (nociceptors) and carried along the spinothalamic tract (Fig. 1) to reach the brainstem, thalamus and cerebral cortex, where nociceptive signals are encoded and perceived as painful.

Pain that persists beyond the time of usual tissue healing (~ 3 months) is considered chronic [2] and is the most frequent reason for seeking consultations at primary care units. In the USA alone, estimated costs of chronic pain exceed US$600 billion annually [3]. Chronic pain can stem from nerve damage (neuropathic pain) often associated

**Key Points**

Pain is the most frequent reason for patients to seek medical care. Efforts have been made to design new non-opioid analgesics.

Targeting the capsaicin receptor (TRPV1 channel) using ligands that cause defunctionalisation of "pain-sensing" nerves has proved to be a promising therapeutic strategy in patients with herpetic neuropathic pain or osteoarthritic pain.

Ongoing clinical trials are investigating the long-term efficacy of new capsaicin formulations and alternative modalities for administering TRPV1 agonists and antagonists to treat intractable pain.

Side effects, sometime severe, that accompany capsaicin administration warrant the development of new capsaicin-derived agonists, or other modality-specific antagonists.

Future clinical studies will address the long-term patient responses and the efficacy of these compounds, thus providing new pain therapeutics for healthcare practitioners.

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with plastic changes in the peripheral and central nervous systems leading to altered detection, transmission, processing and regulation of pain [4, 5]. Abnormal hyperexcitable states that result in persistent and intensified pain sensations appear in conditions that produce continuous stimulation of the pain pathway such as chronic inflammation and cancer-associated pain [1] as well as dysfunctional pain disorders, which include bladder pain syndrome (previously interstitial cystitis), irritable bowel syndrome (IBS) and fibromyalgia [5, 6]. Current treatments for acute and chronic pain are lacking. Most of the drugs used, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, antidepressants, paracetamol or anticonvulsants achieve transient and partial pain relief and their use is often hampered by severe side effects [3, 7]. Insights into the understanding of the mechanisms of nociception at the periphery has been tremendous over the last 30 years and the discovery of the capsaicin receptor TRPV1 channel in the early 1990s has been a real breakthrough to provide new "druggable" targets [8]. TRPV1 is expressed by primary afferent nerve fibres, in which it functions as a sensor for noxious heat and diverse chemical irritants, or toxins produced by plants or pathogens. TRPV1 is a ligand-gated ion channel directly activated by arachidonic acid metabolites produced downstream of the 5-lipooxygenase pathway (5-LOX) and endocannabinoids (N-arachidonoyl dopamine (NADA), or N-oleoyl dopamine (OLDA)). At peripheral nerve endings, TRPV1 acts as a "receptor-operated" channel whose activation downstream of metabotropic receptors elicits inflammatory pain. Accordingly, prostaglandin, bradykinin or serotonin produced in inflamed tissues, through activation of their respective receptors, potentiate the TRPV1 channel response to endogenous agonists, and shift its threshold of activation by heat. Pharmacological and genetic studies have confirmed the contribution of TRPV1 in several models of pathological pain. TRPV1 null mice show virtually no thermal hyperalgesia during inflammation. Rapid desensitization of TRPV1-expressing fibers by administration of capsaicin or the potent agonist resiniferatoxin (RTX), attenuates experimental inflammatory hyperalgesia and neurogenic inflammation as well as naturally occurring cancer pain or debilitating arthritic pain. Overall, decades of fundamental research made the TRPV1 an attractive target for novel analgesic therapies.

With regard to drug development, the long-term analgesic effect of TRPV1 agonists has fostered many clinical trials, and all the research and development efforts have culminated with the introduction of the 8% capsaicin dermal patch for long lasting pain relief in some severe neuropathic pain conditions [9, 10]. In parallel, pharmaceutical companies have designed low molecular weight TRPV1 antagonists to avoid the sometimes severe side effects of TRPV1 agonist therapy. Despite several failed trials in this field, many achievements and new developments have occurred in the last couple of years. This review aimed to present the latest developments on TRPV1 agonists and antagonists undergoing clinical trials that were completed or started in the last 5 years. Perspectives and new achievements in the field of TRPV1 agonists are outlined with a special emphasis on capsaicin and its derivatives. Novel findings regarding the TRPV1 antagonists are presented and summarized and some promising recent findings are outlined.

## 2 The Vanilloid Receptor TRPV1

Although the first transient receptor potential channel was described in 1969 [11], it was not until the end of the 1990s that TRPV1 was identified and cloned [8]. The capsaicin receptor TRPV1 is the prototypical nociceptive channel widely expressed in primary afferent neurons of the dorsal root, trigeminal and nodose ganglia (Fig. 1). These are bipolar neurons that are the initial station in the pathway conveying sensory information from the periphery to the somatosensory cortex via the spinal cord (Fig. 1). TRPV1 is a non-selective cation channel with polymodal mechanisms of activation: temperature > 42 °C, low pH < 6.5, osmolarity changes, arachidonic acid metabolites: 5(S) and 12(s) arachidonic acid 5-hydroperoxide (HPETE); endocannabinoids: NADA and OLDA; and voltage sensitivity [1, 8, 12, 13]. The TRPV1 channel is mainly known for its ability of sensing a variety of pungent plant products, the most well-known being capsaicin, the bioactive compound in chilli peppers. Other compounds from this category include: RTX (from the latex of Eucalyptus resinifera), piperine (the pungent ingredient in black pepper), gingerol and zingerone (from ginger), camphor (from the wood of camphor) and eugenol (an essential oil found in cloves). Furthermore, the TRPV1 channel is activated by a variety of painful venoms from jellyfish, spiders, centipedes and scorpions [14–17].

Following TRPV1 activation, the nociceptors are known to release a variety of neuropeptides [among them substance P and calcitonin gene-related peptide (CGRP)], which activate secondary order neurons in the dorsal horn of the spinal cord, and elicit biochemical cascades at the periphery, known as neurogenic inflammation [1, 4, 18–26]. In the context of inflammation, it was also found that TRPV1 channels are activated by various pro-inflammatory agents such as prostaglandins, serotonin (5-HT), bradykinin, activators of the protease-activated receptors (PAR), ATP, nerve growth factor (NGF), histamine, calcitonin-gene-related peptide α (CGRP α), tumor necrosis factor α (TNFα) and granulocyte-colony stimulating factor (G-CSF) [27–40]. These algogenic mediators induce, through their cognate G protein-coupled receptors (GPCR), conformational changes in the TRPV1

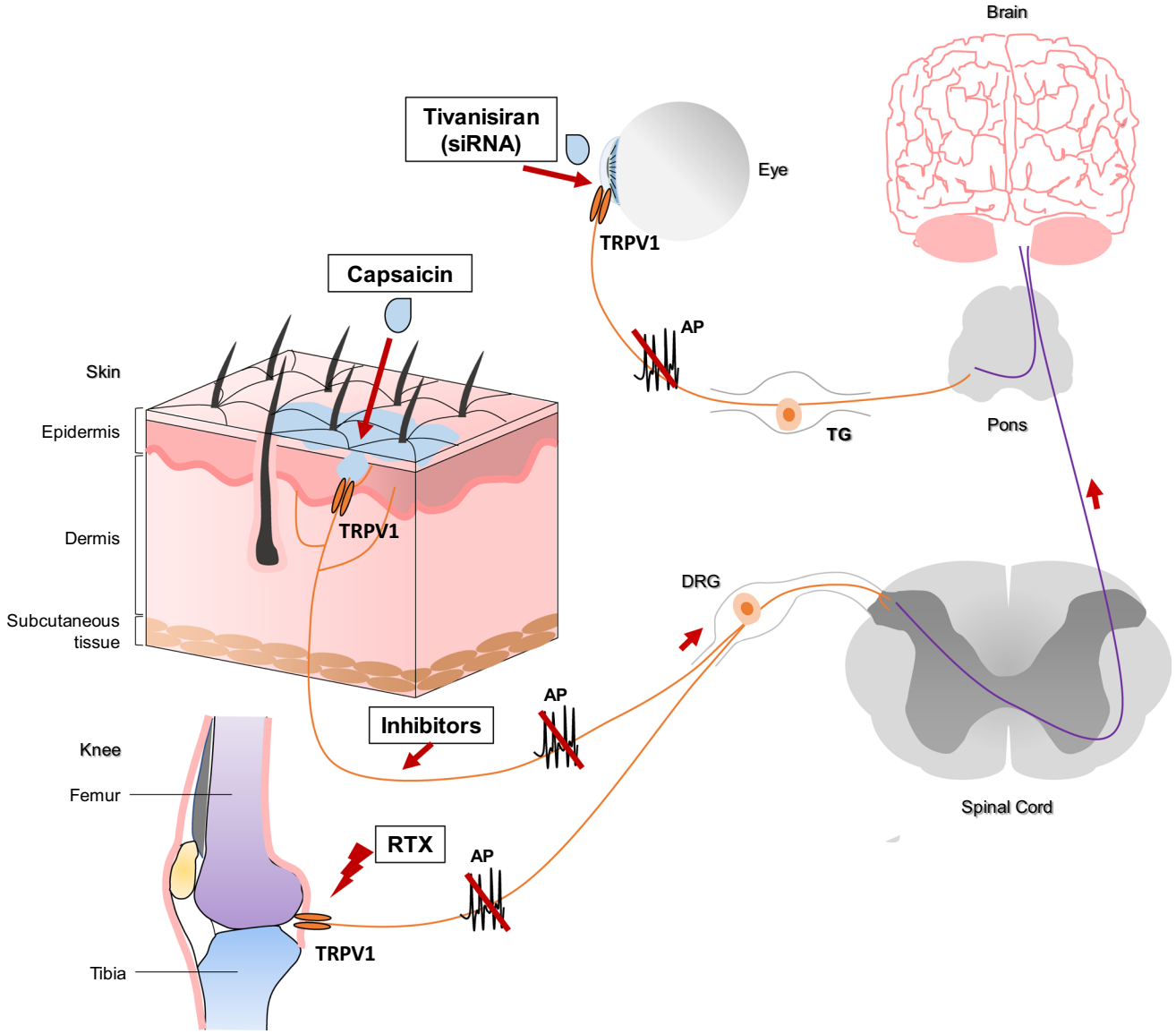


**Fig. 1** TRPV1: an attractive target for novel analgesic therapies. See main text for details and specific references. *TRPV1* transient receptor potential vanilloid-1, *TG* trigeminal ganglion, *DRG* dorsal root ganglion, *RTX* resiniferatoxin, *AP* action potential

channel protein, which elicits an increase in the probability of channel opening by heat, protons and capsaicin [1, 19, 41, 42]. This process of sensitization is an important mechanism leading to nociceptor hyperexcitability that underlies hyperalgesia and allodynia during tissue inflammation [2]. Hence, disrupting the activity or assembly of TRPV1 channels is able to attenuate the development of hyperalgesia [41–43]. Nevertheless, various studies, using genetic manipulation of TRPV1, showed only modest changes in pain sensitivity and acute noxious heat sensitivity in healthy conditions, yet highlighted the critical role of TRPV1 in mediating thermal hyperalgesia under inflammatory pain conditions, thus supporting the notion that targeting TRPV1 channels would be an adequate approach for individual living with pathological pain [44–47]. The use of pharmacological blockers of TRPV1 led to mixed results, depending on the preclinical model used, compared to knockout animal studies. TRPV1 antagonists were able to induce pain relief in various models of nerve injury [4, 48–50]. In models of painful diabetic neuropathy (PDN), animals present a biphasic pain behaviour characterized by hyperalgesia in the early phase of the disease followed by hypoalgesia in the later phase [4, 24, 51]. TRPV1-deficient mice show no signs of diabetes-induced heat hypersensitivity [51], while pharmacological inhibition of the channel reduces mechanical allodynia [52]. The underlying mechanism for these findings could be due to TRPV1 sensitization in conditions of hypoxia and hyperglycemia in the early phase [53, 54] or the direct TRPV1

modulation by insulin [55]. Furthermore, the decreased TRPV1 expression observed in the late phase of the disease in both animal models and patients [51, 56–58] could be the result of a decrease in insulin production. Finally in cancer- and chemotherapy-induced pain, either pharmacological blockade or genetic manipulation of the channel has proved to be effective [59–64].

Altogether, these findings confirmed the central role of TRPV1 as a molecular integrator of noxious stimuli and as an initiator of the neurogenic response. Further insights into the 3D structure of the channel, obtained by cryogenic electron microscopy (CryoEM), and identification of the binding sites for vanilloid compounds, using mutagenesis analysis and computational biology, has shed light on the mechanism of action of TRPV1, and provided key information for designing and developing TRPV1 activators, inhibitors and allosteric modulators for pain management [65–67]. Nevertheless, in recent years it became apparent that TRPV1 is expressed in non-nociceptive neurons and other tissues [41, 68], and thus TRPV1 is implicated, besides pain, in multiple physiological and pathophysiological processes such as: thermosensation [17, 69, 70], energy homeostasis [71, 72], cancer [73–77], regulation of diet-induced obesity [78], insulin and leptin resistance [71, 78–81], development of severe bronchial asthma [82–85], neuroimmunity [86] and itch [35, 87]. As such, tremendous interest has been shown by researchers and pharmaceutical companies to develop TRPV1 channel modulators not only for pain but also other clinical conditions such as stroke, cancer, dysphagia, diabetes and obesity.

## 3 Capsaicin: The Versatile Bioactive Compound of Chili Peppers

One of the striking, and perhaps counterintuitive, characteristics of capsaicin is its capacity to be used as a local analgesic. For millennia, this phytochemical has been used for a multitude of purposes, including medicinal [88–90]. Currently, topical treatment with low-dose (0.075%) capsaicin creams or high-dose (8%) patches is in use for the treatment of arthritis and skin conditions, muscle pain, neuropathic pain and migraine [9, 10, 91–94]. A number of pharmaceutical companies market topical capsaicin under trade names such as Menthacin, Zostrix, Zoderm and Capzasin-P [9, 88–90]. Furthermore, since 2009 the European Union and the US Food and Drug Administration (FDA) approved the use of the capsaicin 8% patch (Qutenza, NGX-4010, Transacin) for the treatment of postherpetic neuralgia, peripheral neuropathic pain and HIV-associated distal sensory polyneuropathy [88, 89, 95]. Although the mechanism by which capsaicin induces analgesia is not completely understood [88–90], it was determined that prolonged (acute or short-term desensitization) or repeated applications of capsaicin, a process named tachyphylaxis, induces a calcium-dependent desensitization of TRPV1, thus rendering the channel insensitive to capsaicin as well as other noxious stimuli [96–99]. This can be viewed as a neuronal protection mechanism preventing calcium overload during repetitive TRPV1 stimulation [98]. Some insight into understanding the process of desensitization came by establishing that capsaicin binds into a hydrophobic cavity constituted by residues Y512, S513, T551 and E571 in the human TRPV1 sequence [100]. While the first two residues are conserved between species, T551 is different in the rabbit and chicken [101]. This observation was an interesting finding since capsaicin detection is abrogated in birds and the avian channel is resistant to the typical desensitization produced by repeated application of protons [102]. Furthermore, it was shown that an important structural determinant for capsaicin-induced channel desensitization was mediated through an interaction with the calcium-binding protein calmodulin (CaM), at specific sites located at the N- and C-terminal regions of the channel [103–105]. In fact, differences in the binding site found in the C-terminal region between human and avian TRPV1 confer resistance to calcium-induced desensitization [102]. This is in concert with the previous findings of there being several possible mechanisms for desensitization, including the one that involved the binding of CaM to TRPV1 [103–107]. Other proposed mechanisms include: (1) dephosphorylation of TRPV1 by calcineurin [108, 109], which correlates with the fact that phosphorylation of TRPV1 by protein kinase C (PKC) and protein kinase A (PKA) reduces calcium-mediated desensitization [109–112] and (2) calcium-dependent stimulation of phospholipase C (PLC), leading to hydrolysis of PI(4,5)P2, which prevents channel function and thus promotes desensitization [113–117]. Therefore, desensitization of TRPV1 is a very useful feature from a pharmaceutical and clinical point of view. It begins a few hours after the treatment and may last up to several months. This process, named "defunctionalisation" of sensory neurons, includes a loss of membrane potential, membrane transport capabilities and a retraction of epidermal and dermal nerve fiber endings [9]. The downstream effect of the desensitization process is a reprogramming of the gene expression profile leading to the depletion of the pro-inflammatory, pro-algesic neuropeptides, such as substance P, and increased expression of the endogenous analgesic peptides, galanin and somatostatin [118–122].

Due to its multiple beneficial functions [90], new ways of using capsaicin in clinical practice have been explored. However, due to poor water solubility, the bioavailability and efficacy of capsaicin in vivo is limited [90]. Furthermore, systemic administration of capsaicin is not currently used to treat pain in a clinical setting partly because direct oral administration induces irritation of the oral cavity and

the stomach leading to stomatitis, orofacial pain and gastric ulcers [123] as well as dangerous body temperature elevation [9, 78, 88, 89, 124]. Accordingly, treating neonatal rats systemically with capsaicin leads to not only lifelong TRPV1 desensitization and reduction in pain perception but also to abnormal body temperature and irregular circadian core body temperature rhythm [125]. To overcome the poor bioavailability and side effects of oral capsaicin delivery, different formulations have been designed, including micelles, lipid vesicles, micro/nano emulsions and nanoparticles [90, 126–129]. However, at this time most efforts have been concentrated on the development of capsaicin derivatives with no effect on body temperature, along with topical application, which is not hampered by severe systemic effects.

Today, many capsaicin topical compounds are used in clinical practice [9, 10, 88–92] and the interest for the use of capsaicin for the treatment of pain of various etiology, alone or in combination with other medications, has not faded. Besides the few that were completed in the last years, numerous clinical trials are still ongoing or will start in the near future (summarized in Table 1).

### 3.1 Capsaicin and Neuropathic Pain

In a randomized, double-blind, Phase 3 study (Boehringer Ingelheim) conducted in two countries on 746 patients with back and neck pain that appeared between 1 and 21 days before capsaicin application, Predel et al. reported that using capsaicin gel (0.075%) alone was sufficient to treat acute back and neck pain [130, 131]. Capsaicin alone was shown to significantly improve the pain. The incidence of adverse effects (skin burning sensation, nasopharyngitis, headache and application site pain) was relatively low (26.5%) and the addition of the diclofenac gel increased the adverse effects with no clinical benefit [130, 131]. In a Phase 4 multicenter study (Astellas Pharma), Galvez et al. reported a good efficacy of the capsaicin patch in the long-term treatment of peripheral neuropathic pain [132, 133]. The study tested the capsaicin patch, over a period of 52 weeks, on 305 patients with postherpetic neuralgia, painful HIV-associated neuropathy, post-traumatic or post-surgery nerve injury, and other peripheral neuropathic pain. A sustained reduction in the average daily pain was observed in these patients, which was associated with a minimal occurrence of sensory loss. In fact, the adverse effects were mild to moderate and only 3.6% of patients were unable to continue the treatment. Another ongoing Phase 4 multicenter randomized clinical trial is comparing the efficacy of the capsaicin (8%) and lidocaine patch (5%) in the treatment of localized peripheral pain secondary to herpes, surgery, amputation, radiation therapy and complex regional pain syndrome type 1 [134]. It would be interesting to determine if local capsaicin patches are as efficient as a local anesthetic, while preserving sensory function.

There are currently a number of clinical trials, either ongoing or recruiting, that suggest a real therapeutic interest for topical capsaicin. The vast majority of these trials are assessing the effect of the capsaicin patch (NGX-4010 or Qutenza) or gel in the treatment of neuropathic pain of various etiologies: following anticancer treatments [135, 136], following spinal cord injury in patients who failed other therapeutical approaches [137], and in the treatment of diabetic neuropathy [138]. Finally, another single-blind trial is testing intranasal capsaicin for the treatment of rhinogenic headache [139].

### 3.2 Capsaicin and Osteoarthritic Pain

Due to the therapeutic benefits of capsaicin formulations for musculoskeletal pain, the American College of Rheumatology/Arthritis recently included topical capsaicin as a therapeutic option in the treatment of knee osteoarthritis [92]. This sparked even more interest in the development of new approaches for capsaicin administration since high concentrations of capsaicin creams caused significant problems both for patients and healthcare providers. A Phase 2 clinical trial comparing the efficacy of 1% (CGS-200-1) versus 5% liquid capsaicin (CGS-200-5) in the treatment of osteoarthritis was started by Vizuri Health Sciences LLC [140, 141]. This was a multicenter, randomized, double-blind, parallel group, vehicle-controlled trial comparing topical CGS-200-1 (1%) or CGS-200-5 (5%) versus CGS-200-0 (no capsaicin) in 122 randomized subjects who had osteoarthritis of at least one knee, according to 1986 ACR criteria, and a Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score of $\geq 250$. Capsaicin treatment was applied for 1 h to both knees on four consecutive days. The study showed that CGS-200-5, but not CGS-200-1, was well tolerated and had a durable effect (more than 60 days). The side effects noted, including application site pain, were only mild to moderate. The same company recently completed a Phase 4 clinical trial validating the efficacy and safety of liquid capsaicin (0.25%) administered once or twice daily in the treatment of knee osteoarthritis [142]. The drug is marketed as an over-the-counter topical analgesic under the name PainBloc24. However, there are unsuccessful clinical studies that were terminated prematurely such as a Phase 3 clinical trial assessing Qutenza in knee osteoarthritis of patients with obesity [143].

**Table 1** Summary of randomized clinical trials of capsaicin

| Compound | Company | Route | Clinical indication | Development stage/status | Identifier | References |
|---|---|---|---|---|---|---|
| Capsaicin gel | Boehringer Ingelheim | Transdermal | Acute back and neck pain | Phase 3—published results | NCT02700815 | [130, 131] |
| Capsaicin patch (Qutenza) | Astellas Pharma Inc | Topical | Neuropathic pain | Phase 4—published results | NCT01252160 | [132, 133] |
| Capsaicin patch | University Hospital, Antwerp | Transdermal | Neuropathic pain of various etiology | Phase 4—ongoing | NCT03348735 | [134] |
| Capsaicin patch (Qutenza) | Institut de Cancérologie de la Loire | Transdermal | Neuropathic pain secondary to anticancer treatment | Phase 2—ongoing | NCT03317613 | [135] |
| Capsaicin patch | Institut de Cancérologie de l'Ouest | Transdermal | Neuropathic pain secondary to surgery for breast cancer | Phase 3—ongoing | NCT03794388 | [136] |
| Capsaicin patch (Qutenza) | The University of Texas Health Science Center at San Antonio | Transdermal | Neuropathic pain secondary to spinal cord injury | Randomized clinical trial—ongoing | NCT02441660 | [137] |
| Capsaicin gel | Thammasat University | Transdermal | Neuropathic pain secondary to diabetes | Phase 3—no results | NCT03113448 | [138] |
| Capsaicin gel | University of Nebraska | Topical | Rhinogenic headache | Recruiting | NCT03330639 | [139] |
| Capsaicin liquid (CGS-200-1 and CGS-200-5) | Vizuri Health Sciences LLC | Topical | Pain secondary to knee osteoarthritis | Phase 4—results | NCT03528369 | [140, 141] |
| Capsaicin liquid (0.25%) (920-CGS-200) | Vizuri Health Sciences LLC | Topical | Pain secondary to knee osteoarthritis | Phase 4—results | NCT03124407 | [142] |
| Capsaicin patch (Qutenza) | Hospital Ambroise Pare | Transdermal | Pain secondary to knee osteoarthritis in obese patients | Phase 3—terminated | NCT03153813 | [143] |
| Cis-capsaicin (Civamide) solution | Wilson Laboratories | Intra-nasal | Postherpetic neuralgia and localized post-incisional neuropathic pain | Phase 2—terminated | NCT01886313 | [147] |
| Cis-capsaicin (Civamide) patch | Wilson Laboratories | Topical | Postherpetic neuralgia and localized post-incisional neuropathic pain | Phase 2—no results | NCT00845923 | [148] |
| Cis-capsaicin (Civamide) solution | Wilson Laboratories | Intra-nasal | Cluster headaches | Phase 3—ongoing | NCT01341548 | [149] |
| Tran-capsaicin (CNTX-4975) | Centrexion Therapeutics | Injectable | Moderate to severe pain secondary to knee osteoarthritis | Phase 1b and 3—published results | NCT03472677<br>NCT03576508<br>NCT03429049<br>NCT03660943 | [150–154] |
| Capsaicin patch (Qutenza) | Astellas Pharma Inc | Topical | Neuropathic pain | Phase 4—published results | NCT01252160 | [132, 133] |
| CA-008 | Concentric Analgesics | Injectable | Postsurgical pain—bunionectomy | Phase 2—published results | NCT03599089<br>NCT03885596 | [163, 164] |

**Table 1** (continued)

| Compound | Company | Route | Clinical indication | Development stage/status | Identifier | References |
|---|---|---|---|---|---|---|
| CA-008 | Concentric Analgesics | Injectable | Postsurgical pain—total knee arthroplasty | Phase 2—ongoing | NCT03731364 | [159] |
| CA-008 | Concentric Analgesics | Injectable | Postsurgical pain—correction of hallux valgus deformity | Phase 2—unpublished results | NCT03307837 | [160] |
| CA-008 | Concentric Analgesics | Injectable | Postsurgical pain | Phase 1 and 2—ongoing | NCT04203537 | [161] |
| CA-008 | Concentric Analgesics | Injectable | Postsurgical pain -complete abdominoplasty | Phase 2—unpublished results | NCT03789318 | [162] |

Compounds' trade names are given in parentheses

## 4 Synthetic Isomers and Precursors of Capsaicin

To avoid the, sometimes severe, side effects of capsaicin, synthetic isomers of capsaicin, with lower pungency, have also been produced. Cis-capsaicin (cis-8-methyl-N-vanillyl-6-nonenamide) (Zucapsaicin, Civanex, Civamide) was tested for neuropathic pain associated with herpes simplex infections, cluster headaches, migraine and also knee osteoarthritis [144–146]. In 2010, under the names Zuacta (Sanofi-Aventis) or Civanex (Winston Labs), cis-capsaicin was approved by Health Canada as a topical cream (0.075%) for the treatment of osteoarthritis. The drug is not FDA approved and it is still undergoing clinical trials. Civamide, in the form of an intranasal spray (0.01%), has been clinically studied for the treatment of postherpetic neuralgia [147]. Despite being a multicenter trial, the study had only 11 subjects and showed moderate to severe side effects that led to early termination of the trial. This was followed by another Phase 2 clinical trial designed to evaluate the safety and efficacy of a topically administered Civamide patch (Winston Laboratories) for the treatment of moderate to severe daily pain associated with (1) postherpetic neuralgia localized to the trunk, and (2) post-incisional neuropathic pain syndromes of the trunk [148]. Although this study has been completed, the results were not available. Intranasal Civamide for the treatment of cluster headaches has also been evaluated, with modest results [146]. Currently, the same approach is undergoing a Phase 3 double-blind, multicenter study employing 180 patients [149]. Another highly purified capsaicin isomer, trans-capsaicin, has been developed by Centrexion Therapeutics, this time in injectable form. This isomer, named CNTX-4975, was recently tested in the treatment of moderate to severe pain associated with osteoarthritis of the knee, in a Phase 1 followed by a Phase 3 clinical trial [150–154]. CNTX-4975 was administered by single intra-articular injection and because of its short half-life (less than 4 h), was expected to achieve a long-term analgesic effect with few side effects. This randomized, multicenter, double-blind study employed 172 patients with stable knee osteoarthritis and showed that a single intra-articular injection decreased pain scores at 12 and 24 weeks versus placebo [153]. This effect was dose dependent since injection of 1.0 mg of CNTX-4975 produced a decrease in osteoarthritis knee pain over 24 weeks while 0.5 mg improved pain, up to 12 weeks only. In addition, nearly one in four patients achieved complete pain relief. The administration of the drug was accompanied by cooling of the knee joint before and after. Only mild to moderate adverse effects were reported by 30%, 47% and 30% of patients in the placebo, CNTX-4975 0.5 mg and CNTX-4975 1.0 mg groups, respectively. The adverse effects included erythema,

peripheral edema, nausea, oral hypoesthesia, hypotension and increased hepatic enzymes, but none of the patients had to drop out of the study. Although the results are promising, as the authors and others pointed out [153, 155], this was a small randomized study in a specific population of patients with moderate to severe osteoarthritis knee pain. Therefore, the findings cannot be generalized to the large population of individuals with knee osteoarthritis, and the data regarding the safety profile are limited.

Another approach has been to develop capsaicin precursors that would provide therapeutic benefits without the severe side effects of capsaicin. Such a compound has been developed by Concentric Analgesics and dubbed CA-008 [156]. This is a water-soluble prodrug that rapidly converts to capsaicin. After going through a series of clinical trials, CA-008 gained Breakthrough Therapy designation in 2018 from the FDA for the treatment of post-surgical pain [157]. The company announced good results in one of their Phase 2 study to control postsurgical pain in bunionectomy patients [157, 158]. The study included 144 patients who underwent bunionectomy at three sites across the USA. The patients were randomized to receive one of the three CA-008 doses or placebo. CA-008 (0.7, 2.1 or 4.2 mg) was infiltrated/instilled in the wound prior to closing the suture and the patients were followed for 29 days. The CA-008 4.2 mg dose group showed significant pain reduction (33%) versus placebo. Another important element was the reduction in opioid consumption by 50% versus placebo, while 26% of subjects required no opioid administration in the first 96 h post-surgery. Additionally, 32% of subjects in the (CA-008) 4.2 mg group compared to 5% in the placebo group were able to discontinue all opioids after 4 h. In terms of safety, 72.1% of subjects reported mild to moderate side effects. The most frequent were burning sensation (2), headache (4), polyuria (3), increased alanine transaminase (ALT) and aspartate transaminase (AST) (2), hypoesthesia and nausea, yet no major side effects caused early termination and no deaths resulted from the study. Of note, there were no relevant differences across CA-008 doses or placebo for wound healing, X-ray exams or neurosensory assessments. Additional studies testing CA-008 for postsurgical pain management are ongoing, including total knee arthroplasty, correction of hallux valgus deformity or complete abdominoplasty [159–164].

## 5 Resiniferatoxin and "Molecular Neurosurgery"

Resiniferatoxin (RTX) is a chemical found in the *Euphorbia resinifera* plant and is the most potent agonist of TRPV1. RTX binds with nanomolar affinity to TRPV1, causing prolonged channel opening and massive increase in intracellular calcium. This calcium increase has cytotoxic effect on the nociceptors, thus leading to rapid retraction and defunctionalisation of the pain fibers [165–167] (Fig. 1). An important observation regarding the RTX mode of action was the fact that RTX-induced defunctionalisation was not observed in the absence of TRPV1 [30], even at concentrations 1,000× higher than normally used. Additionally, cells that do not express TRPV1 remain intact even when adjacent to apoptotic TRPV1+ neurons exposed to RTX [168]. Preclinical data obtained in rodents showed a long-lasting, fully reversible desensitization of the neurogenic inflammatory pathway following one subcutaneous injection of RTX [169]. Both intrathecal and intraganglionic RTX administration leads to the selective targeting and permanent deletion of the TRPV1-expressing Aδ and C-fiber cell bodies in the DRG and trigeminal ganglia [166, 170–173]. As neurons in sensory ganglia collect noxious information from precisely delimited anatomical areas, called dermatomes, the idea to use RTX as a "molecular scalpel" for the treatment of highly localized pain became very attractive [174, 175]. However, the main caveat was that in order to avoid any undesirable effects, RTX had to be applied close to the site of action, on the cell bodies of sensory neurons or their axons (i.e. intrathecally or intraganglionically), or at the peripheral site of injury where pain is generated [174, 175].

Several animal models of cancer and inflammatory pain have been used to show the long-lasting analgesic efficacy of intrathecal or intraganglionic infusion of RTX [171, 172, 175–179], without affecting motor activity, coordination or mechanosensitivity. However, most studies currently agree on a localized route of injection of RTX since systemic administration can generate irreversible changes in the peripheral nervous system [174, 175]. Overall, complete removal of TRPV1 nociceptors using RTX is considered a treatment option for chronic, incurable conditions such as cancer pain, chronic phantom pain or diabetic neuropathy [175, 180].

Recently, intravesical RTX administration was also found to decrease the incidence and severity of catheter-related bladder discomfort in patients undergoing transurethral resection of the prostate, without any significant side effects [181]. In addition, the RTX efficacy in ablating pain secondary to canine osteosarcoma [176] raised the hopes of this treatment in human patients since human bone cancer is pathologically similar to canine osteosarcoma. These results led to a Phase 1 clinical trial with periganglionic RTX administration in human cancer patients [182] (Table 2). The first two human patients with intractable cervical cancer pain were enrolled into this trial at the National Cancer Institute in October 2009 [183]. Both patients reported sustained improvement in the original pain symptoms after RTX administration. So far, a total of ten patients have received intrathecal RTX in this ongoing study, and all have

showed long-lasting analgesia with no significant adverse effects [184].

In pain syndromes affecting multiple dermatomes, RTX may be administered intrathecally [175, 177]. Currently, two clinical trials for cancer pain management using the intrathecal route of administration are ongoing. The first is a Phase 1, single-site, open-label, dose-escalation study to determine the safety and efficacy of intrathecal administration of RTX in patients with severe refractory pain due to advanced malignancy [185]. The study continues to recruit patients and the goal is to reach 45 participants. Another Phase 1b, multicenter study that explores the epidural route of administration of RTX for intractable cancer-induced pain is sponsored by Sorento Therapeutics [186]. In February 2020, Sorrento Therapeutics announced that an interim analysis of this study has generated positive results [187]. Data were available from 14 patients and showed that the lower doses used (0.4, 1, 2 and 4 μg) were ineffective and only three patients who received 8 and 15 μg of RTX showed significant decrease of pain 24 h after administration. The effect lasted for the entire period the patients were observed (weeks) and was accompanied by improvement in physical strength, mood and appetite. There were no dose-limiting toxicities, but one patient had increased blood pressure. The most common treatment-related adverse effect was transient and moderate post-procedural pain (50%). All these effects resolved in less than 2 days following drug administration. Further to this study, patients will be tested for doses up to 25 μg and Sorrento Therapeutics will initiate a Phase 3 study for epidural RTX administration in the treatment of intractable pain in advanced diseases. The results were presented by Nedeljkovic et al. at the American Academy of Pain Medicine Annual Meeting on 27 February 2020 [188]. Knowing the analgesic effects of capsaicin in osteoarthritic pain, it was expected that RTX, injected into the knee joint, would have similar beneficial effects at much lower concentrations than capsaicin. Indeed, preclinical data showed a long-lasting reduction in pain and inflammation, following intra-articular RTX administration in animal models [189–191]. The first clinical study of intra-articular RTX for osteoarthritic pain was initiated by Mestex AG and the first patient was treated in 2016 [192]. This was an open-label, dose-escalating Phase 1/2a study to determine the safety and clinical effects of a single or repeated intra-articular injections of Lopain (MTX-071) in patients with chronic osteoarthritic knee joint pain. No results have been published so far but, according to Mestex AG, as of October 2019 more than 60 patients with marked chronic knee pain have received Lopain in GCP-compliant clinical trials. After a single intra-articular administration, the joint pain was abolished for at least 6 months in most patients and, in some cases, for more than 12 months. Lopain was well tolerated and without any safety concerns. The company has initiated a randomized, double-blind, placebo-controlled Phase 2a [193] followed by a Phase 2b trial in 2019 [194]. Sorrento Therapeutics has also several Phase 1 and a Phase 3 clinical trials to study RTX for knee pain [195–197]. In 2019 the company announced good results for its Phase 1 trial [198]. Post administration of RTX, the patients showed fast relief (in less than a week), which lasted for the duration of the trial (84 days). There were no dose-limiting toxicities (doses between 5 and 30 μg) or any adverse events of interest noted. Five patients agreed to be followed further and showed no or very low levels of pain at day 168, supporting the long-term effect of RTX. These results will be expanded by two multicentre, double-blind Phase 3 trials, each planning to use 400 patients.

Other clinical applications for RTX treatment could be found in the future, including pain associated with thermal injuries [199] or migraine [88].

## 6 TRPV1 Antagonists

The findings that TRPV1 null mice showed attenuated thermal hyperalgesia after inflammation have triggered tremendous interest in developing TRPV1 antagonists with analgesic properties [45, 200]. In less than 20 years, a large array of potent and selective small molecules were identified and expected to provide a new generation of non-opioid analgesics [201–203]. Capsazepine was the first competitive TRPV1 antagonist described [88, 204]. Although a capsaicin derivative, capsazepine had poor selectivity for TRPV1, and was found to block nicotinic receptors, voltage-gated calcium channels and TRPM8, thus making it a poor clinical candidate [204, 205]. This first effort was followed by the development of other, more potent and selective TRPV1 antagonists. Many of these compounds showed promise in preclinical pain models; for example, BCTC (Pardue Pharma), A-784168 and A-425619 (Abbott) and GRC-6211 (Glenmark) were able to reverse pain in animal models of inflammatory and neuropathic pain; ABT-102 and ABT-116 (Abbott) and JNJ-39729209 (Janssen) proved to be efficacious in reversing bone cancer pain, postoperative and chronic inflammatory pain; A-995662 exhibited anti-pain effects in a model of rat knee joint pain; and AS1928370 and AS1725195 (Astellas) potently improved mechanical allodynia in neuropathic pain [201–203, 206–211].

As aforementioned, systemic administration of TRPV1 agonists was found to induce transient hypothermia [41, 89, 212]. Reciprocally, it became clear that numerous preclinical studies and, later on, clinical trials noted the appearance of hyperthermia (febrile reaction) with TRPV1 antagonist [124, 212]. The reported hyperthermic effect was variable depending on the compound. For instance, AZD-1386 (AstraZeneca) induced only a modest increase in body temperature

**Table 2** Summary of randomized clinical trials of resiniferatoxin (RTX)

| Compound | Company | Route | Clinical indication | Development stage/status | Identifier | References |
|---|---|---|---|---|---|---|
| RTX | National Institute of Neurological Disorders and Stroke (NINDS) | Injectable Periganglionic | Cancer-induced pain | Phase 1b—ongoing | NCT02522611 | [182] |
| RTX | National Institute of Dental and Craniofacial Research (NIDCR) | Injectable Intrathecal | Cancer-induced pain | Phase 1b—recruiting | NCT00804154 | [185] |
| RTX | Sorrento Therapeutics | Injectable epidural | Cancer-induced pain | 1b—ongoing | NCT03226574 | [186] |
| RTX (Lopain, MTX-071) | Mestex AG | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 1/2a—completed | NCT02566564 2015-001981-24 (EU) | [192] |
| RTX (Lopain, MTX-071) | Mestex AG | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 1b/2a—completed | 2017-004049-26 (EU) | [193] |
| RTX (Lopain, MTX-071) | Mestex AG | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 2b—ongoing | 2018-000818-37(EU) | [194] |
| RTX | Sorrento Therapeutics | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 1—ongoing | NCT03542838 | [195] |
| RTX | Sorrento Therapeutics | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 3—not yet recruiting | NCT04044742 | [196] |
| RTX | Sorrento Therapeutics | Injectable intra-articular | Osteoarthritic knee joint pain | Phase 3—not yet recruiting | NCT04044742 | [197] |

Compounds' trade names are given in parentheses

*EU* European Union

and the effect disappeared upon repeated administration [124, 213], whereas AMG517 (Amgen) induced a marked (up to 40.2 °C) and long-lasting (1–4 days) effect, which ended in terminating a Phase 1b dental pain study [124]. The mechanism by which TRPV1 channel antagonists elevate the body temperature is still not clear, particularly because some antagonists can induce hypothermia [214]. This phenomenon raises an interesting question. Since all antagonists act on a single target, TRPV1, how do they induce opposite effects? From a pharmacological point of view, it would suggest that antagonists have multiple targets. The most simple model envisioned is that the predominant function of TRPV1 is body temperature regulation [215, 216]. It was postulated that TRPV1 has an endogenous tone that is important for the maintenance of normal body temperature [124, 212, 217]. If this tone is increased (e.g. by administering a TRPV1 agonist such as capsaicin), the core temperature starts dropping, whereas decreasing the tone (i.e. by the use of antagonists) leads to hyperthermia. This model cannot explain the wide range of hyperthermic and hypothermic effects of the various antagonists, and even is inconsistent with some experimental findings. It is interesting that although the target that mediates the effect of capsaicin on body temperature regulation was localized to the brain by microinjection studies [89, 218], both the blood-brain barrier crossing and not crossing TRPV1 channel antagonists caused a hyperthermic response [212, 219]. This led to the alternate explanation that TRPV1 channels involved in body temperature regulation are present in the viscera, probably in the gastrointestinal tract [124, 220]. This theory was, however, short lived since neither intra-abdominal administration of RTX nor vagotomy or transection of the greater splanchnic nerves were able to abolish the hyperthermia induced by TRPV1 channel antagonists [212]. Furthermore, the TRPV1 null mice have normal body temperature, although their circadian rhythm is disrupted [221] and the rats whose TRPV1-expressing neurons have been ablated by a high dose of neonatal capsaicin administration show abnormal body temperature [125]. Another phenomenon that argues against this hypothesis is the fact that administration of intra-abdominal RTX in adult mice is unable to prevent the antagonist-induced hyperthermia [212, 218].

Another deleterious adverse effect of TRPV1 channel antagonists is a long-lasting alteration of the noxious heat sensation that could lead to burn injuries. This could have been expected since the TRPV1 null mice are deficient in acute heat pain sensation, and RTX desensitization markedly increases the temperature required to evoke a nocifensive response [88, 89, 177, 212]. This effect also led to many clinical trials being discontinued. For instance, AZD1386 (AstraZeneca) was dropped after observation of elevated temperature and loss of heat pain perception during the Phase 2 trial [222]. MK-2295 (Merck/Neurogen)

markedly increased the noxious heat pain threshold, and put the study participants at risk of scalding injury [223]. These results triggered the search for second-generation, "cleaner" antagonists that are not hampered by such deleterious side effects [88, 89]. Currently, efforts are made to separate the analgesic and hyperthermic effects of the TRPV1 blockers. One approach could be the development of soft short-lived capsaicin-derived agonists and antagonists [224]. Application of such antagonists in a mouse model of CFA-induced inflammation induced pain and itch relief but no changes in thermal nociception or hyperthermia [224]. Another way could be to specifically target one of the three modalities of channel activation (capsaicin, low pH and heat). Second-generation TRPV1 channel antagonists that do not interfere with proton activation of the receptor (modality-specific antagonists) do not induce hyperthermia in rats while preserving the analgesic activity [211, 225]. However, their action seems to be species specific. For instance JYL1421 had a good analgesic effect, without being accompanied by hyperthermia, in the rat [226], but increased the temperature when used in dogs and monkeys [217]. This raises the question if all the compounds developed using animal models will be able to translate to clinical trials.

SB-705489 (GlaxoSmithKline) was the first selective TRPV1 antagonist to enter clinical studies [227] (Table 3). In single-dose placebo-controlled Phase 1 studies, SB-705489 at 400 mg elevated heat pain thresholds in normal skin (NCT01673529) and reduced capsaicin-evoked rhinitis symptoms (NCT00731250). No hyperthermia or hypothermia adverse events were reported. A Phase 2 dental pain trial was completed [228] followed by a Phase 2 rectal pain trial [229]. The results have been published on the trial web page and show a similar trend like the Phase 1 study: pain reduction with mild and moderate side effects, and no hyperthermia.

Another such compound is NEO06860 developed by Neomed for osteoarthritic pain [230–234] (Table 3). While retaining a good analgesic action, this compound had only a small effect on the body core temperature and heat pain thresholds in the study subjects [230–232]. Several Phase 1 clinical studies with Mavatrep (JNJ-39439335) (Janssen Research & Development) have been completed both in healthy volunteers (NCT01454245, NCT01631487) and patients with osteoarthritis (NCT01343303, NCT00933582). Unfortunately, because of the observed safety issues, the efficacy of only a few TRPV1 antagonists has been reported. Mavatrep was no exception and although most of these trials ended almost a decade ago [235–239] the results have been only recently published [240–243]. The drug was well tolerated in healthy volunteers and none showed an increase in temperature above 38.5 °C following administration of a single 500 mg dose [240, 242, 243]. Mild oral and skin burn injuries were treated in 9% of the osteoarthritis patients taking mavatrep (JNJ-39439335) and there were no discontinuations. The primary goal of the study, to decrease pain, has been met [241]. Another oral TRPV1 antagonist that has been tested is DWP05195 (Daewoong Pharmaceutical). It underwent single- and multiple-dose Phase 1 trials [244–246] that showed a dose-dependent skin temperature increase. The drug showed a potent and dose-dependent decrease in pain, which allowed Daewoong Pharmaceutical to proceed to a, still ongoing, Phase 2 double-blind placebo-control clinical trial to evaluate the efficacy and safety of DWP05195 in the treatment of postherpetic neuralgia [247].

Another TRPV1 antagonist developed by Purdue Pharma was already tested on healthy volunteers [248–250]. V116517 compound could efficiently block capsaicin-induced irritation and inflammation-mediated thermal hyperalgesia, without affecting body temperature. One issue with this compound was the heat pain threshold of the subjects that increased to 50 °C on average and the tolerance to noxious temperature of 52 °C, which is potentially harmful. Nevertheless, two Phase 2 clinical trials have been started to explore the efficacy and safety of V116517 in patients with severe chronic pain associated with postherpetic neuralgia [251] or knee osteoarthritis [252].

A more recent Novartis compound was used in a Phase 2 clinical trial. The SAF312 compound had been tested for managing postoperative dental pain [253] as well as ocular pain associated with corneal epithelial defects such as photorefractive keratectomy surgery [254]. SAF312 showed a good dose effect for reducing dental pain, although a third of the patients developed hyperthermia above 38.5 °C at concentrations above 25 mg [255]. There were no serious side effects or discontinued treatment resulting from the SAF312 clinical trial. In human subjects with ocular pain, SAF312 showed efficacy in decreasing the severity of pain immediately after surgery [256], although one patient developed transient pyrexia.

With the discovery of microRNAs in 1993 [257] and the first gene silencing by RNAi in 1998 [258], a new era of genome editing or silencing emerged. In preclinical studies, mice treated with TRPV1-targeted siRNA had a phenotype similar to the one observed in the TRPV1 knockout mice [46, 47]. One such compound, Tivanisiran (SYL1001), has been developed by Sylentis and underwent both Phase 1 and Phase 2 clinical trials [259–262] followed by a Phase 3 HELIX trial for dry eye disease [263, 264]. The results of the Phase 1 and 2 trials indicated that Tivanisiran at 1.125% was well tolerated and able to reduce hyperemia and ocular pain/discomfort (visual analogue scale (VAS)) after 10 days of treatment. The Phase 3 study was a randomized, multicenter (six countries) study that enrolled 330 patients who received Tivanisiran or artificial tears over 4 weeks. The data,

**Table 3** Summary of randomized clinical trials of TRPV1 (transient receptor potential vanilloid-1) antagonists

| Compound | Company | Route | Clinical indication | Development stage/status | Identifier | References |
|---|---|---|---|---|---|---|
| MK-2295 | Merck Sharp & Dohme Corp | Oral | Postoperative dental pain | Phase 2—completed | NCT00387140 | [223] |
| SB-705489 | GlaxoSmithKline | Oral | Tooth extraction associated pain | Phase 2—completed | NCT00281684 | [228] |
| SB-705489 | GlaxoSmithKline | Oral | Rectal pain | Phase 2—completed | NCT00461682 | [229] |
| SB-705489 | GlaxoSmithKline | Oral | Rectal pain | Phase 2—completed | | |
| NEO6860 | Neomed Institute (Covance) | Oral | Pain | Phase 1—completed | NCT02337543 | [231–233] |
| NEO6860 | Neomed Institute (Covance) | Oral | Knee osteoarthritis-associated pain | Phase 2—completed | NCT02712957 | [230, 234] |
| JNJ-39439335 (Mavatrep) | Johnson & Johnson | Oral | Healthy volunteers | Phase 1—completed | NCT01006304 NCT01454245 NCT01006304 | [236, 238–240, 242, 243] |
| JNJ-39439335 (Mavatrep) | Johnson & Johnson | Oral | Knee osteoarthritis pain | Phase 1—completed | NCT01343303 NCT00933582 | [235, 237, 241] |
| DWP05195 | Daewoong Pharmaceutical | Oral | Healthy volunteers | Phase 1—completed | NCT00969787 NCT01094834 | [244–246] |
| DWP05195 | Daewoong Pharmaceutical | Oral | Postherpetic neuralgia | Phase 2—completed | NCT01557010 | [247] |
| V116517 | Purdue Pharma | Oral | Healthy volunteers | Phase 1—completed | NCT02695745 | [248, 249] |
| V116517 | Purdue Pharma | Oral | Chronic pain due to postherpetic neuralgia | Phase 2—completed | NCT01688947 | [251] |
| V116517 | Purdue Pharma | Oral | Chronic pain due to knee osteoarthritis | Phase 2—completed | NCT01688934 | [252] |
| SAF312 | Novartis | Oral | Pain after 3rd molar extraction | Phase 2—completed | NCT00986882 | [253] |
| SAF312 | Novartis | Topical, ocular | Eye pain following photorefractive keratectomy surgery | Phase 2—completed | NCT02961062 | [254] |
| Tivanisiran (SYL1001) | Sylentis | Topical, ocular | Dry eye disease | Phase 1 and 2—completed | NCT01776658 NCT02455999 | [258–261] |
| Tivanisiran (SYL1001) | Sylentis | Topical, ocular | Dry eye disease | Phase 3—completed | NCT03108664 2016-003903-79 (EU) | [202, 262] |

Compounds' trade names are given in parentheses

*EU* European Union

however, indicated that Tivanisiran was not better than artificial tears at controlling ocular pain. However, Sylentis disclosed other, more positive aspects of the data, starting with a statistically significant improvement in central corneal staining, a measure of cell damage and improving ocular pain symptoms, which were considered secondary endpoints. If the performance against the secondary endpoints is reproducible, it would suggest that Tivanisiran is effective at improving one part but not all of the cornea. The drug's inability to perform better than artificial tears in those areas overshadows its performance against baseline, though, and the company announced it would be discussing the finding and other data points with the FDA before deciding on a path forward. Nevertheless, these findings open the possibility of using a similar approach for treating pain of other etiologies.

## 7 Conclusions

Pain represents a major clinical challenge due to the limited efficacy and side effects of available treatments. Drug combinations and surgical therapies are often required to provide pain relief in affected individuals. The discovery of the nociceptive TRPV1 receptor in primary afferent neurons that carry painful signals was a major breakthrough.

Identification of several endogenous and exogenous ligands of the channel has offered novel therapeutic options for pain management. This was first validated by the use of capsaicin and other TRPV1 agonists in several neuropathic and musculoskeletal pain conditions. Topical capsaicin creams or high-dose capsaicin-containing patches, illustrated by the capsaicin 8% transdermal patch, have been approved as effective adjuvant therapy for the insistent pain of post-herpetic neuralgia and in the treatment of osteoarthritis. Topical capsaicin utilized as a single therapy or in conjunction with other analgesics offers a low-risk choice for patients who do not achieve pain control using other regimens and significantly improve their quality of life. Capsaicin injectable or in suspension formulations have been introduced in clinical trials with the hope of improving delivery and thus decreasing side effects. So far systemic administration was not an option given the adverse effects of capsaicin on blood pressure, breathing and other reflex pathways, but new ways of improving oral capsaicin delivery and decreasing its pungency are being tested [90]. The design and development of capsaicin analogues obtained naturally or synthetically is moving forward [78, 265, 266], and it is likely that, in the near future, we will see a wide range of injectable and topical TRPV1 agonist-based agents that will provide long-lasting analgesia with rapid onset after a single administration. The use of RTX as a "molecular scalpel" and therapies based on capsaicin and other capsaicin-derived TRPV1 agonists with non-pungent properties [265] may also soon be available in diseases associated with acute and/or chronic pain, such as cancer, thermal injuries or migraines. The future challenges to be addressed will be to determine the effective dose levels of capsaicin analogs and developing more efficient modes of administration.

On the other hand, the development of TRPV1 antagonists was marred by numerous setbacks related to hyperthermia or a decrease in noxious heat detection, which led to many roadblocks in the development of these compounds. The second generation of TRPV1 antagonists seem to show less propensity to cause these side effects.

Finally, alternative approaches could emerge in the future: (1) Targeting the expression of the TRPV1 channel using genome-editing tools. This approach could block certain populations of neurons and thus be much better tolerated. (2) Developing drugs that prevent inflammation-driven post-translational modification of the TRPV1 (i.e. phosphorylation, protein interactions, ubiquitination, etc.). In fact, blocking PKC-induced TRPV1 phosphorylation by site-directed mutagenesis has been shown to be effective in preclinical models [267]. This could be a means to prevent pathological hypersensitivity while preserving the thermosensitive function of the channel. (3) Modality-specific antagonists that cause less side effects must be further developed. In summary, a better comprehension of the biological role of the channel, the molecular chaperones that regulate its function, or the signaling effectors engaged upon activation will help to design and develop TRPV1-targeted drugs with a better therapeutic window.

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