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REVIEW

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The rise and fall of TRPV1-targeted analgesia in osteoarthritis: a critical appraisal

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ABSTRACT

Introduction: Transient receptor potential vanilloid 1 (TRPV1) has been pursued as a therapeutic target in osteoarthritis (OA) pain for over two decades. Both systemic antagonism and localized agonism advanced into clinical development, supported by mechanistic rationale and preclinical data.

Areas covered: We critically appraise TRPV1-targeted drug development in OA, examining the biological basis of the target, translational trajectories of antagonist and agonist programs, and clinical trial outcomes that define the current landscape. Literature was identified through a PubMed search for peer-reviewed articles on TRPV1 and OA over the past 5 years, followed by manual selection of key references. We review why systemic TRPV1 antagonists were abandoned, and why intra-articular TRPV1 agonists, despite expedited regulatory designations, failed to meet primary endpoints in Phase III trials.

Expert opinion: TRPV1-targeted therapy in OA has completed a full translational cycle without yielding regulatory approval. The mechanistic rationale remains valid; what failed was clinical translation. Key contributors include over-reliance on preclinical models poorly capturing central sensitization, lack of stratification by peripheral versus central pain phenotypes, and use of composite pain endpoints in phenotypically mixed populations. The TRPV1 experience offers lessons for peripheral analgesic development in OA: patient phenotyping and enrichment must precede pivotal trials.

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Central sensitization; clinical translation; drug development; intra-articular analgesia; osteoarthritis; resiniferatoxin; trans-capsaicin; TRPV1

1. Introduction

Osteoarthritis (OA) affects more than 600 million individuals globally and is among the leading causes of disability worldwide. Global Burden of Disease analyses project that prevalence will exceed one billion cases by 2050, driven by aging populations, obesity, and increased longevity [1–3]. This rising burden, driven largely by population aging, obesity, and sedentary lifestyles, and disproportionately affecting women and individuals in high–sociodemographic index countries [1,4], translates into substantial impairment of health-related quality of life, social participation and work capacity, and a major driver of joint replacement surgery and healthcare expenditure [5,6].

Pain is the predominant symptom driving healthcare seeking in OA and the main determinant of function and disability, yet effective and safe long-term pharmacological options remain limited [7]. Oral non-steroidal anti-inflammatory drugs (NSAIDs) provide modest short-term analgesia in many patients, but their long-term use is significantly constrained by gastrointestinal, cardiovascular and renal adverse effects, particularly in older, multimorbid populations [8]. Simple analgesics such as paracetamol offer, at best, minimal benefit, while opioids are generally recommended against in OA guidelines, with OARSI issuing a strong recommendation against oral and transdermal opioids and most other major bodies conditionally recommending against non-tramadol opioids except as a last resort when alternatives have been exhausted or are contraindicated, due to limited efficacy, tolerance, dependence, and risk of overdose [8,9]. Intra-articular (i.a.) corticosteroids and hyaluronic acid preparations can yield short-lived improvements in pain and function in selected patients, but disease-modifying OA drugs (DMOADs) have yet to achieve regulatory approval [10,11]. Consequently, a substantial proportion of patients cycle through available therapies with inadequate pain relief or unacceptable side effects, sustaining the unmet need for targeted, peripherally acting analgesics [12,13].

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Article highlights

- Systemic TRPV1 antagonists were abandoned across pain indications, including OA, because of class-defining on-target thermoregulatory toxicity (hyperthermia, impaired noxious heat sensation), despite >1 billion USD invested and no regulatory approvals.
- Intra-articular TRPV1 agonists (trans-capsaicin/CNTX-4975, resiniferatoxin/RTX) showed encouraging Phase II knee OA data and received expedited FDA designations, but both lead programs failed their primary WOMAC pain endpoints in Phase III, constituting a class-level failure.
- The most plausible explanation for these Phase III failures is a translational gap: preclinical OA models largely reflect peripheral nociceptive mechanisms, whereas broadly recruited clinical OA populations include substantial central sensitization, which blunts the signal of a peripherally targeted therapy.
- Lack of prospective stratification by peripheral versus central pain phenotypes was a critical error; post-hoc analyses suggest that patients with low central sensitization and high peripheral nociceptive drive do respond, but this subgroup was diluted in unselected Phase III cohorts.
- TRPV1 remains a biologically valid target in OA, but future programs will require prospective phenotyping (for example, quantitative sensory testing, synovial neuropeptide biomarkers, joint innervation imaging) embedded in pivotal trial design rather than added post hoc.
- The TRPV1 experience illustrates a broader principle for peripherally targeted OA analgesics: mechanistic specificity demands matching patient stratification, and regulatory process designations should not be mistaken for evidence of efficacy when planning pivotal trials.

Transient receptor potential (TRP) channels have been considered as attractive targets in OA, owing to their central roles in nociception, inflammation and mechanotransduction within joint tissues [14–17]. Among these, transient receptor potential vanilloid 1 (TRPV1) has a particularly strong mechanistic link to OA pain: it is expressed by small-diameter nociceptive afferents innervating the synovium, subchondral bone, cartilage and periarticular tissues, and is activated by noxious heat, protons, endogenous lipid mediators and exogenous vanilloids such as capsaicin and resiniferatoxin (RTX) [14,18,19]. For over two decades, this mechanistic rationale attracted substantial investment across two principal pharmacological strategies: systemic antagonism to block channel activity, and localized agonism to induce prolonged desensitization or chemo-denervation of nociceptors [20,21].

Neither strategy has yielded a regulatory approval for OA pain. Systemic TRPV1 antagonists were abandoned owing to class-defining on-target thermoregulatory toxicity, including clinically significant hyperthermia and impaired noxious heat sensation, despite more than $1 billion USD invested across multiple programs [22,23]. The subsequent pivot toward locally administered TRPV1 agonists, and particularly i.a. capsaicin and RTX, generated encouraging Phase II results and attracted expedited Food and Drug Administration (FDA) regulatory designations. However, both lead i.a. agonist programs in OA have now failed to meet primary endpoints in Phase III trials. Trans-capsaicin (CNTX-4975) did not demonstrate superiority over placebo on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. The global Phase III program for i.a. RTX (Grünenthal's KF7039 program, encompassing approximately 1,800 patients across two pivotal trials) similarly failed both trials; the program is being wound down.

This Expert Opinion paper is based on a literature search of PubMed to identify peer-reviewed articles on TRPV1 and OA, with particular emphasis on clinical and translational studies of i.a. TRPV1 agonists (such as trans-capsaicin and RTX). The primary search combined terms such as 'TRPV1,' 'transient receptor potential vanilloid 1,' 'capsaicin,' 'resiniferatoxin,' 'intra-articular,' and 'osteoarthritis' and was limited to articles published in English within the last 5 years, with earlier seminal studies added when necessary to provide context. Retrieved records were screened by the authors for relevance to the scope of this review, and reference lists of key publications, clinical trial registries, and recent guidelines were manually examined to ensure inclusion of pivotal Phase II and Phase III trials and other influential reports in the field.

This paper provides a critical appraisal of what TRPV1-targeted drug development in OA has taught us. We review the mechanistic rationale, which remains scientifically valid, and examine where clinical translation failed: in preclinical model selection, patient enrichment strategy, trial design, and the underweighted contribution of central sensitization in OA pain. We situate the TRPV1 experience within the broader context of OA analgesic development and draw lessons applicable to future peripherally targeted drug programs in this indication.

2. Biology and pharmacology of TRPV1 in OA

2.1. Molecular structure and activation mechanisms

TRPV1 was first cloned and characterized in David Julius's laboratory by Michael Caterina and colleagues as the receptor for capsaicin, the pungent constituent of chili peppers [24]. Named vanilloid receptor 1 (VR1) due to homovanillyl moiety in capsaicin, it was identified as a nonselective cation channel structurally similar to the *Drosophila* TRP channel. Subsequent discovery of related vanilloid-activated channels formed the TRPV subgroup, with VR1/TRPV1 as the founding member [25,26]. Like other TRP proteins, TRPV1 features six transmembrane segments (S1–S6), organized into a voltage-sensor domain (S1–S4) and pore-forming domain (S5–S6). Recent high-resolution cryo-electron microscopy studies have revealed its atomic details [27–29].

A functional ion channel is formed from a tetrameric assembly of TRPV1 subunits, with the pore arising from aligned S5-S6 subunits. Pore opening involves allosteric dual gating through conformational changes in the selectivity filter and the lower gate [28,30]. Prolonged activation may result in pore dilation, enhancing conductance and permeability to large cations [30,31]. TRPV1 serves as a noxious heat sensor, activating robustly at 40–43°C [24,32], and acidosis potentiates its activation [32,33]. Classic agonists, such as capsaicin and RTX, activate the channel by binding to the vanilloid binding pocket between S3–S4 and S5–S6 regions of adjacent subunits [27,29], while endogenous lipids, such as lipoxygenase products and the endocannabinoid anandamide also activate TRPV1 [34,35].

2.2. TRPV1 in pain mechanisms in OA

TRPV1 integrates pain-related signaling from multiple sources. Its activity is sensitized by histamine, bradykinin, prostaglandins, extracellular ATP, pro-inflammatory cytokines and protease-activated receptors [36–41], which are mediators abundantly present in the OA joint microenvironment.

Its expression in small- and medium-diameter somatosensory neurons of the dorsal root and trigeminal ganglia aligns with its nociceptive role [42,43]. TRPV1 not only transduces inflammation-related signals into neural excitation, but its activation can also initiate neurogenic inflammation through release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) into peripheral tissues, a function recognized in the OA literature as a bidirectional contributor to synovial pathology [44,45].

Importantly, TRPV1 expression is not restricted to sensory neurons. It is found in synovial fibroblasts, chondrocytes, osteoclasts and various immune cells [19], and inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin 1-beta (IL-1β) further influence TRPV1 expression in chondrocytes [46]. Experimental OA models demonstrate increased TRPV1 expression and function in joint afferents, elevated levels of endogenous TRPV1 ligands, and a key role for TRPV1 in mediating mechanical sensitization and pronociceptive signaling [19,47,48]. In human OA synovium, TRPV1 immunoreactivity is upregulated [19,47,49], confirming the diseased joint as a plausible anatomical and molecular target for localized TRPV1-directed analgesia. The mechanistic case for targeting this pathway was, and remains, scientifically coherent. This paper addresses why that coherent mechanism did not translate into clinical efficacy at the pivotal stage. TRPV1 integrates inflammatory, thermal and chemical stimuli within the OA joint to drive peripheral sensitization and neurogenic inflammation (Figure 1).

3. Therapeutic potential and mechanism of TRPV1 agonists

3.1. Mechanistic basis of TRPV1 agonist-induced analgesia

In OA, TRPV1 agonists are therapeutically interesting because controlled activation can convert a pronociceptive channel into a means of selective peripheral analgesia [50,51]. Acute TRPV1 activation opens a nonselective cation pore, producing sodium and calcium influx, membrane depolarization, and an initial pain response [24,32]. When agonist exposure is sufficiently intense, prolonged, or locally concentrated, the resulting calcium load initiates processes that progressively impair

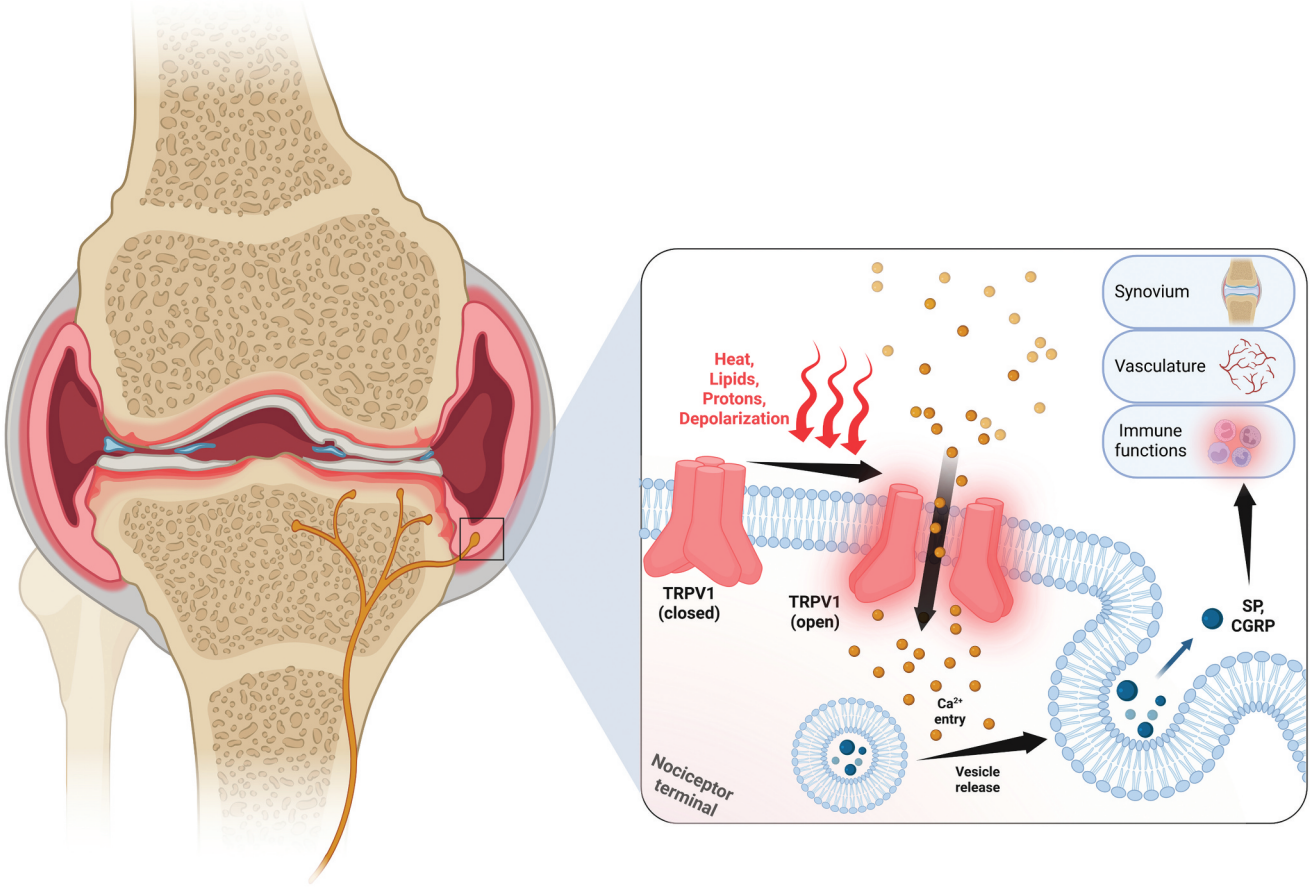

Figure 1. TRPV1 signaling in the osteoarthritic joint. Schematic representation of a knee osteoarthritis joint showing nociceptive afferents innervating synovium, cartilage, subchondral bone and periarticular tissues, with an inset illustrating TRPV1 channels on somatosensory nerve terminals. Noxious heat, protons, endogenous lipids and membrane depolarization open TRPV1, permitting calcium influx, vesicle exocytosis and release of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP). These mediators act on synovium, vasculature and immune cells to amplify neurogenic inflammation and peripheral sensitization, establishing a self-reinforcing loop that drives OA pain. Created in BioRender. Ducza, L. (2026) https://BioRender.com/ye173m1.

the same nerve endings that were initially activated [50,52]. Depending on exposure conditions, this manifests as functional desensitization or more sustained defunctionalization of TRPV1-positive terminals, with reduced excitability, impaired responsiveness to inflammatory algogens, diminished neuropeptide release, and attenuation of peripheral nociceptive drive [50,51]. Current mechanistic models also implicate calcium overload and calpain activation [53], mitochondrial dysfunction [54,55], cytoskeletal disruption [56], and localized terminal ablation followed by reinnervation and functional recovery over time [57,58].

3.2. Capsaicin and resiniferatoxin as TRPV1 agonist strategies

Capsaicin provides the clearest proof of concept for this therapeutic principle [50,51]. Its pharmacology is strongly exposure-dependent: low concentrations generally produce repeated transient activation with limited clinical benefit, whereas high-concentration local exposure drives more substantial desensitization or reversible terminal defunctionalization [20,50]. This mechanism is directly relevant to OA, where joint-targeted delivery can achieve tissue concentrations that are not obtainable through transdermal administration [59,60].

RTX acts through the same mechanism but differs markedly in pharmacological intensity. As an ultrapotent TRPV1 agonist, RTX produces more intense and sustained channel activation than capsaicin [61,62], leading to greater calcium influx and a stronger tendency toward prolonged terminal inactivation or ablation [63,64]. Its principal target remains the TRPV1-expressing nociceptor population, while non-TRPV1 neurons are relatively spared [65–67]. Therapeutically, capsaicin and RTX define a pharmacological potency gradient: capsaicin is better suited to settings where reversible local silencing is sufficient; RTX offers greater durability where that is the primary therapeutic goal [21,59].

3.3. Intra-articular delivery: rationale and inherent constraints

The joint is not simply a convenient site of administration; it is the pathological compartment where TRPV1-positive nociceptive terminals encounter the inflammatory and mechanical signals that sustain pain [47,68,69]. Intra-articular administration delivers agonists directly to relevant peripheral endings in the synovium, capsule, periosteum, and subchondral bone, achieving concentrations sufficient to induce desensitization or defunctionalization while limiting systemic exposure [59,60,70]. This route is especially important for RTX, where localized delivery offers the possibility of more durable silencing of joint afferents after a single procedure [64,70].

However, several inherent constraints were underappreciated in clinical program design. The procedure requires image guidance in some cases to ensure accurate delivery into the most relevant joint compartment and to minimize extra-articular spread of a highly potent nociceptor-active agent [71]. It is also associated with characteristic acute injection-site pain from the initial TRPV1 activation, necessitating peri-procedural anesthesia protocols that add complexity and variability [72]. The VICTORY-3 trial (OA-303) of CNTX-4975, which evaluated streamlined administration procedures and patient comfort, found that cooling and peri-procedural techniques were clinically acceptable based on pain and satisfaction scores, yet the logistical burden of image guidance, structured cooling protocols, and supervised administration settings raises questions about commercial viability at scale that were not resolved before pivotal trials commenced.

Furthermore, reinnervation of nociceptor terminals begins within weeks after ablation, and functional recovery can be substantial over time [57,58]. The durability question of whether clinically meaningful analgesia persists through a course of repeated injections was not resolved at Phase II before pivotal trials commenced.

3.4. Formulation and delivery strategies for TRPV1-targeted analgesia

TRPV1 agonist pharmacology is exposure-dependent: subtherapeutic local exposure may fail to drive durable defunctionalization of TRPV1-positive terminals, whereas excessive or poorly controlled exposure increases the risk of intense procedural pain and local safety concerns [73]. Achieving a therapeutic window in which sufficient activation is induced at joint nociceptor endings, while limiting peak activation and extra-articular spread, therefore depends not only on dose and route but also on the formulation and delivery vehicle [74]. Recent developments in i.a. nanomedicine and depot-based delivery for OA, although not yet applied clinically to capsaicin or RTX, illustrate how drug carriers can be engineered to modulate joint retention, spatio-temporal exposure, and even mechano- or inflammation-responsiveness [74].

Nanocarrier systems for OA have been designed to prolong residence in the joint cavity and to tune the kinetics and localization of drug release [74]. Stimulus-responsive nanoplatforms that react to endogenous cues such as pH, reactive oxygen species, enzymes or temperature, or to exogenous stimuli such as light, ultrasound or magnetic fields, can enhance joint retention, increase loading capacity, and deliver on-demand release in inflamed or mechanically stressed microenvironments, thereby improving effective exposure at diseased tissues while limiting systemic spill-over [74]. Disease-severity-responsive nanoparticles, exemplified by matrix inverse-targeting (MINT) particles carrying ghrelin mRNA, preferentially accumulate in degenerated cartilage and subchondral bone, where they reduce cartilage damage, subchondral bone thickening and nociceptive behavior in experimental OA [75]. In parallel, lubricating nano- and microparticles and surface-engineered liposomes are being developed to combine tribological benefit with sustained drug delivery. Poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)-functionalized liposomes and PMPC-coated mesoporous silica nanoparticles form robust hydration layers that confer boundary lubrication while acting as carriers for i.a. drugs, highlighting how particle size, geometry and surface chemistry can be tuned to prolong residence and improve tissue interactions in OA joints [76–78].

These formulation principles are directly relevant to TRPV1-targeted analgesia. A depot, microsphere, liposomal or nanoparticle platform that locally retains a TRPV1 agonist, attenuates the initial burst of channel activation, and provides a controlled concentration-time profile to synovium, capsule, periosteum and subchondral bone could, in principle, increase the proportion of TRPV1-positive terminals that cross the threshold for durable defunctionalization while reducing peak procedural pain and extra-articular leakage [74]. Recent conceptual work on nanomedicine-based TRPV1 targeting in OA has outlined how vanilloid agonists might be incorporated into targeted carriers, coupled to lubricating or cartilage-affine interfaces, and integrated into stimulus-responsive designs to refine on-target exposure and safety [73]. These strategies remain at a preclinical or conceptual stage, and their translational relevance to TRPV1 agonists should not be overstated. Nonetheless, they underscore our central argument that the failure of i.a. TRPV1 agonists in OA reflects limitations of clinical translation and delivery, rather than invalidation of the TRPV1 pathway itself, and they suggest that future programs will need to consider formulation and exposure control as integral components of mechanism-based trial design.

4. Clinical development of TRPV1-targeted therapies in OA

4.1. Systemic TRPV1 antagonists: abandoned by on-target toxicity

Systemic TRPV1 antagonists demonstrated robust antinociceptive effects across multiple preclinical pain models, but their translation into clinical analgesics was fundamentally compromised by class-defining on-target adverse effects. TRPV1 plays a physiological role in thermoregulation: antagonism produces clinically significant hyperthermia in humans, attributed to blockade at central projections of primary afferent neurons [23,79]. Impaired perception of noxious heat, which is a safety signal with obvious clinical implications, was an additional consistent finding. These effects reflected the fundamental biology of the channel rather than off-target toxicity, and they proved refractory to medicinal chemistry optimization.

Over the past three decades, more than $1 billion USD was directed toward TRPV1 antagonist development across multiple large pharmaceutical programs, yet no compound achieved regulatory approval for pain indications [80]. Modality-selective antagonists such as NEO6860 were developed specifically to dissociate analgesic efficacy from thermoregulatory effects, but these too did not advance beyond early clinical evaluation in OA [81]. The antagonist chapter of the TRPV1 story is closed in OA, and the magnitude of investment required to close it was itself a warning signal about the translational challenges the target posed. Although a purely local, i.a. antagonist strategy could in principle mitigate systemic thermoregulatory toxicity, it was never meaningfully pursued in OA [23]. TRPV1 antagonists were developed primarily as oral or parenteral agents, and by the time thermoneutral and modality-selective compounds emerged, sponsor appetite for further investment in the class had been largely exhausted [81]. In parallel, the mechanistic goal in knee OA shifted toward silencing sensitized joint nociceptors, which is more naturally achieved with local agonist-induced defunctionalization than with intermittent i.a. blockade of TRPV1 channel activity [50].

4.2. Topical TRPV1 agonists: approved in neuropathic pain, limited in OA

The only TRPV1-targeting analgesic to achieve regulatory approval in any indication is the high concentration (8%) capsaicin patch ('Qutenza®,' Grünenthal GmBH), approved by the FDA in 2009 for postherpetic neuralgia and by the EMA for peripheral neuropathic pain, with the US indication extended to diabetic peripheral neuropathy of the feet in 2020 [82]. These approvals are supported by low-to-moderate quality evidence, and the product is positioned as an adjunct rather than first-line therapy [83,84]. Clinical studies of the capsaicin patch in additional neuropathic pain conditions are ongoing (Tables 1 and 2).

Vocacapsaicin (CA-008, Concentric Analgesics) is a water-soluble prodrug of capsaicin designed for surgical site infiltration; it releases capsaicin via pH-dependent intramolecular

Table 1. Local TRPV1 agonists under clinical development in chronic non-OA pain.

Agent	Sponsor	Route	Indication	Status	Identifier	Ref.
Capsaicin	M.D. Anderson Cancer Center	Topical patch	Chemotherapy-induced neuropathic pain	Early Phase 1 – ongoing	NCT06744816	[85]
Capsaicin	CHU Saint-Etienne	Topical patch	Neuropathic pain in cancer patients	Phase 2 – completed	NCT03317613	[86]
Capsaicin	Averitas Pharma, Inc.	Topical patch	Postsurgical neuropathic pain	Phase 3 – enrollment complete; topline results pending (Q4 2025 anticipated)*	2021-001409-64 (EU)	[87]
Vocacapsaicin (CA-008)	Concentric Analgesics	Injectable wound infiltration	Postsurgical pain (bunionectomy)	Phase 2 – completed	NCT03599089; NCT03885596	[88,89]
Vocacapsaicin (CA-008)	Concentric Analgesics	Injectable wound infiltration	Postsurgical pain (total knee arthroplasty)	Phase 2 – completed	NCT03731364	[90]
Vocacapsaicin (CA-008)	Concentric Analgesics	Injectable wound infiltration	Postsurgical pain (abdominoplasty)	Phase 2 – completed	NCT03789318	[91]
RTX	NINDS / NIH	Periganglionic injection	Cancer-induced bone pain	Phase 1/2 – ongoing; interim results published [92]	NCT02522611	[93]
RTX	NIH Clinical Center	Perineural injection	Morton's neuroma pain	Phase 1 – ongoing	NCT05695339	[94]
RTX	Sorrento Therapeutics	Epidural injection	Cancer-induced pain	Phase 2 – suspended (financing)	NCT05067257	[95]

*Note: results have not been publicly reported as of manuscript submission (last checked: June 3, 2026).

Table 2. Local TRPV1 agonists evaluated in clinical development for OA pain, with outcomes.

Agent	Sponsor	Route	Indication	Status	Identifier	Outcome / notes	Ref.
Capsaicin 1% liquid (ASKC200)	Jiangsu Aosaikang Pharmaceutical	Topical liquid	Knee OA pain	Phase 1 – ongoing	NCT06614608	Early-phase safety; no efficacy data reported	[96]
Capsaicin 5% liquid (CGS-200)	Propella Therapeutics	Topical liquid	Knee OA pain	Phase 2 – completed	NCT03528369	Results not publicly disclosed	[97]
Capsaicin 8% patch	University Hospital, Clermont-Ferrand	Topical patch	Digital OA pain	Phase 4 – ongoing	NCT06444919	CADOR study; results pending	[98]
Trans-capsaicin (CNTX-4975)	Centrexion Therapeutics	Intra-articular	Knee OA pain	Phase 3 – completed	NCT03429049; NCT03660943	FAILED primary WOMAC pain endpoint in both trials. No path forward disclosed by sponsor.	[99,100]
RTX (Sorrento)	Sorrento Therapeutics	Intra-articular	Knee OA pain	Phase 2 – inactive	NCT04885972	Program ceased; sponsor insolvency	[101]
RTX (Lopain/MTX-071/RTX-GRT7039)	Grünenthal GmbH	Intra-articular	Knee OA pain	Phase 3 – completed	2021-005046-15 (EU)	BOTH pivotal trials (KF7039-01 and KF7039-02) FAILED primary WOMAC pain endpoint. Program being wound down. Open-label safety study KF7039-03 ongoing through H2 2025. Shionogi assessing its position.	[102–104]

cyclization at physiologic pH within minutes of administration. Four Phase II trials have been completed in postsurgical pain (bunionectomy, total knee arthroplasty, abdominoplasty), including a triple-blinded, randomized, placebo-controlled trial (NCT03599089) in which the 0.30 mg/ml dose reduced pain at rest over the first 96 hours by 33% and opioid consumption by 50% versus placebo, with no differences in adverse event profiles. The program received FDA Fast Track designation; detailed efficacy results from additional trials are not yet fully published [105].

For OA specifically, low-concentration topical capsaicin formulations provide modest adjuvant analgesia at best [80]. Zucapsaicin ('Zuacta®'/"Civanex®," Winston Laboratories) received approval from Health Canada as an adjunct to oral anti-inflammatory agents in adults with knee OA; its designation as an adjunct rather than a primary therapy is informative. These low-dose topical formulations act predominantly on cutaneous nociceptor terminals and are not expected to achieve the deep tissue penetration and articular targeting necessary to address the dominant peripheral nociceptive drivers of OA pain within the joint proper, and they represent a categorically different therapeutic application from the i.a. strategies discussed below [106].

4.3. Intra-articular TRPV1 agonists: from promising Phase II to failed Phase III

The clinical hypothesis tested at the pivotal level was specific: that a single i.a. injection of a high-potency TRPV1 agonist could produce durable, clinically meaningful reductions in OA pain by functionally silencing joint nociceptors. This hypothesis was supported by compelling Phase II data from two distinct programs.

CNTX-4975 (trans-capsaicin, Centrexion Therapeutics) demonstrated clinically meaningful, durable reductions in knee OA pain and improvements in function after a single i.a. injection in Phase IIb evaluation, with effects extending up to 24 weeks and an acceptable safety profile dominated by transient local reactions [60]. On the basis of these results, the program advanced to Phase III (NCT03429049 and NCT03660943). Both trials failed to meet their primary WOMAC pain endpoint. Centrexion has no publicly disclosed path forward for this program. It is also worth noting that the procedural complexity associated with i.a. TRPV1 agonist administration, including the need for cooling protocols to manage injection-site pain from initial TRPV1 activation, potential image guidance, and supervised clinical settings, represents a non-trivial implementation burden. The VICTORY-3 trial (OA-303) demonstrated that such techniques were clinically acceptable to patients, but acceptability under trial conditions does not resolve whether the procedural infrastructure required is commercially viable in routine practice, particularly for a therapy that may require repeat administration.

The i.a. RTX program (Lopain/MTX-071/RTX-GRT7039, Grünenthal GmbH) was initiated following Grünenthal's acquisition of Mestex AG and its global rights to RTX. It was one of the most ambitious analgesic development programs in OA: approximately 1,800 patients across approximately 200 clinical

sites worldwide, targeting WOMAC pain and function improvement over 52 weeks, with the program designed to support regulatory submissions in the US, EU, and Japan. The program obtained FDA Breakthrough Therapy designation in 2023, supported by Phase I and II data demonstrating substantial and durable pain relief with a favorable tolerability profile [72]. Grünenthal also licensed Japanese commercialization rights to Shionogi in a deal valued at up to approximately $525 million. Both pivotal trials (KF7039-01 and KF7039-02) failed to meet their primary WOMAC pain endpoint; according to the sponsor's lay summary, both RTX-GRT7039 and placebo groups improved, but the between-group difference was small and not statistically significant, and detailed endpoint data have not been publicly disclosed. Grünenthal has announced it will conclude the development program upon completion of the open-label safety study KF7039-03, which was expected in the second half of 2025. Shionogi is assessing its next steps. Following the discontinuation of its TRPV1 program, Grünenthal has pivoted its analgesic pipeline toward voltage-gated sodium channel inhibition, recently initiating the Phase I trial (NCT07317063) of an orally administered NaV1.8 inhibitor (GRT6019) in 70 healthy volunteers as a non-opioid approach for acute and chronic pain.

A third i.a. RTX program conducted by Sorrento Therapeutics (NCT04885972) became inactive following that company's financial difficulties, removing another potential developer from the field.

The class record for i.a. TRPV1 agonists in OA is therefore unambiguous: two independent Phase III programs, each with supportive Phase II data and significant regulatory recognition, each failing at the pivotal stage. This is not one program's idiosyncratic failure. It is a class-level finding that demands systematic explanation.

The contrasting approaches to TRPV1 modulation and their distinct safety profiles are summarized schematically in Figure 2.

4.4. Safety: a relative strength that did not compensate for efficacy failure

Locally administered TRPV1 agonists are generally safe and well-tolerated, and this has been a consistent finding across development programs. Intra-articular trans-capsaicin (CNTX-4975) has been associated with adverse events such as transient erythema, peripheral edema, nausea, oral hypoesthesia, hypotension, and asymptomatic elevations of hepatic transaminase enzyme levels [60]. RTX has shown a favorable tolerability profile in clinical studies, with no consistent thermoregulatory signal of the type that terminated antagonist programs [23,72]. This favorable local safety profile, which was the most important differentiation from systemic antagonists, was genuine and meaningful, but it ultimately did not compensate for the efficacy outcomes in Phase III.

5. Why did TRPV1-targeted therapy fail in OA? A systematic analysis

5.1. The limits of preclinical OA models

A recurring pattern in OA analgesic development is compelling preclinical efficacy followed by Phase III failure, and TRPV1 agonists are no exception. The most widely used preclinical OA pain models, including the monosodium iodoacetate (MIA) model and the destabilization of the medial meniscus (DMM) model, reliably produce measurable pain behavior and joint pathology and are responsive to a wide range of pharmacological interventions. However, they do not capture the phenotypic and mechanistic heterogeneity of human knee OA pain. Figure 3 summarizes the TRPV1 pathway in experimental OA models alongside i.a. agonist strategies and their clinically observed efficacy profile.

Human OA pain is a complex, multidimensional experience in which peripheral nociceptive input from the joint, central sensitization, psychological and cognitive factors, and comorbidities all contribute in proportions that vary substantially between individuals [107,108]. Preclinical models predominantly capture the peripheral nociceptive component, which is the precise component that TRPV1 agonists are mechanistically designed to address. They are poorly suited to modeling central sensitization, which is prevalent in clinical OA populations and may account for a substantial fraction of pain in many patients enrolled via standard Phase III inclusion criteria. An intervention that is highly effective in an animal model capturing peripheral pain may produce only modest average effects across a broadly recruited human population in which centrally driven pain dilutes the treatment signal.

This translational gap was not unique to TRPV1, but its relevance should have been more explicitly incorporated into Phase III design assumptions. The consistency of Phase II to Phase III efficacy attrition, which was seen with both CNTX-4975 and RTX despite different formulations, protocols, and sponsors, points strongly to this population-level dilution as a primary driver.

5.2. Patient selection and the central sensitization problem

Intra-articular TRPV1 agonists silence peripheral joint nociceptors. Their mechanism predicts greatest benefit in patients whose pain is predominantly driven by peripheral nociceptive input from the joint, and correspondingly limited benefit in patients with significant central sensitization, in whom peripheral silencing may not adequately reduce the centrally amplified pain experience [109,110]. In Phase III populations recruited primarily on radiographic OA grade and pain severity thresholds on the WOMAC scale, both phenotypes are invariably represented, and central sensitization may be present in patients with moderate-to-severe knee OA pain [111].

In practice, peripheral versus centrally driven OA pain can be approximated using complementary tools. Quantitative sensory testing (QST) at the affected and remote sites (for example, pressure pain thresholds, temporal summation, conditioned pain modulation) quantifies central sensitization, with low pressure pain thresholds and facilitated temporal summation indicating high-level central sensitization [109]. Symptom-based instruments such as painDETECT, pain distribution diagrams and widespread pain indices, together with clinical patterns emphasizing localized, activity-related joint pain versus widespread, spontaneous or nocturnal pain, further help to classify patients toward predominantly peripheral or

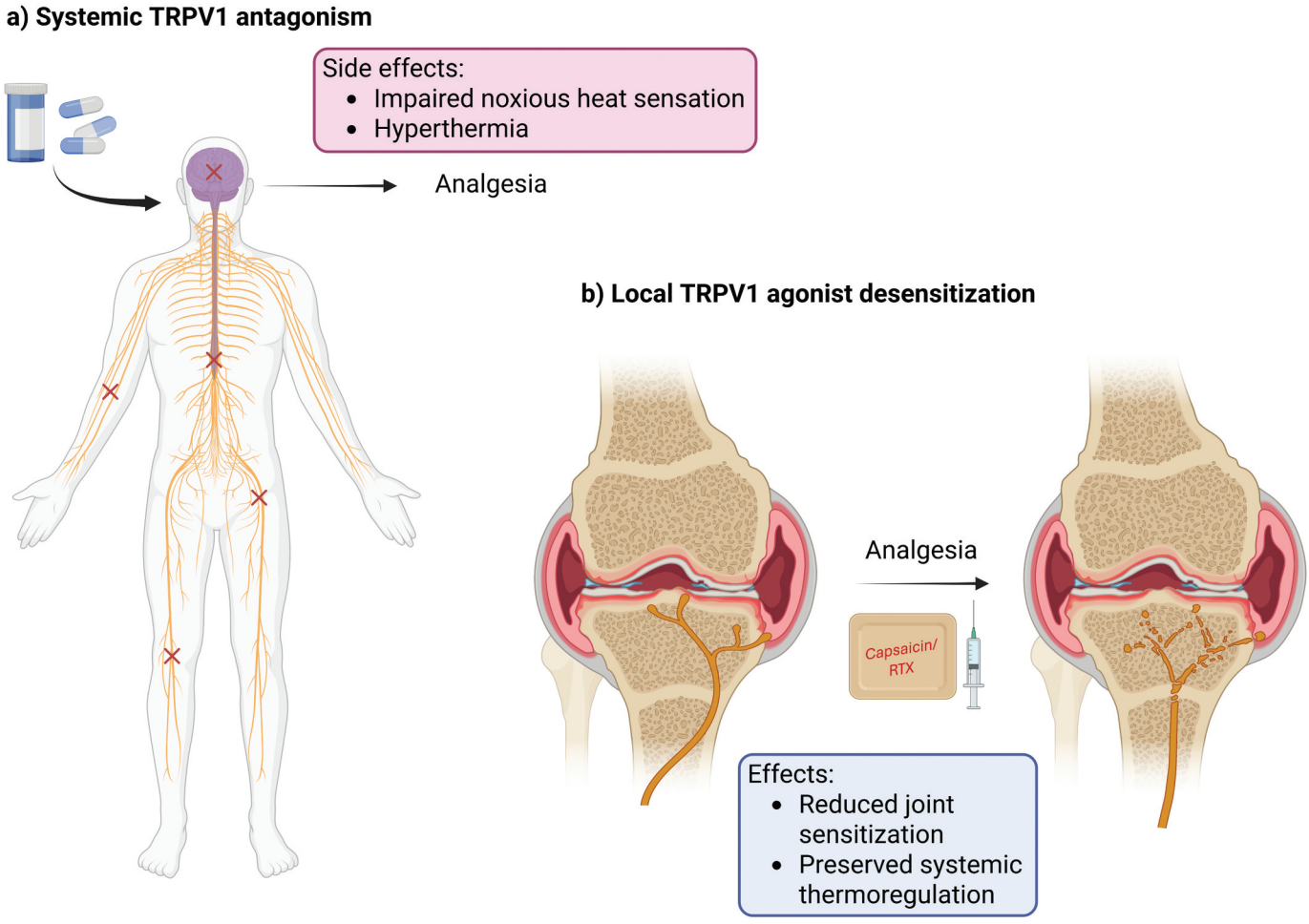

Figure 2. Systemic TRPV1 antagonism versus local TRPV1 agonism in osteoarthritis. (a) Systemic TRPV1 antagonists block channel activity throughout the somatosensory system and central projections, producing analgesia but also class-defining adverse effects including impaired noxious heat sensation and hyperthermia. (b) Intra-articular TRPV1 agonists such as capsaicin or resiniferatoxin are injected directly into the OA knee joint, inducing local nociceptor defunctionalization and reduced joint sensitization while preserving systemic thermoregulation. Created in BioRender. Ducza, L. (2026) https://BioRender.com/fu87ofh.

centrally driven phenotypes and can be used as inclusion or stratification variables for future i.a. TRPV1 trials [112].

QST and related tools can characterize central sensitization in individual patients [109], but these assessments were not used as stratification or enrichment criteria in the pivotal TRPV1 agonist trials. Importantly, the transition from Phase II to Phase III for both CNTX-4975 and RTX did not introduce systematic enrichment for peripherally driven pain beyond standard radiographic and WOMAC inclusion criteria. In the CNTX-4975 Phase IIb trial, subjects were selected on the basis of Kellgren–Lawrence grade 2–4 knee OA and moderate-to--severe index-knee pain despite prior analgesic therapy, with randomization stratified by structural grade and body mass index, but without QST or other central sensitization measures. The ensuing Phase III CNTX-4975 studies and the RTX Phase II/III programs used very similar frameworks, i.e. radiographic OA grade thresholds and minimum WOMAC or VAS pain cut-offs in the index knee, plus failure or intolerance of conventional therapies, but again did not prospectively phenotype or exclude patients with high central sensitization burden (Table 2). Given that pain sensitization is common in knee OA and only weakly related to radiographic severity [109–111], it is highly plausible that the larger Phase III cohorts contained a higher absolute number of centrally sensitized, non-responsive patients, thereby diluting the average treatment effect that had been evident in smaller, somewhat more homogeneous Phase II populations. A treatment that produces robust analgesia in 30–40% of a population (those with predominantly peripheral pain) but is ineffective in the remaining majority will appear to fail a primary endpoint designed around a population mean effect size. The analgesic signal is real, but it is buried in noise from non-responders included on biological grounds that the mechanism cannot address.

This is supported by post-hoc analyses of i.a. capsaicin trials, which suggest that patients with clinical features consistent with predominantly peripheral pain phenotypes, such as localized, activity-related knee pain, absence of major extra-articular pain generators, and identifiable sensory abnormalities at the knee on bedside examination demonstrate greater treatment responses than patients with more widespread or atypical pain presentations, even though formal QST-based central sensitization measures were not incorporated into these studies [60,112]. These signals were present in Phase II

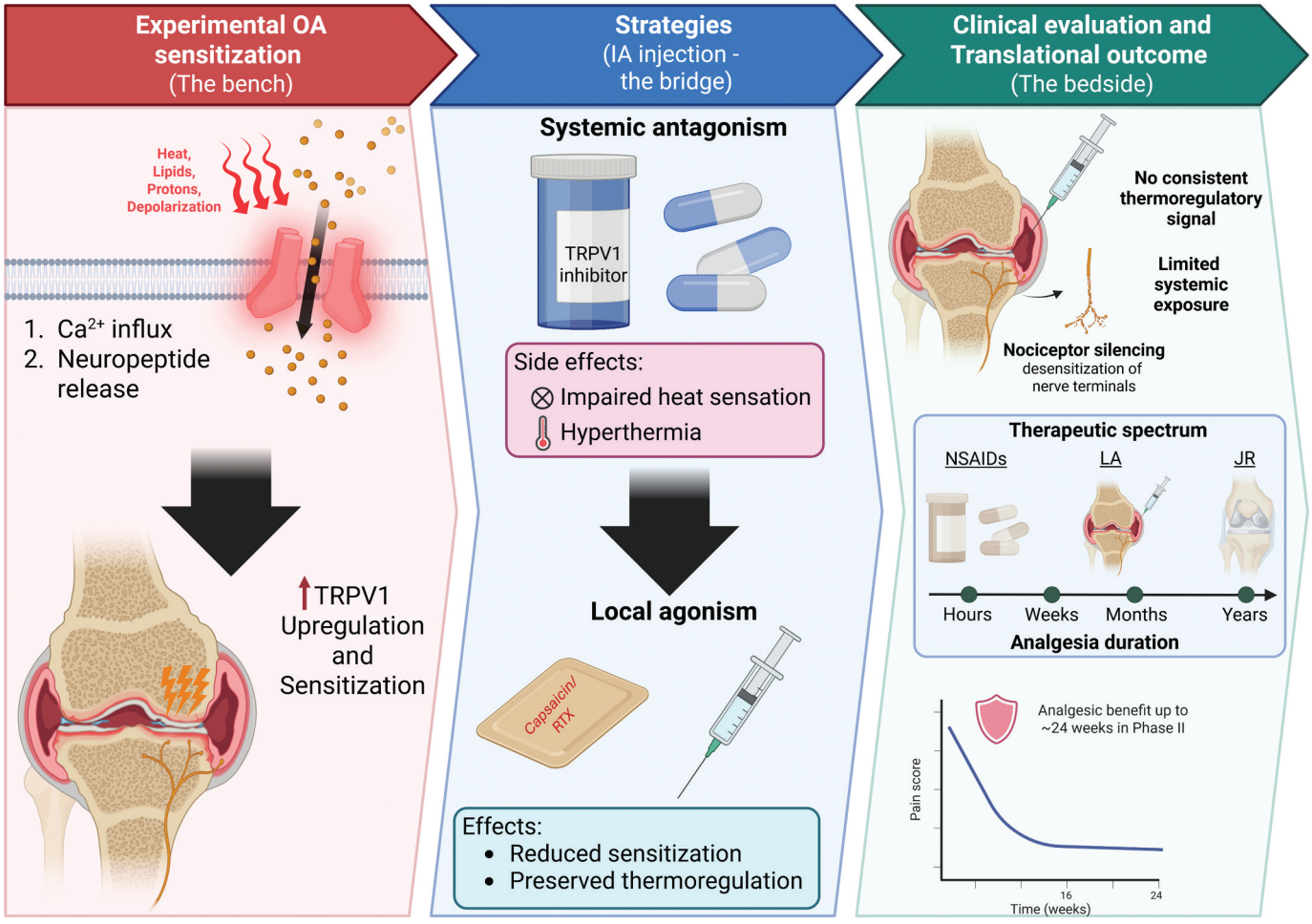

Figure 3. From experimental TRPV1 sensitization to intra-articular TRPV1 agonist strategies and clinical outcomes in osteoarthritis. Experimental OA models (left) demonstrate that inflammatory and mechanical stimuli activate TRPV1 on joint-innervating nociceptors, leading to calcium influx, neuropeptide release, and upregulation and sensitization of TRPV1, which together drive peripheral nociceptive input from the osteoarthritic joint. The central and right panels contrast systemic TRPV1 antagonism, which produces class-defining thermoregulatory adverse effects, with local intra-articular TRPV1 agonism (for example, high-concentration capsaicin or resiniferatoxin), which silences TRPV1-positive terminals and reduces joint sensitization while preserving systemic thermoregulation; clinical development has demonstrated at best months-long analgesic benefit (up to approximately 24 weeks in Phase II) without evidence of years-long pain relief or regulatory approval to date. Created in BioRender. Ducza, L. (2026) https://BioRender.com/vfffvsp.

data and warranted prospective validation as an enrichment strategy before pivotal trials were initiated. Their absence in Phase III design represents a critical and remediable developmental error that the field must not repeat.

5.3. Endpoint sensitivity and the limitations of WOMAC in mechanistically selected populations

The WOMAC pain subscale is the accepted primary endpoint for OA analgesic trials and is approved by both the FDA and EMA. As a composite capturing a mix of pain phenotypes, it is well-suited to detecting effects of broad-spectrum analgesics but relatively insensitive to interventions that target a specific mechanism in a specific patient subset, because it does not distinguish between nociceptive, neuropathic-like and nociplastic components of pain or account for central sensitization burden [110,112].

For a peripheral nociceptor-targeting strategy such as i.a. TRPV1 agonism, the assumption embedded in using WOMAC as a primary endpoint is that the treated population is sufficiently enriched for peripheral nociceptive pain to produce a detectable average treatment effect. This assumption was not validated before Phase III. In experimental OA, TRPV1 contributes to sensitization of joint afferents to mechanical stimulation of the knee and to mechanically evoked pain behaviors, such as altered weight bearing, indicating that joint loading can indirectly drive TRPV1-mediated nociceptive input [47]. WOMAC does not distinguish between pain components likely to be modifiable by peripheral silencing such as activity-related, weight-bearing pain in which joint loading increases mechanical and inflammatory drive to sensitized TRPV1-expressing joint nociceptors, and those less likely to respond (for example, spontaneous rest pain with strong central sensitization components or nocturnal pain) [47]. Future trial designs for peripherally targeted analgesics in OA should incorporate mechanistically aligned primary endpoints, or pre-specified subgroup analyses that test treatment effects in phenotypically appropriate patients. Although endpoint sensitivity and population heterogeneity provide a compelling explanation for the Phase III outcomes, they are unlikely to represent the only contributors.

5.4. Additional contributors to Phase III failure

While inadequate patient phenotyping and dilution of treatment signal by centrally sensitized pain phenotypes likely played a major role in the Phase III outcomes, several additional factors may also have contributed. First, placebo responses in OA analgesic trials are consistently large, particularly in studies involving i.a. interventions, where procedural expectations and contextual effects can meaningfully elevate reported pain improvement. High placebo response rates reduce the detectable treatment–placebo separation and have been implicated in the failure of multiple analgesic programs in OA [113,114].

Beyond these well-recognized issues, there are important delivery-related barriers to achieving sufficient, sustained, and spatially appropriate drug exposure at TRPV1-positive nerve terminals in the joint [115]. Intra-articular TRPV1 agonists need to reach nociceptive endings not only in synovium and capsule, but also in periosteum, subchondral bone, and neoinnervated osteochondral junctions in advanced disease. The compartmentalized and frequently remodeled anatomy of the knee joint in OA, including synovial hypertrophy, osteophytes, septated effusions, meniscal degeneration, and altered joint mechanics can promote heterogeneous i.a. distribution of an injected solution, with preferential pooling in certain recesses and incomplete exposure of relevant nociceptor populations [116]. Experimental work with local capsaicin injections in rodent joints illustrates that even high local doses may produce only partial and regionally restricted depletion of sensory fibers, highlighting the challenge of uniformly targeting all sensory terminals within synovial tissues [117].

Rapid synovial clearance and limited tissue penetration further limit the effective exposure profile after a single bolus injection. Small-molecule solutions injected intra-articularly are typically cleared from the synovial space over hours to days, with substantial systemic redistribution, unless formulated in systems designed to enhance joint retention [115]. Studies of extended-release i.a. triamcinolone acetonide demonstrate that microsphere-based formulations can markedly prolong synovial fluid residence time and lower peak systemic concentrations compared with crystalline suspensions, which illustrates how formulation can influence local pharmacokinetics and pharmacodynamics [118]. By analogy, although CNTX-4975 and RTX are intended to induce long-lasting defunctionalization of TRPV1-expressing terminals after brief exposure, inadequate penetration into deeper joint tissues (subchondral bone, periosteum) or into highly innervated microenvironments could result in incomplete defunctionalization in a proportion of patients, thereby attenuating clinical efficacy [60]. These delivery-related constraints and potential formulation solutions are considered in more detail in section 3.4.

Direct measurements in knee OA patients confirm this pattern: synovial fluid triamcinolone acetonide concentrations after a single i.a. injection of a crystalline suspension are often no longer quantifiable by 6 weeks, whereas an extended-release microsphere formulation (FX006) yields measurable synovial drug levels through at least 12 weeks, with substantially lower and more protracted systemic exposure [118,119]. Preclinical *in vivo* models similarly show that unencapsulated small molecules are cleared from the joint within hours to days, with heterogeneous distribution across synovium, capsule and cartilage, and that depot, nanoparticle or liposomal systems can prolong joint residency and modify tissue penetration profiles [120]. For TRPV1 agonists such as capsaicin and RTX, available animal data primarily describe functional denervation and loss of peptide-positive fibers in synovium and periarticular tissues rather than quantitative joint pharmacokinetic curves, underscoring the need for future programs to incorporate systematic synovial sampling and tissue-level distribution studies alongside clinical endpoints [117].

Procedural variability may also have influenced clinical outcomes beyond its impact on tolerability. Administration of i.a. TRPV1 agonists typically incorporates peri-procedural measures, such as local anesthesia, cooling protocols to mitigate acute nociceptor activation, and occasionally image guidance, to manage the intense but transient injection-related pain [59]. Differences between sites in injection approach (landmark-guided versus ultrasound-guided, superolateral versus anteromedial), joint positioning and mobilization after injection, and the timing and duration of cooling or anesthesia are all plausible modifiers of local distribution and mixing of the injected drug within the joint, and thus the spatial and temporal pattern of TRPV1 exposure [121]. Misplacement of the injection, extra-synovial leakage, or failure to access the most symptomatic compartment would further reduce the proportion of nociceptors exposed to therapeutic concentrations [122]. These limitations applied to earlier-phase trials as well, but their impact on observed effect size is likely to be greater in large, multi-center Phase III programs, where greater procedural heterogeneity and the absence of independent joint-level target-engagement measures (for example, synovial pharmacokinetics or imaging) increase the risk that a proportion of participants receive subtherapeutic i.a. exposure despite protocol adherence.

The durability of TRPV1-mediated nociceptor defunctionalization is also limited by biological recovery processes. Preclinical and human data with topical and intra-tissue capsaicin and RTX indicate that re-innervation of sensory terminals can begin within weeks following capsaicin-induced ablation, and that functional nociceptive responses often recover over weeks to months, which will, in turn, reduce the duration of analgesia [57,58]. If primary outcome assessments in Phase III trials are scheduled at time points when a significant fraction of TRPV1-expressing fibers have at least partially recovered in some individuals, especially those with incomplete initial defunctionalization, then the measured effect size may underestimate the peak therapeutic effect.

Finally, not all drivers of OA pain are mediated by TRPV1-expressing nociceptors. Structural and biomechanical factors such as bone marrow lesions, subchondral bone remodeling, enthesopathy, and joint instability may continue to generate pain signals via TRPV1-negative afferents or non-nociceptive mechanisms [110]. Moreover, central sensitization, cognitive-affective processes, and comorbid pain syndromes can maintain high pain scores even when peripheral TRPV1-positive terminals are effectively silenced [123].

These considerations suggest that the Phase III failures of i.a. TRPV1 agonists most likely reflect an interaction between patient-level factors (phenotype, central sensitization), methodological factors (endpoint choice, placebo response), and delivery-related barriers (heterogeneous i.a. distribution, rapid synovial clearance, limited tissue penetration, procedural variability, and incomplete target engagement), rather than a single dominant cause. As discussed in section 3.4, addressing these delivery and formulation issues prospectively will be essential if TRPV1-targeted strategies are to be revisited in OA.

5.5. Clinical positioning and residual niche for TRPV1-targeted analgesia

From a clinical perspective, TRPV1-targeted agonism is best understood as a peripherally acting analgesic strategy, rather than a disease-modifying approach. It aims to silence nociceptors in and around the joint without directly altering cartilage degeneration, synovitis, subchondral bone remodeling, or abnormal biomechanics [59]. It therefore cannot substitute for structural risk-modifying interventions, but could have a role in carefully selected patients whose dominant problem is refractory peripheral nociceptive pain despite optimized conventional care.

In principle, one attractive niche is patients with advanced knee OA who remain highly symptomatic while waiting for, or declining, arthroplasty. In such individuals, particularly those with predominantly activity-related, mechanically evoked joint pain and low central sensitization burden on quantitative sensory testing, a months-long reduction in peripheral nociceptive drive could function as a bridge therapy without exposing patients to long-term systemic NSAIDs or opioids [60]. A second potential niche comprises patients in whom NSAIDs and other standard oral analgesics are contraindicated or poorly tolerated, for example due to cardiovascular, renal, or gastrointestinal comorbidity; in these patients, a peripherally acting, joint-targeted analgesic with limited systemic exposure would be conceptually attractive if efficacy could be demonstrated [8].

The trial experience and post-hoc responder signals suggest that TRPV1-targeted analgesia, if revisited, should be positioned as a phenotype-guided intervention rather than a broad OA analgesic. Enrichment strategies based on QST-defined low central sensitization, peripheral pain-dominant symptom profiles, high synovial inflammatory burden, and possibly imaging markers of active joint innervation are likely to be essential if future programs are to show clinically meaningful benefit in a definable subgroup. This implies a narrower, more specialized clinical indication than originally pursued in the Phase III programs, but one that is more aligned with the biology of TRPV1-mediated peripheral pain and with the practical realities of OA care.

5.6. Proprioception: an under-characterized concern

TRPV1 is expressed in a substantial subset of articular nociceptive afferents innervating joint tissues such as capsule and periosteum, particularly peptidergic small-diameter fibers [124]. Ablation of TRPV1-positive terminals in the joint therefore raises a theoretically important concern: that dense functional silencing of these periarticular sensory afferents could modify the afferent input that contributes to reflex and sensorimotor control of the joint, with possible consequences for stability and structural load over time, even though TRPV1-expressing fibers are primarily nociceptive rather than classic muscle spindle-type proprioceptors [124]. Preclinical work confirms that TRPV1-positive fibers densely innervate capsule, ligaments and periosteum, and that high--dose i.a. capsaicin can ablate peptide-positive sensory fibers in these tissues [117,124]. However, there are currently no human data demonstrating clinically meaningful impairment of joint position sense or dynamic stability after i.a. TRPV1 agonist administration, and the completed CNTX-4975 and RTX trials did not identify proprioceptive adverse events as a safety signal. Any potential impact of periarticular TRPV1-expressing afferents on joint proprioception therefore remains theoretical and would need to be assessed prospectively with dedicated sensorimotor and biomechanical outcome measures in future programs.

5.7. Breakthrough therapy designation and the limits of regulatory recognition

The FDA's Breakthrough Therapy designation for i.a. RTX (granted in 2023) deserves comment. Breakthrough Therapy designation is a process designation intended to accelerate development and facilitate dialogue with the agency; it is not a prediction of Phase III efficacy. Historically, approximately half of drugs that receive Breakthrough Therapy designation do not achieve approval. In the TRPV1 context, the designation reflected the quality of Phase I/II data and the magnitude of unmet need in OA; it did not, and could not, validate the Phase III design assumptions about population selection and endpoint sensitivity that ultimately proved flawed. The designation likely contributed to strong external confidence in the program and to an accelerated partnering timeline at a point when the critical developmental assumptions had not yet been prospectively tested. This is not a criticism of the regulatory process; it is a caution against conflating process acceleration with evidence of efficacy when making clinical development decisions.

6. The broader OA pain landscape and where the field is moving

The failure of TRPV1-targeted analgesia in OA does not exist in isolation. The indication has a long history of Phase III attrition. Anti-NGF antibodies (tanezumab, fasinumab) demonstrated efficacy but were complicated by rapidly progressive OA and joint safety signals that prevented approval [125]. Intra-articular gene therapy and DMOAD candidates continue to face challenges demonstrating consistent structural and symptomatic benefit [126]. The overall record reflects systemic difficulties in developing novel analgesics for a heterogeneous, centrally influenced pain condition using trial designs calibrated for simpler pharmacological targets.

Several emerging approaches now represent the leading edge of OA pain drug development. GLP-1 receptor agonists have generated significant interest through demonstrated

effects on OA symptoms and structural outcomes, partially mediated by weight reduction but potentially through direct anti-inflammatory and chondroprotective mechanisms. Among these agents, retatrutide, a triple incretin agonist targeting GLP-1, GIP, and glucagon receptors [127], reported positive topline results from the Phase III TRIUMPH-4 trial in adults with obesity and knee OA in December 2025, demonstrating substantial reductions in body weight and WOMAC pain scores – including up to 75.8% reduction in WOMAC pain at the 12 mg dose – and providing the most compelling Phase III evidence to date that metabolic targeting can meaningfully modify OA pain [128]. Additional TRIUMPH program results are expected in 2026. Whether these effects are mediated primarily through weight reduction or through direct joint mechanisms remains an active area of investigation. Its development reflects increasing recognition that metabolic and inflammatory drivers of OA symptoms may be therapeutically modifiable. Oral sodium channel inhibitors targeting Nav1.8, including suzetrigine (VX-548, Vertex Pharmaceuticals), now approved for acute pain [129], represent a mechanistically plausible peripheral analgesic strategy with potential applicability in OA, but without published OA trial data to date. The clinical trajectory of voltage-gated sodium channel inhibitors, particularly Nav1.7, also illustrates the challenges of translating peripheral analgesic mechanisms into chronic musculoskeletal pain indications [130]. Structure-modifying approaches continue in development. Synovial neuroimmune targets are an area of increasing basic science interest. The portfolio is more diversified than it was when the RTX and CNTX-4975 programs were initiated, which is a reasonable response to repeated Phase III failure in a single mechanistic class.

In conclusion, the TRPV1 mechanism is not biologically exhausted. A coherent scientific case still exists that patients with OA pain driven predominantly by peripheral nociceptive input from the joint, such as those with identifiable sensory abnormalities at the knee, high synovial inflammatory burden, and low central sensitization burden on QST, represent a population for whom i.a. TRPV1 agonism could produce clinically meaningful benefit. The question is whether any sponsor will invest in the prospective phenotyping work necessary to identify and enrich for this population, and whether the regulatory and commercial environment supports a program with a narrower label than originally pursued. At present, that path does not appear to be actively in development.

7. Expert opinion

TRPV1-targeted analgesia in OA has now completed a full translational cycle from mechanistic discovery through preclinical validation, Phase I/II development, expedited regulatory recognition, and Phase III testing without yielding an approved therapy. This outcome warrants careful analysis rather than retrospective rationalization.

The mechanistic rationale for targeting TRPV1 in OA pain remains scientifically sound. TRPV1 is upregulated in OA joint tissues, its activation by inflammatory mediators contributes to nociceptor sensitization, and its pharmacological silencing via high-potency local agonists produces demonstrable analgesia in animal models and in appropriately selected human subjects [19,47–49]. The Phase II results for both CNTX-4975 and i.a. RTX were not artifacts; they reflected a real biological effect in appropriately selected trial populations. However, these studies enrolled patients using standard radiographic and pain-intensity criteria without formal phenotyping of pain mechanisms, and the subsequent Phase III programs largely extrapolated these criteria to larger, potentially more heterogeneous populations, in which a higher absolute number of centrally sensitized, non-responsive patients was likely present on epidemiologic grounds.

What failed was not the mechanism but its clinical translation. Several interrelated translational and developmental factors likely contributed to the Phase III outcomes. Among these, three design decisions appear particularly consequential. Other factors, including placebo response magnitude in i.a. OA trials, procedural variability in administration protocols, heterogeneous i.a. drug exposure, and biological reinnervation of nociceptor terminals, may also have contributed to the attenuation of treatment effects observed in Phase III.

First, the field over-relied on preclinical OA models that capture peripheral nociceptive mechanisms well but are poorly suited to modeling the central sensitization that dominates the pain experience in many human OA patients. The preclinical-to-Phase II signal was genuine but reflected a more favorable signal-to-noise ratio in populations better enriched for the responsive phenotype than broadly recruited Phase III cohorts.

Second, patient stratification was inadequate. The core clinical hypothesis that silencing joint nociceptors would meaningfully reduce OA pain is valid only for patients whose pain is predominantly peripherally driven. Enrolling a general knee OA population without prospective enrichment guaranteed inclusion of a substantial fraction of patients for whom the mechanism could not work. This was a known and remediable limitation; QST-based phenotyping was available, and Phase II post-hoc data had identified the responsive subgroup, though it should be noted that the availability of Phase II post-hoc subgroup data relative to the Phase III design lock date varied across programs. The decision not to incorporate this into Phase III design will be a durable lesson for the field. It is, in our view, arguably the most consequential developmental decision in retrospect.

Third, the momentum generated by Breakthrough Therapy designation and a high-value partnering transaction created a dynamic in which the critical Phase III design assumptions received less rigorous challenge than they deserved. Regulatory recognition and commercial momentum are valuable but do not validate biological assumptions.

What does the TRPV1 experience mean for OA analgesic development more broadly? We draw three lessons for future programs, and a fourth, integrative lesson that extends beyond TRPV1.

First, peripheral analgesic targets in OA should be paired, from the earliest stages of clinical development, with patient phenotyping strategies that identify the subpopulation for whom peripheral mechanisms are primary. Enrichment designs or adaptive trials that prospectively stratify on central sensitization burden are feasible, using frameworks that

combine QST, patient-reported pain characteristics, comorbidities and psychological factors, and should be considered standard rather than aspirational for this class of target. Second, the Phase II to Phase III transition should include a prospective replication of the response in phenotypically defined subgroups, using explicit measures of peripheral versus centrally sensitized pain mechanisms, rather than relying solely on an expansion of sample size with essentially identical inclusion radiographic and pain-intensity inclusion criteria. Third, regulatory designations that reflect process optimization should be carefully distinguished from efficacy validation in program communications, particularly those reaching investors and licensing partners.

Fourth, and equally important, phenotyping needs to be integrated with prospective validation of delivery and target engagement. For locally acting, peripherally targeted mechanisms such as TRPV1 agonism, it is no longer sufficient to assume that an injected dose will adequately reach all relevant nociceptor terminals for long enough to produce the intended effect. Future programs should be structured around an explicit development framework that couples: (i) peripheral pain phenotyping and central sensitization assessment; (ii) local pharmacokinetic and pharmacodynamic characterization (for example, synovial fluid drug levels over time, informed by prior work with extended-release i.a. formulations); (iii) imaging or biomarker-based readouts of target engagement at the joint (such as changes in synovial neuropeptide levels, nerve-related imaging signals, or other markers linked to TRPV1-expressing afferent activity); and (iv) mechanism-aligned clinical endpoints, focusing on activity-related, weight-bearing pain and other symptom domains that are most likely to change when peripheral joint nociceptors are silenced.

Is there a residual clinical future for TRPV1 agonists in OA? In our opinion, yes, but the case is conditional and the commercial path is narrow. A carefully designed program that prospectively selects patients with predominantly peripheral OA pain phenotypes, using validated QST criteria, synovial fluid or serum biomarkers of joint inflammation and neuropeptide release, and imaging readouts of joint innervation or bone remodeling, and that embeds synovial pharmacokinetic sampling and other target-engagement measures in early-phase studies, could plausibly demonstrate the benefit that Phase II data suggested and Phase III diluted away. Such a program would carry a narrower label, a smaller initial market, and would require a sponsor willing to build both the patient selection and delivery-validation infrastructure before initiating pivotal recruitment. We believe the scientific case exists. We are less confident that the investment will follow in the near term.

We are particularly interested in research that integrates TRPV1-directed interventions with detailed evaluation of neuroimmune interactions within the OA joint, their relationship to central pain processing, and their modulation by well-characterized joint exposure profiles. Such work could simultaneously refine patient selection for future programs and illuminate broader principles for developing peripherally targeted analgesics in a condition where the peripheral-central pain balance is highly variable and clinically decisive. Until that work is done, the field should not repeat the error of advancing a peripherally targeted mechanism against a broadly defined, phenotypically mixed OA population without the stratification infrastructure to determine both who will respond and whether the drug is truly reaching and modulating its intended peripheral target.

8. Conclusion

TRPV1 was a scientifically compelling target for OA pain. Its pursuit generated important knowledge about nociceptive mechanisms in the OA joint, the translational limits of standard preclinical models, and the fundamental challenge of developing peripherally targeted analgesics for a condition in which central sensitization is prevalent and often dominant. Systemic TRPV1 antagonists were abandoned owing to on-target thermoregulatory toxicity. Intra-articular TRPV1 agonists, including trans-capsaicin and RTX, produced encouraging Phase II results and achieved significant regulatory recognition, but both lead programs failed their Phase III primary endpoints. The class has not yielded an approved therapy for OA pain.

The reasons for this failure are comprehensible and correctable. Over-reliance on preclinical models that favor peripheral mechanisms, absence of prospective patient stratification for central sensitization burden, and use of a composite pain endpoint calibrated for broad analgesic effects rather than mechanism-specific interventions likely contributed substantially to the population-level effect size in Phase III that was insufficient to demonstrate superiority. These are not fundamental limitations of the target.

The legacy of the TRPV1 program in OA should not be one of wasted investment and abandoned promise. It should be read as a case study in the importance of phenotype-guided trial design for mechanism-based analgesics, and as a compelling argument for integrating patient stratification infrastructure into clinical development from Phase II rather than treating it as a post-hoc refinement. These lessons extend well beyond TRPV1 and are applicable to any peripheral analgesic strategy evaluated in the heterogeneous, centrally influenced pain landscape of OA.

Author contributions

CRediT: **Csaba Matta:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing; **Roland Takács:** Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing; **Eun-Jung Jin:** Investigation, Validation, Writing – original draft, Writing – review & editing; **Zsuzsanna Helyes:** Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing; **Ádám István Horváth:** Data curation, Investigation, Writing – original draft, Writing – review & editing; **Krisztián Zoltán Juhász:** Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing; **Balázs István Tóth:** Formal analysis, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing; **Ron Ellis:** Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing; **Ali Mobasheri:** Conceptualization, Formal analysis, Funding acquisition, Investigation,

Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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A Mobasheri served as former President of the Osteoarthritis Research Society International (OARSI) (May 2019–May 2022) and a member of the OARSI Board of Directors from 2013 to 2022. He currently serves as an advisor for the World Health Organization Collaborating Center for Public Health Aspects of Musculoskeletal Health and Aging, Member-at-Large on the Steering Committee Osteoarthritis Action Alliance, and Member of the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). The author acknowledges consortium funding from Horizon Europe (PROTO - Advanced Personalised Therapies for Osteoarthritis–TACKLING INFLAMMATION TO IMPROVE PATIENT OUTCOMES, Grant agreement ID: [101095635], https://cordis.europa.eu/project/id/101095635; ENgineered CArtilage from Nose for the Treatment of Osteoarthritis (ENCANTO), Grant agreement ID: [101137315], https://cordis.europa.eu/project/id/101137315); the European Structural and Social Funds through the Research Council of Lithuania (Lietuvos Mokslo Taryba), according to the Program Attracting Foreign Researchers for Research Implementation [Grant No.01.2.2-LMT-K-718-02-0022]. A Mobasheri has also received funding from EURONANOMED through the Research Council of Lithuania (LMTLT), agreement No [S-EURONANOMED-22-1]. C Matta was supported by the National Research, Development and Innovation Office, Hungary[grant number: 152166]. This work was supported by the Hungarian–Korean Applied R&D Cooperation Program, grant no. [2025-1.2.3-TÉT-IPARI-KR-2025-00002]. This work was supported by the Brain Pool Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT. This research was supported by the EKÖP-25-4 University Research Fellowship Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund, Hungary, awarded to R Takács [EKÖP-25-4-II-DE-249]. C Matta, R Takács and A Mobasheri also acknowledge financial support from the European Cooperation in Science and Technology COST Association Action [CA21110] - Building an open European Network on OsteoArthritis research (NetwOArk); https://www.cost.eu/actions/CA21110/). This research was supported by the University of Debrecen Program for Scientific Publication. Z Helyes was supported by the Hungarian Research Network-University of Pécs (HUN-REN-PTE) Chronic Pain Research Group, NKFIH [OTKA-138046], and the Hungarian Brain Research Program 3.0 (NAP 3.0). ÁI Horváth was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences. IB Tóth was supported by the National Research, Development and Innovation Office, Hungary [grant number: ADVANCED 153649]. C Matta, R Takács and A Mobasheri would also like to acknowledge financial support from the European Cooperation in Science and Technology COST Association Action CA21110 - Building an open European Network on OsteoArthritis research (NetwOArk); https://www.cost.eu/actions/CA21110/).

Declaration of interest

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