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What is new in pain modification in osteoarthritis?

Rachel E. Miller[1], Joel A. Block[1] and Anne-Marie Malfait[1]

Abstract

There is a big need for the development of novel therapies for the safe management of chronic pain associated with OA. Here we reviewed PubMed (2015 onward) and ClinicalTrials.gov for ongoing and recently completed trials where pain in OA is the primary outcome measure. Three broad categories were identified: biological therapies, small molecules and cryoneurolysis. The most promising new strategy is blockade of nerve growth factor with antibodies. Two anti-nerve growth factor antibodies, tanuzemab and fasinumab, are in active development after the 2010 hold on trials was lifted in 2015. In addition, several active clinical trials are testing distinct mechanism-based interventions, including cytokine inhibition, selective μ, δ or κ opioid receptor agonists, zoledronate and intra-articular capsaicin. In addition to pharmacological approaches, cryoneurolytic strategies that directly target peripheral nerves may play a role in OA pain management, but efficacy profiles and long-term effects of such treatments need more study. Clearly, the therapeutic landscape for OA pain is rapidly expanding. Since symptomatic OA is a heterogeneous disease, the challenge will be to identify patients that will benefit the most from specific approaches.

Key words: osteoarthritis, pain, clinical trials, biologics, nerve growth factor, cryoneurolysis, small molecules, G-protein coupled receptors, ion channels

Rheumatology key messages

- Anti-nerve growth factor therapy is a promising therapeutic for OA pain, despite reported adverse effects.
- Therapies for OA pain are rapidly transforming beyond traditional painkillers toward more mechanism-based interventions.
- Neurolysis is being investigated for OA pain, but efficacy profiles and long-term effects require further study.

REVIEW

Introduction

OA of the knee, hip, hands and spinal joints is a painful and disabling chronic condition that constitutes a major challenge to health care worldwide. In 2005, an estimated 26.9 million US adults had OA, an increase from 21 million in 1990 [1]. The prevalence of hip and knee OA is still rising, because of the ageing of the population and the rise of obesity, two major risk factors for the disease. The most recent update of the Global Burden of Disease figures (2013) estimated that 242 million people were living with symptomatic and activity-limiting OA of the hip and/or knee [2]. Thus, OA represents an enormous health burden, and, furthermore, the economic burden on patients and societies is huge due to hospital costs associated with joint replacements, and indirect costs due to loss of productivity [3–6].

For several decades now, the major efforts of the OA research community and the pharmaceutical industry have gone into identifying agents that delay the structural progression of joint damage in OA. These efforts have resulted in the identification of several attractive targets, but approved drugs that can prevent, slow, halt or reverse the progression of OA remain unavailable [7]. From the patient's perspective, pain control remains the most significant unmet need in OA treatment. NSAIDs have been the mainstay of therapy for more than a century, and despite the potential risks associated with their prolonged use, they continue to represent the primary effective strategy for pain palliation [8]. The more recent appreciation that there is a major contribution of the CNS to chronic musculoskeletal pain [9] has led to the exploration of centrally acting medications for OA, and resulted in the approval of the serotonin and norepinephrine reuptake inhibitor, duloxetine, several years ago for the treatment of musculoskeletal pain [10]. Nonetheless, despite the available options, OA patients continue to suffer from inadequate pain relief.

[1]Department of Internal Medicine, Division of Rheumatology, Rush University Medical Center, Chicago, IL, USA

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Correspondence to: Anne-Marie Malfait, Department of Internal Medicine, Division of Rheumatology, Rush University Medical Center, 1611 W Harrison Street, Suite 510, Chicago, IL 60612, USA.
E-mail: anne-marie_malfait@rush.edu

In December 2016, the Osteoarthritis Research Society International led an effort to submit a White Paper to the US Food and Drug Administration (FDA) in support of the designation of OA as a serious disease with no known cure, and no interventions currently available for stopping disease progression or loss of mobility, or managing pain, with an acceptable benefit-to-risk profile [11]. Clearly, while it is important that we continue our attempts to develop drugs that can halt structural disease progression, it needs to be considered how these future disease-modifying OA drugs will affect pain associated with joint damage [7]. Further, there is a big need for the development of novel therapies for the safe management of chronic pain associated with OA. Recent years have witnessed several prominent clinical trials for OA pain, and among those, trials with antibodies that neutralize nerve growth factor (NGF) appear particularly promising.

In this narrative review, we discuss recently completed and ongoing non-surgical trials for symptomatic OA. We searched PubMed for the following terms: OA, pain, clinical trials, cryoneurolysis, NGF, antibodies, symptom; papers published since 2015 were included. In addition, we searched www.clinicaltrials.gov for active and recently completed clinical trials testing agents for OA pain. Most drugs also have trials registered at www.clinicaltrialsregister.eu. Trials with platelet-rich plasma and stem cell therapy were excluded, because there is substantial heterogeneity in the quality of these trials and further high quality research is needed to establish the value of these approaches, as was recently discussed elsewhere [12, 13]. Trials with hyaluronan and corticosteroids were also excluded, since these are not novel mechanisms.

Biologics

MAb are powerful therapeutics that are being developed for the treatment of a wide range of diseases, and pain is no exception. Several antibodies are being tested in OA pain and antibodies against NGF, in particular, have recently generated tremendous expectation for the field.

Antibodies against NGF

The neurotrophin, NGF, has been extensively studied as a pain target because its expression is markedly increased in human pain states, including OA, and it has profound sensitizing effects on the nociceptive system (reviewed in [14]). NGF blockade is an attractive target for analgesia, and several companies have developed humanized mAb that bind NGF with high specificity and affinity, preventing it from binding its receptor. These antibodies include tanezumab (Pfizer and Eli Lilly), fasinumab (Regeneron and Teva) and fulranumab (Janssen and Amgen). Publication of the first large randomized double-blind controlled trial of anti-NGF therapy for OA [15], in which many patients experienced dramatic relief, generated enormous enthusiasm and expectation. However, careful evaluation of adverse events among patients treated with anti-NGF therapy suggested an association with rapidly progressive OA and, less commonly, with osteonecrosis, and the FDA imposed a hold on all clinical trials of NGF antagonists in 2010. This hold was extended because of the observation of autonomic nervous system toxicity in pre-clinical models [16], but was ultimately lifted in 2015 subject to the imposition of stringent monitoring and enrolment restrictions. As part of the risk mitigation strategy for the tanezumab trials, radiographic imaging is being used pre-enrolment in order to exclude patients with pre-existing shoulder, hip and knee joint abnormalities, including subchondral insufficiency fracture, atrophic or hypotrophic OA, excessive malalignment of the knee, osteonecrosis, severe chondrocalcinosis, RA, systemic metabolic bone disease, tumours, fractures and large cystic lesions [17]. In addition, radiographic follow-up will be performed as part of the trial design [17].

Among the anti-NGF agents in development (listed in Table 1), tanezumab is the best studied and is the closest to completing critical phase 3 trials in preparation for an application for approval for clinical use. The US FDA has recently granted Fast Track designation (a process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs) for tanezumab for the treatment of chronic pain in patients with OA or chronic low back pain. Regeneron/Teva are recruiting for phase 3 trials. Janssen has discontinued clinical development of fulranumab, with no active trials underway [18]. Although the primary initial licensing efforts for the NGF antagonists were focused on the US market, these agents have also been on the agenda of the European regulators (EMA), and it may be expected that they will become broadly available in Europe as well as Asia in a comparable timeframe to that of the USA.

Efficacy

There appears to be consensus among systematic reviews [19–21] that inhibition of NGF through targeted mAb therapy effectively relieves pain and results in improved function in OA, although the total literature base is fairly small. A review of all three anti-NGF agents that

Table 1 Summary of active NGF antibody programs for OA pain

Target	Antibody name(s)	Active trial IDs	Completed trial IDs
NGF	Tanezumab	NCT02709486; NCT02697773; NCT02528188; NCT02674386; NCT03031938	NCT00863304; NCT00744471; NCT00830063; NCT00733902; NCT01030640; NCT00669409
NGF	Fasinumab (MT-5547)	NCT03161093; NCT02683239; NCT03245008	

NGF: nerve growth factor.

had been in clinical development prior to the US FDA hold in 2010 identified 13 multicentre placebo-controlled trials of OA of the hip or knee that met their inclusion criteria [19]. Kan *et al.* [20] and Chen *et al.* [21] restricted their analyses to the use of tanezumab in OA; the former identified four studies of knee OA that met their inclusion criteria, whereas the latter included 10 studies (in 9 publications) of OA of the hip or knee. All studies were funded by the pharmaceutical industry. As the literature base was small, and there was extensive overlap among the systematic reviews, it is not surprising that the conclusions of each review were similar: compared with placebo, NGF inhibition yielded substantial improvement in both pain and function. In studies of tanezumab monotherapy compared with either NSAIDs or with opiates, tanezumab in doses of 5 and 10 mg intravenously were statistically significantly superior to the active comparators, with standardized effect sizes of 0.22–0.24 [19, 22]. Importantly, Chen *et al.* reported that low-dose ($\leqslant$2.5 mg) treatment had comparable efficacy to high dose, but with significantly fewer adverse effects [21].

Risks

Safety concerns led to the US FDA hold on all clinical testing in 2010, based on reports of rapidly progressive OA and of osteonecrosis among patients who had received anti-NGF therapy, including involvement of joints without known OA. An expert adjudication committee funded by Pfizer performed detailed reviews of the adverse events reported during clinical trials with tanezumab and fulranumab. A dose–response relationship was noted between the serious events (rapidly progressive OA) and doses of tanezumab between 2.5 and 10 mg [23] or doses of fasinumab between 3 and 9 mg [24, 25]. Trials were resumed in 2015, with reduced doses for hip or knee OA, maximally 5 mg. Interestingly, the incidence of osteonecrosis may be lower than previously thought. Of the 86 reported osteonecrosis cases, the Pfizer-funded adjudication committee could demonstrate unambiguous osteonecrosis in only two (although eight had insufficient information to distinguish primary osteonecrosis and the committee failed to reach consensus on another five) [26]. Importantly, the risk of developing rapidly progressive OA appeared to be significantly greater when tanezumab was used in conjunction with NSAIDs, compared with tanezumab monotherapy [23, 26]. This observation has resulted in strict limits on the duration of NSAID use during exposure to anti-NGF therapy in subsequent trials. In spite of the risks, cost-effectiveness analyses suggest that the pain palliation provided by anti-NGF therapy is sufficiently significant that even a rate of rapidly progressive OA occurring in up to 10% of patients would not nullify the overall improvement in quality-adjusted life years achieved [27], and that anti-NGF therapy could be cost effective at up to $400 per dose [27]. It should be noted, of course, that such analyses are based entirely on models using arbitrary values of the costs of pain, and are intended to inform policy rather than to be used clinically, as individuals have markedly disparate views of risk and benefit.

In conclusion, anti-NGF therapy offers great potential to palliate pain and function in patients with severely symptomatic OA. Nonetheless, it appears that the benefit carries a risk of exacerbating structural OA. A small number of studies have tested NGF blockade in animal models of OA, and these studies have also highlighted the risk for accelerated joint damage (recently reviewed in [28]) but the mechanisms of these side-effects remain poorly understood. As these trials are ongoing, the actual benefits and risks of anti-NGF therapy remain to be fully elucidated. In a recent review, Jayabalan and Schnitzer [29] discussed the use of tanezumab and suggested that it will be important to define the population of patients for whom this treatment will be most appropriate. They propose that it will be key to identify those individuals who should not receive the antibody, and these will likely be individuals with preexisting joint abnormalities that may be put at increased risk of rapidly progressive OA, such as subchondral insufficiency fractures. On the other hand, tanezumab may be a particularly useful agent for specific populations of individuals for whom NSAIDs are contraindicated and/or not advised (e.g. patients with chronic renal insufficiency, or elderly patients in whom NSAIDs and opioids should be used with care).

Other antibodies

Antibodies against different targets, often developed for other indications, are also being tested for efficacy against OA pain. Table 2 lists ongoing and recently completed trials, as reported on ClinicalTrials.gov. Cytokines in particular are being targeted, for their pro-inflammatory role

Table 2 Other antibody programs for OA pain

Target	Antibody name(s)	Active trial IDs	Completed trial IDs
IL-6	Tocilizumab	NCT02477059	
GM-CSF	GSK3196165	NCT02683785	
NGF/TNF	MEDI7352	NCT02508155	
IL-1α/β	ABT-981		NCT02384538; NCT01668511; NCT02087904
TNF	Adalimumab	NCT02471118	NCT00296894; NCT00597623
CGRP	LY2951742		NCT02192190 (terminated)

NGF: nerve growth factor; CGRP: Calcitonin gene-related peptide.

and because they may have a direct pro-algesic effect (reviewed in [30]). For painful knee OA, there are ongoing trials with a bi-specific NGF/TNF antibody (MEDI7352) and with the anti-TNF antibody, adalimumab. Abbvie recently completed a phase 2 knee OA trial with a dual variable domain immunoglobulin that specifically and potently neutralizes IL-1α and IL-1β (ABT-981). Baseline characteristics of the subjects enrolled were reported at the 2017 Osteoarthritis Research Society International meeting [31], but trial results are not yet available.

In addition, there are several ongoing trials with antibodies targeting different cytokines or growth factors for hand OA. An antibody against GM-CSF, GSK3196165 (formerly MOR103), is being tested in inflammatory hand OA, with a primary outcome measure of change from baseline in pain intensity at week 6. This and other GM-CSF antibodies were introduced for the treatment of RA, and phase 2 trials have been completed for that indication with positive results (for review see [32]). Other hand OA trials include a trial with an antibody against the IL-6 receptor, tocilizumab and a phase 2a trial with the IL-1α/β dual-specific antibody, ABT-981. Results of the latter were reported at the 2017 EULAR meeting, and the antibody failed to show significant improvements in the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) pain measure at week 16 compared with placebo [33]. Finally, adalimumab failed to show benefit when tested for hand OA in two separate trials [34, 35].

The neuropeptide, calcitonin gene-related peptide, has been studied as a pain target for many years [36]. Eli Lilly has a calcitonin gene-related peptide antibody in the pipeline for migraine [37], and positive phase 3 results were recently announced [38]. However, a phase 2 trial for OA knee pain was terminated due to lack of efficacy [39].

Small molecules

Chronic pain associated with OA can be generated, modified and maintained at different levels along the neuraxis (reviewed in [40]). Since many of these pain mechanisms can be selectively and potently targeted, they offer an exciting opportunity for analgesic drug development (recently reviewed in [41]). Two broad classes of molecules, in particular, are being targeted for pharmacological modulation: G-protein coupled receptors (GPCRs) and ion channels. There are several ongoing or recently completed clinical trials with small molecules targeting these molecules for OA pain (Table 3).

GPCRs

Approximately 4% of the human genome codes for GPCRs (about 800 in total), and these receptors are well represented in all of the cells that constitute the peripheral and central components of the pain pathway. GPCRs have proved to be highly druggable targets in the past [50]. Depending on the G-protein involved in signalling, GPCRs may have excitatory or inhibitory effects on pain; examples of this include the pro-algesic effects of bradykinin and the analgesic effects of morphine.

Concerns about the safety of opioids has led companies to work on developing novel drugs in this class with improved safety profiles. To this end, a number of drugs are under development for OA pain that selectively target each of the three opioid receptors, δ, κ or μ. Positive results have been reported for the peripherally selective κ opioid receptor agonist, CR845, while investigators reported no benefit over placebo for two different δ opioid receptor agonists (Table 3). A unique new drug, cebranopadol, combines nociceptin/orphanin FQ peptide receptor and μ opioid receptor agonism, which may have a better safety profile than traditional opioids [51]. Positive results

Table 3 Completed randomized, double-blind, placebo-controlled clinical trials for OA pain drugs

Target	Drug	Trial ID	Results
GPCRs			
Bradykinin (BK) B2 receptor	Fasitibant	NCT02205814	No particular dose different from placebo (WOMAC A) [42]
Delta opioid receptor	ADL5859	NCT00979953	No difference from placebo [43]
Delta opioid receptor	ADL5747	NCT00979953	No difference from placebo [43]
Kappa opioid receptor	CR845	NCT02944448	Positive results for hip OA [44]
Nociceptin/orphanin FQ peptide (NOP) and mu opioid receptors	GRT6005 (cebranopadol)	NCT01709214	No results; Depomed appears to be continuing development [45]
CB2	GW842166	NCT00479427	No results
Ion channels			
$Na_V1.7$ and other sodium channels	TV-45070	NCT02068599	No difference from placebo [46]
$Na_V1.8$	VX-150	NCT02660424	Positive results [47]
TRPV1	CNTX-4975	NCT02558439	Significant improvement *vs* placebo in WOMAC A1 scores at week 12 [48]
TRPV1	NEO6860	NCT02712957	Preliminary data suggests an analgesic effect compared with placebo [49]

GPCRs: G-protein coupled receptors; TRPV1: Transient vanilloid receptor 1.

have just been published for a low back pain trial, but OA results have not yet been disclosed [51]. Cannabinoid receptors are also heavily studied analgesic targets, and GlaxoSmithKline (GSK) has recently completed a phase 2 trial for their CB2 agonist, GW842166; trial results have not yet been reported. A randomized double-blind study testing the effects of vaporized cannabis on knee OA pain is currently ongoing in Canada (NCT02324777). Finally, another GPCR, the bradykinin B2 receptor, has been targeted with the intra-articular therapy fasitibant, but this approach did not show statistically significant differences from placebo in a phase 2 knee OA trial [42], and it appears to have been discontinued by Menarini.

Ion channels

Ion channels are critical components of the pain pathway, since they drive hyperexcitability of neurons in a variety of chronic pain states. Therefore, they are widely believed to be suitable drug targets for the treatment of chronic pain conditions [52], including OA [41]. A number of drugs targeting different ion channels have recently been tested in clinical trials for OA pain. A recently completed clinical trial with intra-articularly delivered CNTX-4975, a synthetic trans-capsaicin that targets the transient receptor potential vanilloid 1 and reversibly deactivates free terminals of primary afferent pain fibres within the joint, showed very promising analgesic effects [48]. In addition, an oral transient receptor potential vanilloid 1-blocker, NEO6860, also shows positive trial results (Table 3), while topical capsaicin derivatives (creams) are also being used to treat OA pain (reviewed in [53]). The voltage-gated sodium channels, $Na_V1.7$ and $Na_V1.8$, have also been targeted for OA pain. Vertex has recently reported positive phase 2 trial results for their oral $Na_V1.8$ inhibitor, while Teva has reported that their topically applied $Na_V1.7$ inhibitor showed no benefit over placebo.

Ongoing trials for other targets

A search of ClinicalTrials.gov for studies that are active, recruiting or not yet recruiting for evaluation of treatments for OA pain yielded seven ongoing randomized, double-blind, placebo-controlled trials (Table 4). Among the seven trials, three target different components of the NGF signalling pathway. The small molecule TrkA inhibitor, GZ389988, and the pan-selective Trk inhibitor, ONO-4474, are both in phase 2 trials. The novel approach of targeting NGF through injection of a p75 neurotrophin receptor fusion protein (LEVI-04) is earlier in development and is currently undergoing a phase 1 trial. A drug targeting the A_3 adenosine receptor, CF101, is also undergoing a phase 2 trial for knee OA, but has yet to report results. Finally, the Rottapharm website mentions that a phase 2 trial for OA pain was completed with CR4056, a first-in-class imidazoline-2 ligand that reduced pain behaviour in two different rat models of OA pain [54]. The trial is not registered in ClinicalTrials.gov, and results are not yet available.

In addition, traditional disease-modifying OA drug targets are now being considered for their analgesic effects. AXS-02 (disodium zoledronate tetrahydrate), uniquely targeted at knee OA associated with bone marrow lesions, has been fast-tracked by the FDA for this indication, as well as for pain associated with complex regional pain syndrome. AXS-02 is currently undergoing a phase 3 clinical trial for knee OA associated with bone marrow lesions; the primary end point is the change in pain intensity from baseline to week 24. According to the Axsome website, results from an interim analysis of the first 60 subjects are expected late December 2017 to early January 2018. Additionally, a drug targeting the Wnt pathway, SM04690, is undergoing two phase 2 trials for knee OA, both of which include pain and functional changes as primary outcome measures, while one trial also includes change from baseline in medial joint space width of the target knee at 24 weeks as a primary outcome measure (NCT03122860). No results have been reported yet. A phase 1 trial for a single intra-articular injection of SM04690 in knee OA patients appeared safe, with no evidence of systemic exposure [55].

Cryoneurolysis

In addition to pharmacological approaches, a great deal of attention has recently been given to the technique of cryoneurolysis, based on the results of a recently published randomized sham-controlled trial in knee OA [56]. Cryoneurolysis (also termed cryoneuroablation, cryoanalgesia, cryogenic nerve blockade or cryolesioning) is a

Table 4 Ongoing randomized, double-blind, placebo-controlled clinical trials for OA pain drugs

Target	Drug	Trial ID
A_3 adenosine receptor (A_3AR)	CF101	NCT00837291
TrkA (NGF receptor)	GZ389988	NCT02845271; (NCT02424942 recently completed)
Wnt pathway	SM04690	NCT02536833; NCT03122860
NGF and other neurotrophins	LEVI-04 (p75NTR-Fc)	NCT03227796
Trk (TrkA, TrkB, TrkC)	ONO-4474	NCT02997696
Osteoclasts	AXS-02 (disodium zoledronate tetrahydrate)[a]	NCT02746068

[a]Granted fast track designation by the Food and Drug Administration for the treatment of knee OA associated with bone marrow lesions. NGF: nerve growth factor.

technique whereby peripheral nerves are exposed to local freezing, which causes axonal damage and blocks nerve conduction. In cryoneurolysis, temperatures in the range of −60 to −100°C cause a grade II nerve injury according to Sunderland's classification and affect all nerve fibre types, as observed in a variety of animal models [57–60]. Nerve injuries in this category cause Wallerian degeneration of the axon without killing the cell body and are generally reversible over a period of weeks to months [58]. In addition, this type of freezing injury does not appear to cause inflammation and fibrosis, which may also contribute to the reversibility of both structure and function of the nerve.

Cryoneurolysis has been used clinically to provide post-operative pain relief in addition to treatment of certain chronic pain conditions, including craniofacial and low back pain [61], and the trial by Radnovich *et al.* [56] locally targeted the infrapatellar branch of the saphenous nerve in patients with knee OA. In that trial, patients treated during one session with cryoneurolysis achieved clinically significantly greater pain improvement than those in the sham-treatment group, according to the primary end point, least squares mean change from baseline to day 30 in the WOMAC pain subscale score (treatment = −16.65; sham = −9.54). This improvement in WOMAC pain score compared with sham was maintained through day 90. Some caution is warranted in interpreting the results, as the blinding was incomplete during the trial. Nonetheless, the technique had few adverse events, with the majority of these events being mild in severity; the most common adverse events attributed to the study device included numbness, tenderness upon palpation and local pain. Only one device- or procedure-related adverse event was rated as severe (administration site altered sensation in a sham treatment patient). Moreover, cryoneurolysis has been considered a safe procedure in other settings. On this basis, the iovera° device (Myoscience, Fremont, CA, USA) has recently received US FDA clearance under the 510(k) mechanism to be marketed [62].

It should be noted that 510(k) clearance is used to obtain permission to market devices that are considered substantially equivalent to a previously cleared device. The clearance process focuses on safety and technical performance, and does not necessarily require supportive clinical data [63]; in contrast to approved drugs or biologics, there is no formally approved indication. Cryoneurolysis has been widely available worldwide for decades for the treatment of various neuropathic conditions and the technique may be used anywhere. Thus, the recent US FDA clearance for use in OA was a technical rather than a medical clearance.

The idea of using cold as a medical therapy has existed for centuries, but tools specifically built to freeze nerves at extreme temperatures using nitrous oxide gas began with Cooper and Amoils in the 1960s [58, 61, 64, 65]. Myoscience has had a number of cryogenic devices on the market since 2010 [fda.gov; Patent US9610112 shows results of an initial prospective non-blinded trial on OA pain using an earlier device (ClinicalTrials.gov identifier: NCT01704157)], and other companies have been approved by the FDA for marketing of similar devices for the treatment of chronic pain since the late 1970s. Often, a diagnostic injection of lidocaine is used to assess whether blocking a particular nerve will likely result in pain relief or not [58, 61], and successful reduction in pain >50% (visual analogue scale) following diagnostic lidocaine block of the infrapatellar branch of the saphenous nerve was one of the inclusion criteria in the Radnovich *et al.* [56] trial. Repeated diagnostic blocks may more accurately predict patients likely to benefit from treatment, since there may be a placebo effect to overcome [61]. Finally, cyroneurolysis has been used to induce neuropathic pain in rats [66], and thus further long-term follow-up in patients will be important to rule out this potential adverse effect [67].

A different neurolysis approach that has recently attracted attention for the treatment of OA pain is thermal radiofrequency (or water-cooled radiofrequency, brand name Coolief). Despite the use of cool in the name, this technology actually applies heat to cause denervation, which is less likely to be reversible and more likely to be accompanied by neuroma formation, hyperalgesia and deafferentation pain compared with cryoneurolysis [68]. A recent systematic review has summarized the available results from trials conducted so far for treating chronic knee pain [69], which concluded that while the results reported appear promising, more rigorous trials are needed to make clear conclusions on whether this technology may improve clinical practice. There are multiple ongoing clinical trials testing the use of this technology for OA pain. For low back pain, the efficacy of this technology has been mixed to date (review of the technology for other indications including low back pain can be found in [68, 70–72]).

Conclusions

A critical need exists for new analgesics that can be used for the management of chronic pain associated with OA. Several promising therapeutics are in the clinical trial pipeline. In particular, ongoing trials with antibodies against NGF are setting high expectations for the near future due to their pronounced efficacy and in spite of ill-understood side-effects, including rapidly progressive OA. From our survey of the recent literature and clinical trial activity, it is apparent that the therapeutic landscape for OA pain is rapidly transforming beyond traditional painkillers such as NSAIDs, toward more mechanism-based interventions, such as disodium zoledronate tetrahydrate, selective opioid receptor agonists or locally delivered capsaicin. Beyond pharmacological approaches, neurolytic strategies directly targeting peripheral nerves may play a role in joint pain management, but the efficacy profiles and long-term effects of such treatments have to be further studied.

Finally, just as it is increasingly appreciated that OA is a heterogeneous disease, where distinct pathogenic pathways may operate in distinct subsets of OA, it should be

considered that symptomatic OA may also comprise overlapping but distinct phenotypes that present with common clinical features [73]. The pain experience in OA is not homogeneous, and sufferers describe different pain qualities, including pain on weightbearing or joint movement. Frequently, the pain has a strong mechanical component and is relieved by rest, but as structural joint disease advances, pain becomes more constant, and has been described as dull aching or throbbing, punctuated with episodes of a more intense pain [74, 75]. Some patients display signs of central sensitization, including temporal summation and mechanical allodynia (pain evoked by an innocuous stimulus) [76–78]. These different pain qualities and the presence of signs of sensitization may indeed reflect distinct underlying mechanisms [40, 79]. Therefore, as we continue to develop novel mechanism-based therapies, it needs to be considered that distinct phenotypes may warrant different therapeutic approaches. Methods for improved patient stratification in order to optimize tailored analgesia will be the next test for this challenging disease.

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References

1 Lawrence RC, Felson DT, Helmick CG *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26–35.

2 Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800.

3 Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004;(427 Suppl):S6–15.

4 Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. J Rheumatol 1997;24:719–25.

5 Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective. Am J Nurs 2012;112:S13–9.

6 Yelin E, Murphy L, Cisternas MG *et al*. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. Arthritis Rheum 2007;56:1397–407.

7 Karsdal MA, Michaelis M, Ladel C *et al*. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage 2016;24:2013–21.

8 Hochberg MC, Altman RD, April KT *et al*. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:465–74.

9 Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. J Rheumatol 2011;38:1546–51.

10 Smelter E, Hochberg MC. New treatments for osteoarthritis. Curr Opin Rheumatol 2013;25:310–6.

11 Osteoarthritis: A Serious Disease. Pre Competitive Consortium for Osteoarthritis Osteoarthritis Research Society International, 2016. https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf

12 Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. Curr Rheumatol Rep 2017;19:24.

13 Chakravarthy K, Chen Y, He C, Christo PJ. Stem cell therapy for chronic pain management: review of uses, advances, and adverse effects. Pain Physician 2017;20:293–305.

14 Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. Annu Rev Neurosci 2017;40:307–25.

15 Lane NE, Schnitzer TJ, Birbara CA *et al*. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 2010;363:1521–31.

16 Mullard A. Drug developers reboot anti-NGF pain programmes. Nat Rev Drug Discov 2015;14:297–8.

17 Roemer FW, Miller CG, West CR *et al*. Development of an imaging mitigation strategy for patient enrolment in the tanezumab nerve growth factor inhibitor (NGF-ab) program with a focus on eligibility assessment. Semin Arthritis Rheum 2017;47:323–30.

18 Janssen Announces Discontinuation of Fulranumab Phase 3 Development Program in Osteoarthritis Pain. Titusville, NJ, 2016. https://www.jnj.com/media-center/press-releases/janssen-announces-discontinuation-of-fulranumab-phase-3-development-program-in-osteoarthritis-pain.

19 Schnitzer TJ, Marks JA. A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee. Osteoarthritis Cartilage 2015;23 (Suppl 1):S8–17.

20 Kan SL, Li Y, Ning GZ *et al*. Tanezumab for patients with osteoarthritis of the knee: a meta-analysis. PLoS One 2016;11:e0157105.

21 Chen J, Li J, Li R *et al*. Efficacy and safety of tanezumab on osteoarthritis knee and hip pains: a meta-analysis of randomized controlled trials. Pain Med 2017;18:374–85.

22 Schnitzer TJ, Ekman EF, Spierings EL *et al*. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain. Ann Rheum Dis 2015;74:1202–11.

23 Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthritis Cartilage 2015;23 (Suppl 1):S18–21.

24 Lane NE, Corr M. Osteoarthritis in 2016: anti-NGF treatments for pain - two steps forward, one step back? Nat Rev Rheumatol 2017;13:76–8.

25 Maloney J, Kivitz A, Schnitzer TJ *et al*. Efficacy and safety of fasinumab for osteoarthritic pain in patients with moderate to severe osteoarthritis of the knees or hips [abstract]. Arthritis Rheumatol 2016;68.

26 Hochberg MC, Tive LA, Abramson SB *et al*. When is osteonecrosis not osteonecrosis?: adjudication of reported serious adverse joint events in the tanezumab clinical development program. Arthritis Rheumatol 2016;68:382–91.

27 Losina E, Michl G, Collins JE *et al*. Model-based evaluation of cost-effectiveness of nerve growth factor inhibitors in knee osteoarthritis: impact of drug cost, toxicity, and means of administration. Osteoarthritis Cartilage 2016;24:776–85.

28 Miller RE, Block JA, Malfait AM. Nerve growth factor blockade for the management of osteoarthritis pain: what can we learn from clinical trials and preclinical models? Curr Opin Rheumatol 2017;29:110–8.

29 Jayabalan P, Schnitzer TJ. Tanezumab in the treatment of chronic musculoskeletal conditions. Expert Opin Biol Ther 2017;17:245–54.

30 Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. Cytokine 2014;70:185–93.

31 Levesque MC, Chen S, Peterfy C, Wang L, Medema JK. Baseline characteristics of knee osteoarthritis subjects enrolled in the ILLUSTRATE-K study of the anti-interleukin-1alpha/beta dual variable domain immunoglobulin ABT-981 and factors associated with exclusion from the trial. Osteoarthritis Cartilage 2017;25:S350–1.

32 Hamilton JA, Cook AD, Tak PP. Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases. Nat Rev Drug Discov 2016;16:53–70.

33 Kloppenburg M, Peterfy C, Haugen I *et al*. OP0168 A phase 2a, placebo-controlled, randomized study of ABT-981, an anti-interleukin-1ALPHA and -1BETA dual variable domain immunoglobulin, to treat erosive hand osteoarthritis (EHOA). Ann Rheum Dis 2017;76 (Suppl 2):122.

34 Aitken D, Pan F, Laslett L *et al*. A randomised double-blind placebo-controlled crossover trial of humira (adalimumab) for erosive hand osteoarthritis: the humor trial. Osteoarthritis Cartilage 2017;25:S9.

35 Chevalier X, Ravaud P, Maheu E *et al*. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis 2015;74:1697–705.

36 Schou WS, Ashina S, Amin FM, Goadsby PJ, Ashina M. Calcitonin gene-related peptide and pain: a systematic review. J Headache Pain 2017;18:34.

37 Dodick DW, Goadsby PJ, Spierings ELH *et al*. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 2014;13:885–92.

38 Lilly Announces Positive Results for Three Phase 3 Studies of Galcanezumab for the Prevention of Episodic and Chronic Migraine. Indianapolis, IN, 2017. https://investor.lilly.com/releasedetail.cfm? releaseid=1026201.

39 Jin Y, Smith C, Monteith D *et al*. LY2951742, a monoclonal antibody against CGRP, failed to reduce signs and symptoms of knee osteoarthritis. Osteoarthritis Cartilage 2016;24:S50.

40 Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol 2013;9:654–64.

41 Malfait AM, Miller RJ. Emerging targets for the management of osteoarthritis pain. Curr Osteoporos Rep 2016;14:260–8.

42 Werner CG, Pavelka K, Nizzardo A *et al*. A double-blind, randomized, controlled, four parallel arm, dose-finding study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of single intra-articular (IA) injections of Fasitibant in patients with symptomatic OA of the knee [abstract]. Arthritis Rheumatol 2015;67.

43 Adolor Corporation Provides Clinical Update. Exton, PA, 2010. https://www.sec.gov/Archives/edgar/data/1076167/000110465910034818/a10-12253_1ex99d1.htm.

44 Cara Therapeutics Announces Top-line Results From Phase 2b Trial of Oral CR845 in Chronic Pain Patients With Osteoarthritis of the Hip or Knee. Stamford, CT, 2017. http://ir.caratherapeutics.com/releasedetail.cfm?releaseid=1031842.

45 Product Pipeline Depomed. http://www.depomed.com/pipeline.

46 Teva and Xenon Provide Update on TV-45070 Phase 2b Study in Osteoarthritis Pain. Jerusalem & Burnaby, British Columbia, 2015. http://www.tevapharm.com/news/teva_and_xenon_provide_update_on_tv_45070_phase_2b_study_in_osteoarthritis_pain_07_15.aspx.

47 Vertex Reports Full-Year and Fourth-Quarter 2016 Financial Results. Boston, MA, 2017 http://investors.vrtx.com/releasedetail.cfm? ReleaseID=1009133.

48 Stevens R, Petersen D, Ervin J *et al*. OP0167 efficacy and safety of CNTX-4975 in subjects with moderate to severe osteoarthritis knee pain: 24-week, randomized, double-blind, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017;76:121.

49 NEOMED Institute Announces Publication and Clinical Update for NEO6860 an Oral Therapeutic in Development for the Treatment of Chronic Pain. Montreal, Quebec, 2017. http://neomed.ca/en/2017/03/28/neomed-institute-announces-publication-clinical-update-neo6860-oral-therapeutic-development-treatment-chronic-pain/.

50 Roth BL, Kroeze WK. Integrated approaches for genome-wide interrogation of the druggable non-olfactory G Protein-coupled receptor superfamily. J Biol Chem 2015;290:19471–7.

51 Christoph A, Eerdekens M-H, Kok M, Volkers G, Freynhagen R. Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial. PAIN 2017;158:1813–24.

52 Bagal SK, Brown AD, Cox PJ *et al*. Ion channels as therapeutic targets: a drug discovery perspective. J Med Chem 2013;56:593–624.

53 Laslett LL, Jones G. Capsaicin for osteoarthritis pain. Prog Drug Res 2014;68:277–91.

54 Comi E, Lanza M, Ferrari F *et al*. Efficacy of CR4056, a first-in-class imidazoline-2 analgesic drug, in comparison with naproxen in two rat models of osteoarthritis. J Pain Res 2017;10:1033–43.

55 Yazici Y, McAlindon TE, Fleischmann R *et al*. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. Osteoarthritis Cartilage 2017.

56 Radnovich R, Scott D, Patel AT *et al*. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthritis Cartilage 2017;25:1247–56.

57 Beazley RM, Bagley DH, Ketcham AS. The effect of cryosurgery on peripheral nerves. J Surg Res 1974;16:231–4.

58 Barnard D. The effects of extreme cold on sensory nerves. Ann R Coll Surg Engl 1980;62:180–7.

59 Carter DC, Lee PW, Gill W, Johnston RJ. The effect of cryosurgery on peripheral nerve function. J R Coll Surg Edinb 1972;17:25–31.

60 Zhou L, Kambin P, Casey KF *et al*. Mechanism research of cryoanalgesia. Neurol Res 1995;17:307–11.

61 Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician 2003;6:345–60.

62 K161835. Silver Spring, MD: FDA, 2017. https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161835.pdf.

63 Beitzel K, Allen D, Apostolakos J *et al*. US definitions, current use, and FDA stance on use of platelet-rich plasma in sports medicine. J Knee Surg 2015;28:29–34.

64 Amoils SP. The Joule Thomson cryoprobe. Arch Ophthalmol 1967;78:201–7.

65 Cooper IS, Lee AS. Cryostatic congelation: a system for producing a limited, controlled region of cooling or freezing of biologic tissues. J Nerv Ment Dis 1961;133:259–63.

66 DeLeo JA, Coombs DW, Willenbring S *et al*. Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat. Pain 1994;56:9–16.

67 Walsh DA. Osteoarthritis: nerve ablation - a new treatment for OA pain? Nat Rev Rheumatol 2017;13:393–4.

68 Malik KM. Pulsed radiofrequency, water-cooled radiofrequency, and cryoneurolysis. Essentials of pain medicine, 3rd edn. Philadelphia, PA: Elsevier Inc.; 2011: 431–8.

69 Gupta A, Huettner DP, Dukewich M. Comparative effectiveness review of cooled versus pulsed radiofrequency ablation for the treatment of knee osteoarthritis: a systematic review. Pain Physician 2017;20:155–71.

70 Leggett LE, Soril LJ, Lorenzetti DL *et al*. Radiofrequency ablation for chronic low back pain: a systematic review of randomized controlled trials. Pain Res Manag 2014;19:e146–53.

71 Poetscher AW, Gentil AF, Lenza M, Ferretti M. Radiofrequency denervation for facet joint low back pain: a systematic review. Spine (Phila Pa 1976) 2014;39:E842–9.

72 van Tilburg CW, Stronks DL, Groeneweg JG, Huygen FJ. Randomised sham-controlled double-blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. Bone Joint J 2016;98-B:1526–33.

73 Lane NE, Brandt K, Hawker G *et al*. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011;19:478–82.

74 Hawker GA, Stewart L, French MR *et al*. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415–22.

75 Wagstaff S, Smith OV, Wood PH. Verbal pain descriptors used by patients with arthritis. Ann Rheum Dis 1985;44:262–5.

76 Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:1043–56.

77 Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145–53.

78 Suokas AK, Walsh DA, McWilliams DF *et al*. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2012;20:1075–85.

79 Moreton BJ, Tew V, das Nair R *et al*. Pain phenotype in patients with knee osteoarthritis: classification and measurement properties of painDETECT and self-report Leeds assessment of neuropathic symptoms and signs scale in a cross-sectional study. Arthritis Care Res 2015;67:519–28.