Emerging Non-Opioid Drugs for the Management of Chronic Non-Cancer Pain
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Acknowledgements: Jantz Selk

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Context

Chronic non-cancer pain (defined as any painful condition that persists for at least three months and is not associated with malignancy) is a prevalent condition that has significant negative effects on daily physical function and quality of life. Specific disorders that cause chronic non-cancer pain include osteoarthritis, low back pain, neuropathic pain (including post-herpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia), migraines, and fibromyalgia. An estimated 15% to 19% of Canadian adults live with chronic non-cancer pain, making it a leading cause of health care resource utilization and disability among working-age adults.

In North America, opioids are used extensively in the treatment of chronic pain, despite limited long-term efficacy for many patients that is due, in part, to the development of tolerance to their analgesic effects. Even with the growing awareness of the risks associated with opioids—such as misuse, addiction, and overdose—as well as increased recognition of the current opioid crisis, the number of prescriptions for opioids is still rising in Canada. A total of 3.8 million Canadians over the age of 15 (representing 13% of the total population) reported using opioid pain relievers in the past year, according to a Statistics Canada survey conducted in 2015. Among users of opioid pain relievers, 2% (83,000 Canadians, representing 0.3% of the total population) reported misusing them. According to a report from the Canadian Institute for Health Information, the rate of hospitalizations due to opioid poisoning in Canada increased by 53% between 2007 and 2008 as well as 2016 and 2017, with a current average of 16 hospitalizations a day. Preliminary data from all the provinces and territories (excluding Quebec) from 2016 indicate that there were more than 2,800 apparent opioid-related deaths in Canada. The significant burden opioid misuse places on the Canadian health care system has triggered multi-pronged efforts in various jurisdictions to identify key factors contributing to the epidemic and address the unmet treatment needs of patients with opioid use disorder.

Safe and effective pharmaceutical alternatives to opioids could potentially have a significant impact on the opioid crisis and the treatment of chronic pain in Canada. Guidelines released in 2017 by the National Pain Centre at McMaster University recommend optimization of non-opioid pharmacotherapy and non-pharmacologic therapy before initiating treatment with opioids in patients with chronic non-cancer pain. Currently, there are several available non-opioid drugs that are used for the treatment of chronic pain, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitor antidepressants, and anticonvulsants. The use of these non-opioid drugs is also associated with adverse events, and the non-opioid drugs that are currently available in the market have not been able to eliminate the use of opioids in the treatment of chronic pain. There are, however, several non-opioid drugs in development, some of which have been approved by regulatory agencies outside Canada (including, most notably, the FDA). It is important to identify and describe these emerging non-opioid drugs to evaluate if any could potentially replace or reduce the use of opioids in the treatment of chronic pain in Canada.
Objectives
The objective of this Environmental Scan is to identify pharmaceutically manufactured non-opioid drugs that are not yet available in Canada but have received approval from regulatory agencies outside Canada (e.g., the FDA), or which are in the late stages of development for the management of chronic non-cancer pain. This information is being identified because these emerging non-opioid drugs are likely to enter the Canadian market in the near future and could potentially have a significant impact on the opioid crisis and the treatment of chronic pain in Canada.

The following questions are addressed:

- What non-opioid drugs have been approved by regulatory agencies outside Canada (e.g., the FDA) or are in development for the management of chronic non-cancer pain?
- What is the indication (proposed indication, if currently in development) and mechanism of action of these drugs?
- What trials have been completed or are ongoing for these drugs?

Notes on exclusions (see further details in the Limitations section):

- The current Environmental Scan does not consider drugs approved in Canada for non-pain indications that may be used “off-label” for the management of pain.
- Medical cannabis and cannabis-derived products have traditionally been used to treat pain. However, they are not considered pharmaceutical-grade drugs by Health Canada and are therefore excluded from this Environmental Scan. Furthermore, purified or synthetic cannabinoid drugs currently available in Canada are outside the scope of this report, which is limited to drugs not yet approved in the country. Evidence available from CADTH on medical cannabis and cannabinoid drugs can be found at www.cadth.ca/cannabis.
- The following drugs were also excluded from this Environmental Scan:
  - Drugs that do not directly target pain signals, such as those targeting biochemical mediators of inflammation
  - Drugs compounded in pharmacies (i.e., not pharmaceutically manufactured)
  - Drugs developed and approved for the treatment of pain associated with cancer
  - Drugs used to treat acute or perioperative pain
  - New and emerging drugs targeting the opioid receptors.

Methods
The findings of this Environmental Scan are based on searching for non-opioid drugs used in the management of chronic non-cancer pain in online sources. Below is a description of the literature search strategy and information selection criteria that were used.

Literature Search:
A limited literature search was conducted using key resources, including MEDLINE via OVID, Embase via OVID, PubMed, and the Cochrane Library. Grey literature was identified by searching a selected list in the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters) — including the University of York Centre for Reviews and Dissemination databases and Canadian and major international health technology agencies — and through a focused Internet search. Methodological filters were applied to limit retrieval to clinical trials. The search was also limited to English language documents published between January 1, 2012 and September 29, 2017.
Information Selection:
A review of information from the literature search was conducted to identify non-opioid drugs that are not currently available in Canada. Drugs used in the treatment of chronic non-cancer pain that have received approval from regulatory agency outside Canada (e.g., the FDA) or that are in late-stage development with evidence of efficacy from phase II or phase III randomized controlled trials were selected.

Findings
A summary of the non-opioid drugs identified is presented in Table 1. Study details for the drugs that have either received approval from a regulatory agency outside Canada (which was the FDA, in all such cases) or are in phase III development and have received a Fast Track designation from the FDA are discussed in the text that follows.

Table 1: Non-Opioids for the Management of Chronic Non-Cancer Pain

<table>
<thead>
<tr>
<th>Drug (Other Names)</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Key Trials</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Severe Treatment-Refractory Chronic Pain</strong></td>
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<tr>
<td>Ziconotide (Prialt)</td>
<td>Jazz Pharmaceuticals</td>
<td>Selective blocker of N-type calcium channels to inhibit pain signalling at the level of the spinal cord</td>
<td>Three completed pivotal phase III trials (see study details in text below)</td>
<td>FDA approved in 2004 for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or intrathecal morphine.</td>
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<tr>
<td><strong>Osteoarthritis</strong></td>
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<tr>
<td>Tanezumab (Pf-04383119)</td>
<td>Pfizer/Eli Lilly</td>
<td>Humanized monoclonal antibody that selectively binds to pain-mediating nerve growth factor NGF</td>
<td>Four completed phase III trials (see study details in the text below)</td>
<td>FDA granted Fast Track designation in 2017. Ongoing phase III trials are evaluating subcutaneous administration.</td>
</tr>
<tr>
<td>Fasinumab (REGN4775)</td>
<td>Teva Pharmaceuticals/Regeneron Pharmaceuticals</td>
<td>Fully human monoclonal antibody that selectively binds to pain-mediating NGF</td>
<td>One completed phase II trial (abstract)</td>
<td>One ongoing phase II trial in patients with chronic low back pain.</td>
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<tr>
<td>CNTX-4975</td>
<td>Centrexion Therapeutics</td>
<td>Highly purified synthetic trans-capsaicin targets the capsaicin receptor (TRPV1) to inactivate local pain fibres that transmit pain signals to the brain</td>
<td>One completed phase III trial (abstract)</td>
<td>No ongoing clinical trials</td>
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</table>

* A process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs.
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<tr>
<th>Drug (Other Names) Route of Administration</th>
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| **Capsaicin 8%** *(Qutenza, NGX-4010)* Patch | Acorda Therapeutics | Highly selective TRPV1 channel agonist that reduces pain signalling in peripheral neurons[^36] | **Post-Herpetic Neuralgia:** Two pivotal phase III trials[^37,38] (see study details in text below)  
**HIV-Associated Neuropathy:** Two completed phase III trials[^39,40] (see study details in text below)  
**Diabetic Neuropathy:** One completed phase III trial[^41] (see study details in text below) | FDA approved in 2009 for the management of neuropathic pain associated with post-herpetic neuralgia[^42]  
One ongoing phase III trial in patients with osteoarthritis[^43] |
| **Vixotrigine** *(Raxatrigine, BIIB074, CNV1014802)* Oral | Biogen | Nav1.7-selective sodium-channel blocker that inhibits pain signalling in peripheral neurons[^44] | **Trigeminal Neuralgia:** One completed phase II trial[^44]  
One ongoing phase III trial[^45]  
**Lumbosacral Radiculopathy:** One completed phase II trial (abstract[^46])  
Two ongoing phase II trials[^47,48] | NA |
| **VM202** Intramuscular | VM Biopharma | Plasmid DNA (gene therapy) containing human HGF that induces angiogenesis and acts as a neurotrophic factor to repair the nerve damage associated with neuropathic pain[^49] | **Diabetic Neuropathy:** One completed phase II trial[^50]  
One ongoing phase III trial[^51] | NA |
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<tr>
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<tr>
<td><strong>Neuropathic Pain</strong></td>
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<tr>
<td><strong>Mirogabalin (DS-5565) Oral</strong></td>
<td>Daiichi-Sankyo</td>
<td>Selectively binds to the alpha-2 delta-1 subunit of calcium channels found in the nervous system in areas that mediate pain transmission and processing&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Diabetic Neuropathy: One completed phase II trial&lt;sup&gt;52&lt;/sup&gt; One completed phase trial (preliminary results)&lt;sup&gt;53,54&lt;/sup&gt; Post-Herpetic Neuralgia: One completed phase trial (preliminary results)&lt;sup&gt;55,56&lt;/sup&gt;</td>
<td>No ongoing clinical trials</td>
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<tr>
<td><strong>EMA401 Oral</strong></td>
<td>Novartis Pharmaceuticals</td>
<td>Highly selective angiotensin II type 2 receptor antagonist that may inhibit neuropathic pain signalling&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Post-Herpetic Neuralgia: One completed phase II trial&lt;sup&gt;57&lt;/sup&gt; One ongoing phase II trial&lt;sup&gt;58&lt;/sup&gt;</td>
<td>One ongoing phase II trial in patients with diabetic neuropathy&lt;sup&gt;69&lt;/sup&gt;</td>
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<tr>
<td><strong>CNTX-4975 Intra-articular injection</strong></td>
<td>Centrexion Therapeutics</td>
<td>Highly purified synthetic trans-capsaicin targets the capsaicin receptor (TRPV1) to inactivate local pain fibres that transmit pain signals to the brain&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Morton’s Neuroma (orphan disease): One completed phase II trial (abstract)&lt;sup&gt;60&lt;/sup&gt;</td>
<td>No ongoing clinical trials. FDA granted Fast Track designation in 2016&lt;sup&gt;61&lt;/sup&gt;</td>
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<tr>
<td><strong>Chronic Low Back Pain</strong></td>
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<tr>
<td><strong>Tanezumab (PF-04383119) Intravenous Infusion</strong></td>
<td>Pfizer/Eli Lilly</td>
<td>Humanized monoclonal antibody that selectively binds to pain-mediating nerve growth factor&lt;sup&gt;18&lt;/sup&gt;</td>
<td>One completed phase II trial&lt;sup&gt;62&lt;/sup&gt; (see study details in text below) Two ongoing phase III trials&lt;sup&gt;53,64&lt;/sup&gt;</td>
<td>FDA granted Fast Track designation in 2017&lt;sup&gt;12&lt;/sup&gt; Ongoing phase III trials are evaluating subcutaneous administration</td>
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<tr>
<td><strong>Chronic Migraine (Prevention)</strong></td>
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<tr>
<td><strong>Fremanezumab (TEV-48125, LBR-101, RN-307) Subcutaneous Injection</strong></td>
<td>Teva Pharmaceuticals</td>
<td>Human monoclonal antibody designed to inhibit the calcitonin gene-related peptide CGRP receptor, which plays a role in vasodilation, inflammation, and the transmission of pain in migraines&lt;sup&gt;65&lt;/sup&gt;</td>
<td>One completed phase III trial&lt;sup&gt;66&lt;/sup&gt; Three ongoing phase III trials&lt;sup&gt;67,69&lt;/sup&gt;</td>
<td>BLA submitted to the FDA in 2017 for the preventive treatment of chronic and episodic migraine&lt;sup&gt;70&lt;/sup&gt; One ongoing phase III trial in patients with chronic cluster headache&lt;sup&gt;71&lt;/sup&gt;</td>
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<tr>
<td><strong>Chronic Migraine (Prevention)</strong>*</td>
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<tr>
<td><strong>Galcanezumab</strong>&lt;sup&gt;a&lt;/sup&gt; (LY2951742) Subcutaneous Injection</td>
<td>Eli Lilly</td>
<td>Human monoclonal antibody designed to inhibit the CGRP receptor, which is believed to play a role in vasodilation, inflammation, and the transmission of pain in migraines&lt;sup&gt;72&lt;/sup&gt;</td>
<td>One ongoing phase III trial&lt;sup&gt;73&lt;/sup&gt; Preliminary phase III trial results&lt;sup&gt;72,74&lt;/sup&gt;</td>
<td>No completed phase II trials identified Two ongoing trials phase III in patients with chronic cluster headache&lt;sup&gt;75,76&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Eptinezumab</strong> (ALD 403) Intravenous Infusion</td>
<td>Alder Biopharmaceuticals</td>
<td>Human monoclonal antibody designed to inhibit the CGRP receptor, which is believed to play a role in vasodilation, inflammation, and the transmission of pain in migraine&lt;sup&gt;77&lt;/sup&gt;</td>
<td>One completed phase II trial (abstract)&lt;sup&gt;78,79&lt;/sup&gt; One ongoing phase III trial&lt;sup&gt;80&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Erenumab</strong> (Aimovig, AMG 334) Subcutaneous Injection</td>
<td>Amgen/Novartis</td>
<td>Human monoclonal antibody designed to block the CGRP receptor, which is believed to play a role in vasodilation, inflammation, and the transmission of pain in migraine&lt;sup&gt;81&lt;/sup&gt;</td>
<td>One completed phase II trial&lt;sup&gt;81&lt;/sup&gt;</td>
<td>No ongoing clinical trials</td>
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<sup>a</sup>Crisis is defined as headaches occurring at a rate of 15 days a month, of which eight or more are migraines. New monoclonal antibodies for migraine prevention were also reviewed in a recent CADTH Issues in Emerging Health Technology bulletin.<sup>82</sup>

BLA = Biologic License Application; CGRP = calcitonin gene-related peptide; HGF = hepatocyte growth factor; NA = not applicable; NGF = nerve growth factor; TRPV1 = transient receptor potential cation channel subfamily V member 1.
Ziconotide:
Ziconotide (Prialt, Jazz Pharmaceuticals) was approved by the FDA in 2004 for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or intrathecal morphine. Ziconotide is a synthetic conopeptide analgesic that acts by selectively blocking N-type calcium channels to inhibit pain signalling at the level of the spinal cord.

Key Trials in Patients with Severe Treatment-Refractory Chronic Pain:
The efficacy of ziconotide in the management of severe chronic pain was studied in three pivotal multi-centre, double-blind, placebo-controlled, randomized phase III trials.

Staats et al. assessed the effectiveness of intrathecal ziconotide in patients with refractory pain due to cancer or AIDS. Patients were randomly assigned to receive ziconotide titrated over five to six days followed by a five-day maintenance phase (n = 68) or the placebo (n = 40). The primary efficacy outcome was the mean percentage change in the Visual Analog Scale of Pain Intensity (VASPI) score from baseline to the end of the initial titration period. Mean VASPI scores improved by 53.1% (95% confidence interval [CI], 44.0% to 62.2%) in the ziconotide group and 18.1% (95% CI, 4.8% to 31.4%) in the placebo group (P < 0.001), with no loss of efficacy for ziconotide in the maintenance phase. The most common adverse effects associated with ziconotide were abnormal gait, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea, and vomiting.

Wallace et al. studied the effectiveness of intrathecal ziconotide in patients with severe chronic non-cancer pain who were unresponsive to conventional therapy. Patients were randomly assigned to receive ziconotide titrated over six days followed by a five-day maintenance phase (n = 169) or placebo (n = 86). The primary efficacy outcome was the mean percentage change in VASPI score from baseline to the end of the initial titration period. The mean per cent reductions in VASPI score from baseline were 31.2% and 6.0% for ziconotide- and placebo-treated patients, respectively (P ≤ 0.001). During the initial titration phase, a significantly greater percentage of patients in the ziconotide group reported adverse events, including abnormal gait, amblyopia, dizziness, nausea, nystagmus, pain, urinary retention, and vomiting, compared with the placebo group.

Rauck et al. evaluated intrathecal ziconotide (using a slower titration schedule over a three-week period and a lower maximum dose) for the management of severe chronic pain. Participants were randomly assigned to receive ziconotide (n = 112) or placebo (n = 108). The primary efficacy outcome was the mean percentage change in VASPI score from baseline to week 3. The authors reported a small but significant improvement in pain from baseline in the ziconotide-treated group (14.7%) relative to the placebo group (7.2%; P = 0.036). Ziconotide was better tolerated than in previous trials. However, significant adverse effects were still reported in the ziconotide group, including dizziness, confusion, ataxia, abnormal gait, and memory impairment. Discontinuation rates for adverse events were comparable for both groups.

Tanezumab:
Tanezumab (Pfizer/Eli Lilly) is a humanized monoclonal antibody that targets nerve growth factor (NGF), a neurotrophic protein that binds to receptors on peripheral nociceptive neurons that are involved in pain modulation. As a result, NGF cannot bind to these receptors, and pain signals are dampened.
In 2010, the FDA imposed a hold on all clinical trials of NGF monoclonal antibodies due to reports of rapidly progressive osteoarthritis and osteonecrosis leading to joint replacement. The hold was subsequently extended due to the observation of sympathetic nervous system toxicity in pre-clinical animal models. A dose-response relationship as well as concomitant NSAID use were found to be contributing factors to the development of these adverse events. In 2015, the hold was lifted subject to the following conditions: increased patient surveillance for joint adverse events and sympathetic nervous system dysfunction; limits on NSAID use during treatment with NGF monoclonal antibodies; a restriction to patients who were unresponsive to or intolerant of multiple standard-of-care analgesics; dose limitations; and pre-enrolment radiographic imaging to exclude patients with pre-existing shoulder, hip, and knee joint abnormalities. In 2017, the FDA granted tanezumab Fast Track designation in order to expedite review of its clinical efficacy and safety for the management of pain in patients with osteoarthritis or chronic low back pain.

**Key Trials in Patients with Osteoarthritis of the Knee or Hip:**

Four multi-centre, double-blind, randomized phase III trials have evaluated the efficacy of intravenous tanezumab versus placebo or active controls for reducing pain in patients with osteoarthritis of the hip or knee. Patients were randomized to treatment with tanezumab (2.5 mg, 5 mg, or 10 mg) or placebo at eight-week intervals for 16 weeks, with follow-up at 32 weeks. The co-primary efficacy end points were defined as the changes from baseline to week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale, the WOMAC Physical Function subscale, and the patient's global assessment. Each tanezumab group showed significant improvement for the three co-primary end points versus placebo ($P \leq 0.001$ for all). Compared with placebo, the incidence of adverse effects was greater overall in the tanezumab groups. Patients who received a 10 mg dosage experienced the largest proportion of adverse events, which included abnormalities of peripheral sensation such as paresthesia and hypoesthesia. Total joint replacements were reported in eight patients (five out of the 466 patients receiving therapy with tanezumab and three out of the 155 patients receiving placebo). In a corresponding study, the same research team used an identical study design to investigate the analgesic effect of tanezumab versus placebo in patients with osteoarthritis of the hip and knee ($n = 690$). Findings were similar to those from the previous trial, showing all tanezumab dosages to be significantly superior to placebo ($P \leq 0.015$ for all). Abnormal peripheral sensations, most commonly paresthesia and hypoesthesia, were reported more frequently among patients receiving the two highest dosages in the tanezumab treatment group (0.6%) than among patients in the placebo group (0%). Total joint replacements were reported in four patients (three out of the 518 receiving therapy with tanezumab and out of the 172 receiving placebo).

Spierings et al. compared the effect of two doses of tanezumab (5 mg or 10 mg at eight-week intervals) with controlled release oral oxycodone (10 mg to 40 mg every 12 hours) or placebo in 610 patients with osteoarthritis of the hip or knee. The primary end point was the mean change from baseline to week 8 in the WOMAC Pain score. Both tanezumab groups demonstrated significant improvements in the WOMAC Pain score versus placebo ($P < 0.001$) and oxycodone ($P \leq 0.018$). Adverse event frequency was higher with oxycodone (63.3%) than with tanezumab (40.7% to 44.7%) or placebo (35.5%); serious adverse event frequency was similar among treatments. The adverse event of abnormal peripheral sensation was reported more frequently in the tanezumab groups than in the placebo or oxycodone groups. Across all
treatments, 0% to 1.3% of patients had new or worsened abnormality at the last neurological examination that the investigator considered clinically significant. Hip osteonecrosis reported in two patients in the tanezumab 10 mg group led to total joint replacements. However, a treatment-blinded external adjudication committee did not confirm osteonecrosis in either patient. The committee concluded that one patient had rapidly progressive osteoarthritis and the other had normally progressing osteoarthritis.21

Schnitzer et al. evaluated whether a large cohort of patients with knee or hip osteoarthritis pain (n = 2,700) would receive greater benefit when tanezumab monotherapy replaced or was co-administered with NSAIDs.22 Patients received tanezumab (5 mg or 10 mg) every eight weeks for 16 weeks, with or without oral naproxen (500 mg twice daily) or celecoxib (100 mg twice daily), and this treatment regimen was compared with the same dosages of naproxen or celecoxib alone. Efficacy was assessed as the change from baseline to week 16 in three co-primary end points: the WOMAC Pain subscale, the WOMAC Physical Function subscale, and the patient’s global assessment of osteoarthrosis. Results showed that all tanezumab treatments provided significant improvements in the WOMAC Pain and Physical Function subscale scores over either NSAID alone. Only tanezumab in combination with NSAIDs provided a significant improvement versus NSAIDs for the patient global assessment of osteoarthrosis outcomes. Combination treatment did not substantially improve pain or function over tanezumab monotherapy. There was a higher incidence of paresthesia, hypoesthesia, arthralgia, and peripheral edema in all groups treated with tanezumab compared with NSAIDs alone, with the combination tanezumab and NSAID groups generally having the highest frequencies. Higher incidence of all-cause total joint replacements occurred with tanezumab in combination with an NSAID versus tanezumab or NSAID monotherapy. The incidence of rapidly progressive osteoarthritis was significantly greater in all tanezumab groups versus groups receiving NSAID monotherapy, except among those receiving tanezumab 5 mg monotherapy (0.19% among patients receiving NSAID monotherapy, 0.74% among patients receiving tanezumab 5 mg, 1.29% among patients receiving tanezumab 10 mg, 1.68% among patients receiving tanezumab 5 mg plus NSAID, and 2.4% among patients receiving tanezumab 10 mg plus NSAID).

There is preliminary evidence that the efficacy and safety of tanezumab following subcutaneous administration is similar to that of intravenous administration in patients with osteoarthritis of the knee or hip.37 Three pivotal phase III trials are currently studying the safety and efficacy of subcutaneous tanezumab compared with placebo23,25 or celecoxib24 for the management of osteoarthritis of the hip or knee. The trials are estimated to be complete in 2018 or 2019.

Key Trials in Patients with Chronic Low Back Pain:
Kivitz et al. investigated the efficacy and safety of intravenous tanezumab for chronic low back pain in a multi-centre, double-blind, randomized phase II trial.62 Patients (n = 1,347) were randomized to receive tanezumab (5 mg, 10 mg, or 20 mg every eight weeks) or naproxen (500 mg twice daily) and were compared with a placebo group. The primary efficacy end point was defined as the mean change in daily average low back pain intensity from baseline to week 16. Tanezumab 10 mg and 20 mg had similar efficacy profiles and significantly improved low back pain intensity versus both placebo and naproxen (P ≤ 0.05). The incidence of adverse events was comparable across tanezumab dosages but higher than among patients receiving the placebo or naproxen. Arthralgia, pain in the extremities, headache, and paresthesia were the most commonly reported adverse events among tanezumab-treated patients. There were no reports of osteonecrosis or total joint replacements for any reason in this study.
Two pivotal phase III trials are currently studying the safety and efficacy of subcutaneous tanezumab compared with prolonged release tramadol or NSAIDs for the management of chronic low back pain. Both trials are estimated to be completed in 2019.

**Capsaicin Patch:**
The capsaicin 8% patch (Qutenza, Acorda Therapeutics) was approved by the FDA in 2009 for the management of neuropathic pain associated with post-herpetic neuralgia. The patch contains a high concentration of synthetic capsaicin, a highly selective transient receptor potential cation channel subfamily V member 1 agonist that reduces pain signalling in peripheral neurons.

**Key Trials in Patients with Post-Herpetic Neuralgia:**
The efficacy of the capsaicin patch in patients with post-herpetic neuralgia was established in two pivotal multi-centre, double-blind, randomized 12-week phase III trials. The primary efficacy end point for both trials was the percentage change in the Numeric Pain Rating Scale (NPRS) score from baseline to weeks two through eight.

Backonja et al. randomly assigned participants to receive either one 60-minute application of the capsaicin 8% patch (n = 206) or a capsaicin 0.04% control patch (n = 196). Participants receiving treatment with the capsaicin 8% patch had a significantly greater reduction in pain during weeks two through eight, with a mean change in NPRS score of −29.6% versus −19.9% with the control patch (treatment difference: −9.7%; 95% CI, −15.47 to −3.95; P = 0.001). The most common adverse effects with the capsaicin 8% patch included self-limiting mild-to-moderate erythema and pain at the site of application.

Irving et al. randomly assigned participants to receive a single 60-minute application of the capsaicin 8% patch (n = 212) or a capsaicin 0.04% control patch (n = 204). Recipients of the capsaicin 8% patch had a significantly greater mean reduction in pain from baseline during weeks 2 through 8 compared with the control group (32.0% versus 24.4%; P = 0.011). Most treatment-emergent adverse events were application site–specific (notably erythema and pain), transient, and generally mild-to-moderate in severity.

**Key Trials in HIV-Associated Distal Sensory Polyneuropathy:**
Two multi-centre, double-blind, randomized 12-week phase III trials evaluated the efficacy of the capsaicin patch for management of HIV-associated distal sensory polyneuropathy. The primary efficacy end point for both trials was the percentage change in the NPRS score from baseline to weeks 2 through 12.

Simpson et al. randomized patients to receive the capsaicin 8% patch (n = 225) or a capsaicin 0.04% control patch (n = 82). Either patch was applied once for 30, 60, or 90 minutes to painful areas on the feet. Overall, patients receiving treatment with the capsaicin 8% patch had a mean reduction in pain of 22.8% during weeks 2 through 12 compared with a 10.7% reduction for patients receiving the control (P = 0.0026). Mean pain reductions in the capsaicin 8% patch 30-, 60-, and 90-minute groups were 27.7%, 15.9%, and 24.7%, respectively (P = 0.0007, 0.287, and 0.0046, respectively, versus the control). The most common adverse effects were self-limited mild-to-moderate local skin reactions.

Clifford et al. randomly assigned participants to receive a single 30-minute or 60-minute application of the capsaicin 8% patch (n = 332) or a 0.04% capsaicin control patch (n = 162). Overall, results did not show a significant difference between groups in pain reduction (~29.5%...
with the capsaicin 8% patch versus −24.5% with the control patch; \( P = 0.097 \). Mild-to-moderate transient application site pain and erythema were the most common adverse effects.

**Key Trials in Patients with Diabetic Peripheral Neuropathy:**

Simpson et al. evaluated the efficacy and safety of the capsaicin 8% patch in patients with painful diabetic peripheral neuropathy in a multi-centre, double-blind, randomized 12-week phase III trial. Patients were randomized to receive one 30-minute treatment with the capsaicin 8% patch (n = 186) or a placebo patch (n = 183) on painful areas of the feet. The primary efficacy end point was the percentage change in the NPRS score from baseline to weeks 2 through 8. Mean pain reduction was statistically significant for the capsaicin 8% patch versus placebo (–27.4% versus −20.9%; \( P = 0.025 \)). The most common treatment-emergent adverse effect was application site pain of mild-to-moderate severity.

**Summary Statistics:**

The following figures illustrate the identified non-opioid drug distribution by indication, molecule type, development phase, and route of administration.

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**Figure 1 Distribution by Indication**

- Refractory Chronic Pain: 20%
- Osteoarthritis: 27%
- Neuropathic Pain: 6%
- Chronic Low Back Pain: 7%
- Chronic Migraine: 40%

**Figure 2 Distribution by Molecule Type**

- Small Molecules: 46%
- Monoclonal Antibodies: 46%
- Gene Therapy: 8%
Limitations

The findings of this Environmental Scan present an overview of non-opioid drugs that are not currently available in Canada, but which have been approved by regulatory agencies outside of Canada (e.g., the FDA) or completed phase II or III development; they do not represent a comprehensive review of all the non-opioid drugs being investigated for the treatment of chronic pain. Drugs with analgesic properties that may also be of interest to health care providers but were considered beyond the scope of this Environmental Scan include the following:

- Oral cannabinoids that are currently available in Canada (such as nabiximols and nabilone) or various non-pharmaceutical preparations of cannabis that have been investigated in clinical trials.88
- Compounded formulations, including creams, gels, and patches that are not commercially available in Canada89 (Topical therapies may contain one or a combination of drugs,
including NSAIDs, lidocaine, gabapentin, ketamine, and amitriptyline.90 Patches containing varying concentrations of lidocaine or diclofenac are also being used91.

- Drugs that are be used off-label for pain while being approved for indications other than pain in Canada, such as clonidine administered through an epidural, intrathecal, or local/topical route.92

The submission status or marketing plans in Canada for the identified drugs were not investigated in this Environmental Scan. Critical appraisal of the evidence and information on cost-effectiveness or other economic assessments were also beyond the scope of this report.

**Conclusion**

There are several non-opioid drugs not yet available in Canada that either have been approved by a regulatory agency outside Canada (e.g., the FDA) or are in clinical development for the management of chronic non-cancer pain. Ziconotide and the capsaicin 8% patch have been approved by the FDA for severe treatment-refractory chronic pain or post-herpetic neuralgia, respectively. The majority are in phase III clinical development for the indications of neuropathic pain, chronic migraine, or osteoarthritis. Novel biologic drugs make up more than half of the new products in development; human monoclonal antibodies constitute the bulk of this category, which also includes a gene therapy product. Of the non-opioid drugs currently in the pipeline for the management of chronic non-cancer pain, tanezumab appears to be the closest to receiving FDA approval for the management of patients with osteoarthritis or chronic low back pain.

This Environmental Scan has identified emerging non-opioid drugs that could enter the Canadian market and have a significant impact on the opioid crisis in Canada. Further assessment of the clinical effectiveness and cost-effectiveness of these novel drugs is needed to understand their potential to replace or reduce the use of opioids in the management of chronic non-cancer pain.

This Environmental Scan is just one of many reports that CADTH has completed to inform and guide decisions related to pain management and opioids as part of our commitment to the [Joint Statement of Action to Address the Opioid Crisis in Canada](https://www.cadth.ca). These reports, including many on non-opioid options for the management of pain, can be found in the [Pain](https://www.cadth.ca) and [Opioid Evidence Bundles](https://www.cadth.ca), available free of charge on the CADTH website.
References


70. Teva Announces Submission of Biologics License Application for Fremanezumab to the U.S. FDA [Internet]. Tivka (IL): Teva Pharmaceutical Industries Ltd.; 2017 Oct 17. [cited 2017 Nov 3].


85. Mullard A. Drug developers reboot anti-NF


