A Novel Therapeutic Approach to Chronic Low Back Pain

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CASE STUDY:

Nancy is a 42-year-old woman who works in a day-care centre looking after children aged 3-6 years. She injured her low back nine months ago picking up one of the children. Since that time, she has had dull pain localized to the central low back, with some radiation to the left buttock. There is no leg pain. Prior to this episode, she had minor twinges of low back pain when lifting or carrying, but these always settled quickly without needing medical attention.

After the incident, Nancy took six weeks off work, during which time she tried rest, stretching exercises, heat and cold, and had a course of physiotherapy and chiropractic care with limited benefit. She returned to work on modified duties, but continues to experience difficulties. There is some pressure from her employer to return to full duties.

Currently, she takes acetaminophen 500 mg tablets as needed, averaging four per day. She has also used ibuprofen tablets, over the counter, 400 mg up to t.i.d. She had some codeine 30 mg tablets left over from prior dental work, but these were of little benefit and resulted in constipation, which aggravated her back pain.

Nancy is otherwise well, although she has gained 15 pounds due to reduced activity since her back pain began. She has no lower extremity weakness or sensory loss, no fever, and no impairment of bowel or bladder control. There is no history of direct trauma to the back. Her pain improves with rest and worsens with activity. Plain X-rays of her lumbar spine taken after three months of symptoms were normal, other than minor degenerative spurring at the L4-5 level.

Patient Evaluation

Based on a nine-month duration of symptoms, Nancy has chronic low back pain. She has no red flag symptoms suggesting etiologies such as tumour, infection, fracture, inflammatory spinal arthritis or spinal cord compression. Her back pain fits into the pattern of non-specific mechanical low back pain. She rates her pain intensity on the 11-point numerical rating scale (NRS) as 7 at worst, 3 at best, and 5 on average. This fits into the moderate pain category.

Pain is affecting her function at work and also limiting leisure activities, such as dancing and going to the gym. This has led to weight gain and deconditioning. Her sleep is sometimes impaired. She admits to feeling a bit down in terms of mood, but there is no history of prior depression. Yellow flags for psychosocial factors which might prolong her pain are absent. There is no history of substance abuse, and her score on the Opioid Risk Tool is 0. She enjoys her work with children, and would like to return to full function.

Patient Treatment Plan

The goals of Nancy's treatment are: decrease pain, improve function, allow her to return to full duties at work, and enable her to participate in the social and leisure activities that she enjoys. At the same time, side effects of treatment are to be kept to a minimum.

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A combination of non-pharmacologic and pharmacologic treatments is always required. Non-pharmacologic treatments would include an exercise program to improve core stability and abdominal muscle strength, diet to return to her baseline weight, and education on proper back posture and lifting techniques. Meditation and relaxation techniques may also be helpful.

Pharmacologic therapy for chronic low back pain should aim for improvement across the 24 hours of each day. Prior therapy with simple analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and codeine has not been effective. A controlled-release pain medication is often useful in this situation, improving compliance while minimizing sleep disturbance and maintaining steady pain control through the day and night.

Patient Follow-up

Nancy initiates a program of exercise, diet and relaxation training. She is started on extended-release tramadol (tramadol ER) at 100 mg/day. After two weeks, this is increased to a dose of 200 mg/day. She finds this provides 24-hour improvement in pain, with better sleep and improved mood. Her pain is reduced to a worst score of 5 and a best score of 2 on the NRS, with an average score of 3.

Nancy's function greatly improves and she is able to resume full duties at work. She also returns to dancing and socializing with her friends better than previously. Side effects of tramadol ER* included initial mild somnolence and nausea, which settled within 10 days. Mild constipation was noted as well, but settled with an increase in dietary fibre and fluid consumption.

*Please refer to respective Product Monograph for inclusive lists of all side effects.

Introduction

The majority of individuals with chronic non-cancer pain (CNCP) experience pain at more than one site, with the back the most commonly reported site of chronic pain.[1] In a Canadian survey, physicians estimated that 95% of CNCP patients in their practices complained of back pain, followed by pain in the knees (49%), neck (37%), head (36%), and hips (34%).[2] Overall, back pain is the second most common chronic condition in Canada after non-food allergies, followed closely by arthritis/rheumatism.[3]

Back pain is often caused by stresses on the muscles and ligaments that affect the spine. While back pain can occur at any point on the spine, the lower back is most commonly affected since it bears the most weight and physical stress.[4] The prevalence of a history of low back pain is high. In Canadian and North American studies, up to 80% of people experienced acute low back pain at some point in their lifetime.[5,6,7]

While the majority of acute cases of low back pain resolve within three to four weeks, 10% to 40% of cases develop into chronic low back pain (CLBP).[7] CLBP typically refers to pain that lasts for longer than 12 weeks. Attempts to identify specific anatomical sources of low back pain have proven difficult in clinical practice, as pain is highly subjective and classification schemes frequently conflict with one another.[8] Given the large percentage of patients diagnosed with "non-specific" CLBP, inconsistencies in the management of their pain undoubtedly arise.

Evaluating CLBP

As recommended by the American College of Physicians, American Pain Society and *Réseau provincial de recherché en adaptation et en réadaptation du Québec* (*REPAR/FRSQ*), physicians assessing CLBP should perform a focused patient history and physical examination to determine the likelihood and presence of specific neurological conditions.[8,9]

A clinician should evaluate the following:

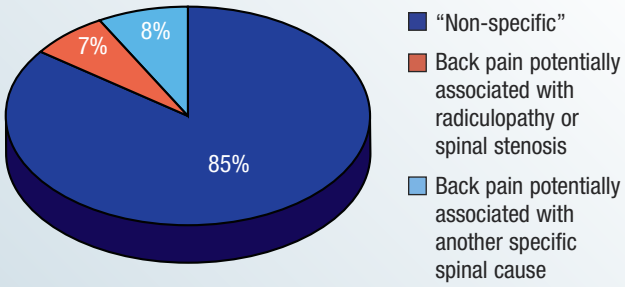
- Duration of symptoms,
- Risk factors for potentially serious conditions,
- Symptoms suggesting radiculopathy or spinal stenosis,
- Presence and severity of neurologic deficits, and
- Psychosocial risk factors.

Following this evaluation, and to facilitate subsequent decision making, patients can be classified into one of three categories[8,9]:

1. Non-specific (simple) low back pain,
2. Back pain potentially associated with radiculopathy or spinal stenosis,
3. Back pain potentially associated with another specific spinal cause.

Diagnosis of CLBP that is potentially associated with a specific, identifiable condition may require a number of diagnostic imaging techniques (*e.g.*, magnetic resonance imaging [MRI] or computerized tomography [CT]), as well as surgery or spinal injections.[8] The majority (85%) of cases of CLBP, however, are classified as "non-specific" (Figure 1); imaging or other diagnostic tests are therefore not recommended in these patients.[8,10] There is currently no evidence to suggest that a specific anatomical diagnosis improves patient outcomes in patients correctly classified as having non-specific CLBP.[8,9] Instead, treatment should focus on improving the patient's symptoms, such as pain intensity, physical function and quality of life.

FIGURE 1 Prevalence of CLBP Classifications



Adapted from Chou R et al. Ann Intern Med 2007; 147(7):478-91.

The Treatment Gap

CLBP usually arises between the ages of 30 and 50, and can have a dramatic impact on these patients' quality of life.[11] Patients with moderate to severe CNCP often face unemployment or a reduction in pay, causing a great deal of emotional and financial strain.[12] An appropriate long-term strategy to manage CLBP is therefore extremely important to allow these patients to regain function and return to work.

While a specific diagnosis may not be necessary to improve patient outcomes, it is important to assess the severity of a patient's pain to determine the optimal therapeutic approach. A variety of tools have been developed to allow patients to best describe their pain. The 11-point visual analogue or numeric rating scale is often used to measure pain intensity in patients with CLBP, where 0 is "no pain" and 10 is "severe pain".[13,14]

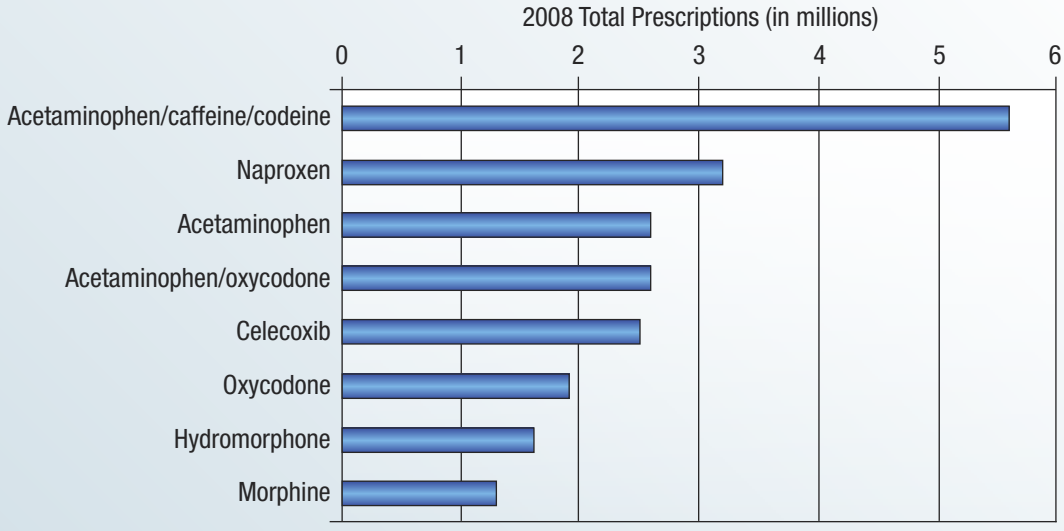
In particular, moderate to severe CNCP in Canada reportedly affects 25% to 33% of all Canadians.[2,12] In a 2004 survey, primary care practitioners considered moderate to severe chronic pain to not be well managed in 60% of patients; only 1% considered it to be well managed.[2] In this same survey, fewer than 50% of Canadians with chronic pain reported taking a prescription analgesic. In fact, approximately two-thirds of patients with moderate chronic pain and one-third of patients with severe chronic pain were taking no prescription medication at all.[2] While an unacceptable number of patients with moderate or severe chronic pain remain untreated, physicians prescribe analgesics for severe pain more often than for moderate pain. Similarly, given the high prescription levels of NSAIDs and cyclooxygenase-2 (COX-2) inhibitors in Canada (see Figure 2),[15] physicians also prescribe analgesics for mild pain more often than for moderate pain.

These findings reflect the "treatment gap" experienced by patients with moderate to moderately severe chronic pain, who are often left untreated, undertreated, or inappropriately treated. Reasons for the "treatment gap" may include barriers to prescribing opioids, such as fear of addiction and abuse, regulatory scrutiny, the subjective nature of pain, or the abundance of treatment options.[16]

Therapeutic Approach to CLBP

A multimodal therapeutic approach to CLBP is advocated, and may include rehabilitation, spinal injections, surgery and pharmacological treatments.[17] While pharmacologic treatments are administered for the purpose of alleviating pain symptoms, both pharmacologic and non-pharmacologic treatments primarily focus on increasing functionality. Both also aim to improve the quality of life of the patient. Recall that the main goals of pain treatment are to relieve pain, increase physical function, and improve quality of life.

FIGURE 2 Most Prescribed Prescription Analgesics in Canada in 2008



Adapted from Carter B, Campeau L. Pharmacy/Practice 2009; Feature: 30-8.

Non-pharmacologic Options for CLBP

Primary non-pharmacologic treatment options for CLBP include educating patients on their diagnosis and treatment options, advising patients to remain active, and providing options for self-treatment of their pain (*e.g.*, heating pads for short-term relief of acute back pain). These are less expensive options and may only be slightly inferior to other interventions.[8,10]

For patients who do not improve with self-care options, clinicians may consider*:

- Intensive rehabilitation
- Exercise therapy
- Acupuncture
- Massage therapy
- Spinal manipulation
- Yoga
- Cognitive-behavioural therapy
- Progressive relaxation.

Non-pharmacologic treatments are primarily prescribed in cases of acute or mild CLBP, or as adjunctive therapy to the pharmacologic options in moderate to severe cases of CLBP.

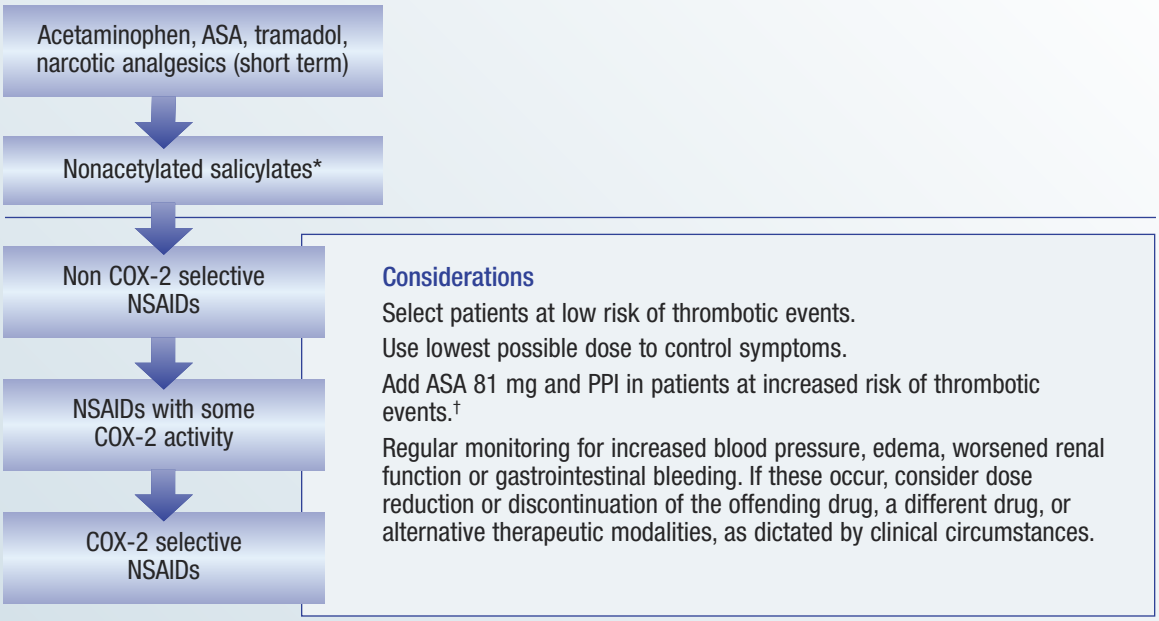
*Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens).

Pharmacologic Options for CLBP

When treating CLBP, physicians must weigh the benefits and risks associated with each analgesic before choosing an appropriate treatment for their patient. NSAIDs and COX-2 inhibitors are known to be associated with gastrointestinal (GI) and renal toxicity, as well as an increased risk of cardiovascular (CV) complications.[18] The American Heart Association (AHA) does not recommend using NSAIDs/COX-2 inhibitors as a first-line treatment in patients with known CV disease or risk factors for ischemic heart disease (Figure 3).[18] In fact, the European Medicines Agency and Health Canada issued the recommendation that all patients—regardless of CV/GI risk—take the lowest dose of NSAID/COX-2 inhibitor for the shortest period of time in order to effectively control symptoms.[18,19]

Unlike NSAIDs, long-term therapy with opioid analgesics does not cause organ damage and is not associated with GI bleeding or CV risks.[16] Some health-care professionals may be hesitant to prescribe opioids due to fears of addiction, diversion and regulatory scrutiny.[16] These fears have been reinforced by the growing problem of opioid misuse in Canada. Between 1997 and 2004, the number of opioid-related deaths in Canada doubled.[20] The rising

FIGURE 3 Stepped Care Approach to Pharmacologic Therapy for Musculoskeletal Symptoms with Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease



*Not available in Canada

†Addition of ASA may not be sufficient protection against thrombotic events.

ASA: acetylsalicylic acid; PPI: proton-pump inhibitor

Adapted from Antman EM et al. Circulation 2007; 115(12):1634-42.

number of prescriptions for drugs containing oxycodone has received particular attention, with prescriptions soaring by 850% between 1991 and 2007.[20] Respiratory depression, sedation and severe constipation are also commonly associated with this class, and can be a particular concern when treating opioid-naïve or elderly patients.[16]

In spite of their drawbacks, NSAIDs, COX-2 inhibitors and traditional opioids still play a role in managing CLBP. When used correctly in the appropriate patient populations, these analgesics are generally safe and effective. However, a substantial unmet need still remains for effective and safe pain medications that can be used long-term to treat moderate to moderately severe CLBP.

Tramadol—An Atypical Opioid

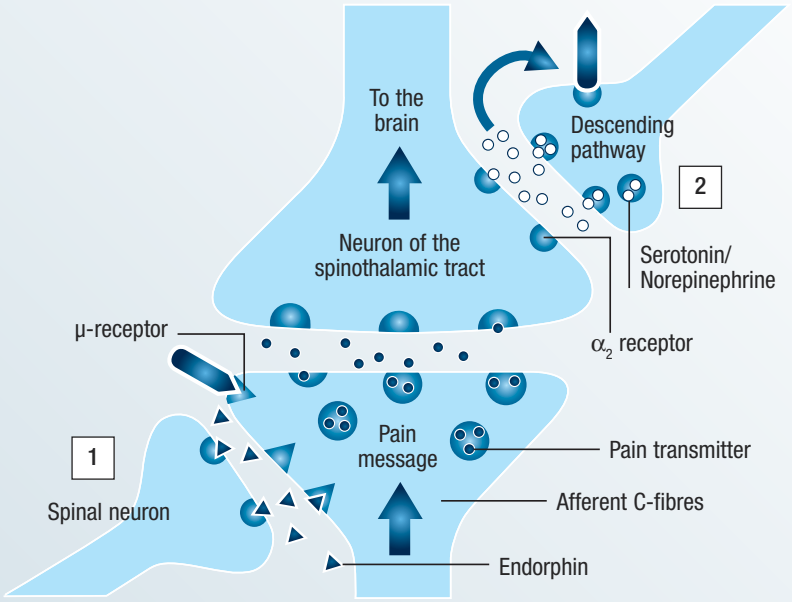
Tramadol, one of the newest opioid analgesics on the Canadian market, is classified as an "atypical" centrally acting opioid analgesic. This is due to its unique mechanism of action, which combines both opioid and non-opioid components. In fact, the majority (two-thirds) of tramadol's analgesic effect is mediated through noradrenergic and serotonergic pathways, whereas its opioid effect is dependent on its conversion to an active metabolite (M1; Figure 4). This unique pharmacology distinguishes tramadol from traditional opioids such as morphine or codeine.[21]

In comparison to other opioids, tramadol has a significantly weaker binding affinity for the μ-opioid receptor, with one-six-thousandth the potency of morphine.[22] Tramadol's active M1 metabolite is produced via hepatic metabolism (CYP2D6) and has a greater affinity for the μ-opioid receptor, making it primarily responsible for tramadol's opioid-related analgesia.[22] Despite its greater binding affinity, M1's potency is still only similar to codeine, which is approximately one-tenth the potency of morphine.[23]

Tramadol OD in the Management of CLBP

In 2005, an immediate release (IR) tramadol/acetaminophen formulation became available in Canada,

FIGURE 4 Suggested Dual Mechanism of Action of Tramadol Once Daily



1. Weak inhibition of reuptake of norepinephrine (NE) and serotonin (5-HT), which contributes to approximately two-thirds of tramadol's analgesic effect.[38,39]
2. Weak binding to μ-opioid receptors by the M1 metabolite, which contributes to approximately one-third of tramadol's analgesic effect. [38,39]

Adapted from Schug SA. Ther Clin Risk Manag 2007; 3(5):717-23.

followed by three once-daily (OD) tramadol formulations in 2007. Recently, another tramadol IR product (50 mg tablets) has received approval in Canada.[24]

Tramadol OD is indicated for the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more.[22,25,26] This broad indication applies to a number of chronic pain conditions commonly seen in clinical practice (Table 1).

Tramadol OD is available in 100, 150, 200, 300 and 400 mg dosage strengths.[22,25,26] Although titration may occur relatively rapidly (2, 5, 7 days depending on the formulation) studies have shown that a slower 10-day titration reduces discontinuations due to adverse events.[27]

The convenience of a once-daily dosing schedule allows improved patient adherence compared to multiple-daily dosing schedules because of an easier pill count.[28,29] Monitoring of proper use by pill count is also easier with a once-daily formulation. Unlike multiple-dosing regimens, once-daily opioid analgesics also offer around-the-clock pain relief.[29] This is particularly important to prevent breakthrough pain episodes, since opioid concentrations are maintained within a patient-specific effective range over 24 hours—likely due to more uniform opioid concentrations and fewer fluctuations.[29] Once-daily opioids also offer improved sleep; patients awaken less frequently due to breakthrough pain or to take additional doses of analgesic, contrary to what is observed with short-acting opioids or non-opioid analgesics.[29]

In clinical studies, the safety and efficacy of tramadol formulations available in Canada have been confirmed in approximately 8,000 patients with moderate to moderately severe chronic pain.[22,25,26,30] In particular, tramadol ER was found to be safe and effective in a homogenous population of 619 patients with moderate to severe CLBP.[31] This 12-week, randomized, double-blind, placebo-controlled trial found that pain intensity decreased by greater than 50% in patients who received tramadol ER 300 mg during an open-label run-in, and this improvement

TABLE 1 Common Chronic Pain Conditions

- Low back pain
- Osteoarthritis (OA)
- Fibromyalgia
- Neuropathic pain
- Rheumatoid arthritis (RA)*
- Cancer-related pain

*Effective anti-inflammatory treatment still required.

Reviewed in Canadian Pain Society 2007.

TABLE 2 Tramadol Once Daily: Contraindications

Tramadol OD is contraindicated:

- In patients who have previously demonstrated hypersensitivity to tramadol, opioids, or any other component of the formulation.
- In any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol OD may worsen central nervous system and respiratory depression in these patients.
- With concomitant MAOIs (or within 14 days of such therapy).
- In severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C).[22,25,26]

was maintained more effectively over a 12-week period compared to placebo ($p = 0.009$). These patients also reported significant improvements in function and sleep quality.

Patients taking tramadol ER (300 mg) saw significant reductions in their scores on the Roland Disability Index ($p < 0.001$). The Roland Disability Index is a good predictor of the impact of pain on activities of daily living. This 24-question survey assesses a patient's level of disability in completing everyday chores, such as needing to use a handrail to get up stairs, lying down to rest more often than usual, getting dressed more slowly, and having to change positions frequently to stay comfortable.[32] In addition to limiting the functionality of the patient, chronic pain has a debilitating effect on sleep quality. Poor sleep affects 64% to 88% of patients with chronic pain, and can have a significantly negative impact on quality of life.[33] Patients with CLBP who received tramadol ER (200 and 300 mg) saw a significant improvement in overall sleep quality compared to placebo ($p = 0.001$; $p = 0.008$).[31]

Tramadol Long-term Safety

Tramadol is now available in more than 100 countries and has an exposure of approximately 1 billion patient treatment days per year worldwide.[12] Globally, tramadol has been used for over 30 years and has been found to be generally safe. Unlike NSAIDs/COX-2 inhibitors, tramadol is not associated with an elevated risk of GI, CV or renal toxicity.[34]

Tramadol OD shares some common adverse events with typical opioids, such as nausea, dizziness and constipation.[22,25,26] Unlike typical opioids, tramadol's opioid-dependent analgesia accounts for only one-third of its effect. The incidence of constipation with tramadol is therefore expected to be significantly lower compared with traditional opioids; this is in fact what is observed in clinical trials with tramadol ER, wherein constipation was reported in 17.9% of tramadol-treated patients versus 3.8% of placebo-treated patients.[22] In comparison, up to 100% of patients who take morphine will experience constipation.[35]

Contraindications for tramadol OD are shown in Table 2.[22,25,26] Moreover, concomitant use of selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs) and other tricyclic compounds (*e.g.*, cyclobenzaprine, promethazine, etc.), or neuroleptics increases the seizure risk and these combinations should be used with caution.[22]

Serotonin syndrome has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and monoamine oxidase inhibitors (MAOIs).[22] This condition may include symptoms of mental status change, hyper-reflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma.[22]

Tramadol's unique pharmacology discourages misuse. The abuse and diversion risk of tramadol has been extensively evaluated using data from epidemiological and post-marketing surveillance studies.[12] The overall consensus is that the risk of abuse/addiction with tramadol is low,[36,37] with a reported abuse rate of approximately one case per 100,000 patients.[37]

Tramadol OD—Bridging the Gap

CLBP is a common condition affecting Canadians. Patients with CLBP should be thoroughly evaluated

for specific neurological conditions. However, the majority (85%) of CLBP is classified as nonspecific, therefore, imaging or other diagnostic tests are not recommended in these patients.[8] As there is currently no evidence to suggest that a specific anatomical diagnosis improves patient outcome, the therapeutic approach should instead focus on improving the patient's symptoms based on the severity of their pain.[8] Moderate to severe chronic pain is of particular importance because, despite its high prevalence, it has been shown to be undertreated and not well managed in Canada.[2] Tramadol, an atypical opioid analgesic, has over 30 years experience worldwide in the management of moderate to moderately severe pain. For patients with CLBP, tramadol OD may be used long-term without the GI, CV or renal toxicity commonly associated with NSAIDs and COX-2 inhibitors. In CLBP, tramadol OD has demonstrated efficacy, reducing pain intensity by more than 50%, while improving overall function and sleep quality. Tramadol OD also offers a generally safe and effective alternative to traditional opioids, with less risk of respiratory depression, constipation and abuse.

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