

Early optimized pharmacological treatment in patients with depression and chronic pain

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Review

Cite this article: Oluboka OJ, Katzman MA, Habert J, Khullar A, Oakander MA, McIntosh D, McIntyre RS, Soares CN, Lam RW, Klassen LJ, and Tanguay R (2023). Early optimized pharmacological treatment in patients with depression and chronic pain. *CNS Spectrums* 28(2), 145–156.

<https://doi.org/10.1017/S1092852922000128>

Received: 27 September 2021

Accepted: 03 February 2022

Key words:

Antidepressant drugs; chronic pain; comorbidity; depression; depressive disorder; major

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Abstract

Major depressive disorder (MDD) is the leading cause of disability worldwide. Patients with MDD have high rates of comorbidity with mental and physical conditions, one of which is chronic pain. Chronic pain conditions themselves are also associated with significant disability, and the large number of patients with MDD who have chronic pain drives high levels of disability and compounds healthcare burden. The management of depression in patients who also have chronic pain can be particularly challenging due to underlying mechanisms that are common to both conditions, and because many patients with these conditions are already taking multiple medications. For these reasons, healthcare providers may be reluctant to treat such patients. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines provide evidence-based recommendations for the management of MDD and comorbid psychiatric and medical conditions such as anxiety, substance use disorder, and cardiovascular disease; however, comorbid chronic pain is not addressed. In this article, we provide an overview of the pathophysiological and clinical overlap between depression and chronic pain and review evidence-based pharmacological recommendations in current treatment guidelines for MDD and for chronic pain. Based on clinical experience with MDD patients with comorbid pain, we recommend rapidly and aggressively treating depression according to CANMAT treatment guidelines, using antidepressant medications with analgesic properties, while addressing pain with first-line pharmacotherapy as treatment for depression is optimized. We review options for treating pain symptoms that remain after response to antidepressant treatment is achieved.

Introduction

Major depressive disorder (MDD) is the leading cause of disability worldwide,¹ with an estimated global point prevalence of 4.7% and a 12-month prevalence of 3.7%.² In the United States in 2017, 7.1% of all adults had at least one major depressive episode,³ and in Canada, 11.3% of adults had a major depressive episode over their lifetime, with a 12-month prevalence rate of 4.7%.⁴

Patients with MDD have high rates of comorbidity with other mental conditions, such as anxiety disorders or substance abuse,⁵ and an increased risk of depression or depressive symptoms is reported in patients with general medical conditions including asthma,⁶ diabetes,^{7–9} cardiovascular disease,¹⁰ epilepsy,⁶ and chronic pain.^{11,12} Together with MDD, chronic pain conditions are associated with the greatest number of disability days per year at the population level among a wide range of mental and chronic physical conditions.¹³ The most recent prevalence estimate of chronic pain in Canada is 18.9%,¹⁴ while estimates from the United States suggest nearly 2 out of 3 patients with depression also have chronic pain.¹²

In 2017, the 3 leading causes of years lived with disability worldwide were low back pain, headache disorders, and depressive disorder.¹⁵ The estimated total annual cost of chronic pain in adults in the United States, including both direct healthcare costs and cost of lower worker productivity, is at least \$560 billion.¹⁶ In Canada, total annual healthcare spending for chronic pain management (direct costs only) was estimated to be \$7.2 billion (\$CAD).¹⁷ Depression with comorbid pain has been associated with increased economic burden through both increased costs and work disability.¹⁸ In a questionnaire given to patients (n = 1204) attending

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a specialty pain clinic in the United Kingdom, patients with depression reported significantly more visits to their general practitioner and increased likelihood of seeking care from other doctors, using emergency room services, and being admitted to the hospital, compared with patients with pain who did not have depression.¹⁹

The management of depression in patients with chronic pain can be challenging due to common mechanisms and physiological associations between conditions, which may raise concerns among clinicians about prescribing medications for both conditions simultaneously. Using multiple drugs increases the risk of drug–drug interactions or additional risk for common adverse effects, particularly in patients with MDD who already have a high likelihood of polypharmacy.^{20–22} The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines outline evidence-based recommendations for the management of MDD,^{21,23,24} including antidepressant medication selection and a treatment optimization algorithm.²¹ Recommendations for the management of mood disorders in patients with psychiatric and medical comorbidities, including comorbid anxiety disorders, attention-deficit/hyperactivity disorder, substance use disorders, and medical disorders such as cardiovascular disease and multiple sclerosis, are addressed in a separate set of CANMAT reviews.^{25–29} However, management of patients with MDD and comorbid chronic pain has yet to be specifically addressed.

A collaboration was therefore undertaken to consider guidelines for the management of chronic pain together with the CANMAT Guidelines for Treatment of Major Depressive Disorder,^{21,23} in order to develop recommendations for the treatment of MDD in patients with comorbid chronic pain. The *International Classification of Diseases* of the World Health Organization defines chronic pain as pain lasting or recurring for more than 3 months.³⁰ It comprises painful conditions that differ in their etiology and pathophysiology, including, but not limited to: chronic cancer pain arising from the cancer or the cancer treatment; chronic neuropathic pain, caused by a lesion or disease of the somatosensory nervous system; chronic musculoskeletal pain, arising as disease of the bone, joint, muscle, or related soft tissue; chronic visceral pain, originating from the internal organs (which can be perceived as referred pain in skin or muscle tissue); chronic headache and orofacial pain; and chronic primary pain, which includes conditions such as low back pain that is not found to be musculoskeletal or neuropathic in origin.³⁰ Because these chronic pain types are managed differently, we examined multiple guidelines addressing different types of chronic pain, including the 2017 Guideline for Opioid Therapy and Chronic Non-Cancer Pain,³¹ the revised consensus statement from the Canadian Pain Society,³² the American College of Physicians Clinical Practice Guideline for Low Back Pain³³ and the Guideline for the Evidence-Informed Primary Care Management of Low Back Pain.³⁴

The author group participated in multiple discussions, via email, telephone and videoconference, to reach consensus on treatment recommendations for this patient population. No formal process was used, and the result is a consensus of expert opinion that should be considered in conjunction with treatment guidelines. The aims of this article are to outline links between depression and pain in their occurrence, pathophysiology, and functional effects, and to provide clinical guidance, based on published evidence, on early and optimal pharmacological treatment for patients with MDD and comorbid chronic pain. Our goal is to provide a practical guide to help physicians treat this patient population based on the understanding that connections exist between

depression and pain, both in terms of patient experience and potential treatment options.

Links between depression and chronic pain

Depression and chronic pain are intimately linked in a bidirectional relationship. Patients with chronic pain are at increased risk for mood disturbances including depression,^{35,36} and individuals with depression are more likely to experience painful conditions compared with those without mood symptoms.^{37–39} Predictors of depression in patients with chronic pain include more severe pain, greater number of pain sites, pain day and night, lack of identifiable cause of pain, and poor pain control.^{40,41}

Estimates of comorbidity for chronic pain and MDD vary widely, depending on measures used to define both pain and depression. In a comprehensive review of studies published from 1966 to 2002, MDD was present in 2% to 100% of patients with chronic pain (or pain more than 6 months in duration), with a mean rate of 52%.¹¹ In the same study, rates of pain in patients with MDD ranged from 15% to 100%, with a mean of 65%. In several more recent studies, chronic pain was reported in approximately 45% to 65% of patients with MDD.^{12,39,40,42}

Comorbid chronic pain in patients with MDD has negative impacts on both depression and pain outcomes. Patients with chronic pain and depression are more likely to have greater severity and longer duration of pain, and patients with higher pain scores experience longer time to response and remission of depression compared with patients with lower pain scores.⁴³ Increasing levels of pain severity are associated with progressively decreasing likelihood of improvement in depression overall.⁴³

Common neurophysiology in depression and pain

Although the exact cause of the links between depression and pain are unknown, several possible mechanisms for their association have been posited. First, pain and depression are both known to affect several anatomic brain regions that are involved in emotional processing,⁴⁴ including the anterior cingulate cortex, hippocampus, prefrontal cortex (PFC), amygdala, and thalamus.^{45–47} Pain and depression also share serotonergic, dopaminergic, and noradrenergic neurotransmitter pathways arising primarily from limbic structures that are associated with emotional processing.^{45,46,48–50} Neuromodulation of pain via descending efferent pathways may also be impaired in depression, as a negative emotional state increases the perceived unpleasantness of pain via anterior cingulate cortex—PFC—periaqueductal gray circuitry,⁵¹ and cognitive variables such as pessimism and catastrophizing has been found to magnify pain-related stimuli.^{50,52} Some antidepressants that target serotonergic, dopaminergic, or noradrenergic pathways for the treatment of depression have also demonstrated efficacy in the treatment of pain,^{45,48–50} providing further evidence of shared mechanisms between depression and pain.^{48,53}

Central and peripheral neuroinflammation have been associated with pain and depression in preclinical studies.^{54,55} Increases in pro-inflammatory biomarker levels have been linked to both depression and pain,^{50,56} and evidence of chronic and sustained neuroinflammation has been observed in brain areas associated with mood and pain.⁵⁶ It is notable that some antidepressant medications have anti-inflammatory effects,⁵⁶ and that some patients with treatment-resistant depression have shown improvements in depression-related outcomes when treated with

monoclonal antibodies to the inflammatory mediator anti-tumor necrosis factor- α .⁵⁷

Sleep and fatigue symptoms form an additional link between pain and depression. Sleep disturbances or fatigue caused by depression or by medications used to treat it may increase pain directly by disrupting reparative or restorative functions or heightening pain experience indirectly by impairing adaptive mechanisms.⁵⁸ Conversely, the use of opiates for pain can cause insomnia⁵⁹ and sleep disordered breathing,⁶⁰ which might worsen the course of depression or cause symptomatic overlap. Again, the exact underlying cause of this association is not known, but there may be a shared pathophysiology linking sleep symptoms to those of pain and depression. It has been suggested that insomnia, chronic pain, and depression may have a common underlying dysfunction in the mesolimbic dopaminergic system.⁶¹ Other neurological substrates common to insomnia, depression, and chronic pain include stress/Hypothalamic-pituitary-adrenal axis (HPA) activity, Brain-derived neurotrophic factor (BDNF), proinflammatory cytokines, and serotonin.⁶² Chronic pain and depression have been conceptualized as overlapping central sensitivity syndromes linked with sleep and fatigue,⁶³⁻⁶⁵ and sleep and pain have been construed as competing neurological states.⁵⁸ Insomnia is a potential activating influence between chronic pain and suicide.⁶⁶ Therefore, screening for and treating insomnia and sleep disordered breathing are warranted, using caution to avoid nonspecific over-sedation in chronic pain patients. Nonpharmacological treatments can improve sleep in patients with pain⁶⁷ and should always be considered before medication. However, sleep and fatigue symptoms may also improve with aggressive treatment of pain and depression.

Potentiation of depression and pain

Results of studies on patients with pain and/or depression show that these conditions can each intensify the experienced symptoms of the other. A systematic review of 16 studies examining mental health risk factors for knee pain demonstrated a strong association between knee pain and depression,⁶⁸ with an increased severity of pain associated with an increased likelihood of depression.⁶⁸ Ongoing pain can worsen depressive symptoms,⁴⁴ as well as intensify the loss of function and reduced quality of life associated with depression.^{12,43}

Evidence also indicates that depression can amplify pain perception⁴⁴ and exacerbate impairment caused by pain.⁶⁹ For example, in one study, a significantly larger proportion of patients with MDD rated chronic pain as being severe or unbearable compared with nondepressed individuals (65% vs 43%, respectively; $P < .001$).⁴⁰ Patients with MDD also report higher frequency of pain and a higher number of pain sites than nondepressed individuals with chronic pain.⁴⁰ Depression is believed to reduce pain thresholds and increase pain perception,⁴⁴ especially in neuropathic pain, which can be worsened or magnified with coexisting depression or anxiety.⁶⁹

Pharmacotherapy for depression with comorbid pain

Rapid diagnosis and early optimization of treatment are critical for providing the best possible outcomes for individual patients with MDD.^{70,71} Delaying effective treatment of major depression can have negative impacts on patients' brain structure and function⁷² and reduce the likelihood of achieving remission with antidepressant treatment.⁷³⁻⁷⁵ Because improvement in depression alone

often reduces pain symptoms, the imperative for patients with MDD and comorbid pain is to focus on aggressive treatment of depression, while managing pain with first-line pain medication such as nonsteroidal anti-inflammatory drugs (NSAIDs; Table 1).^{31,33} After optimizing MDD treatment, the clinician can determine whether concomitant analgesic medication is needed and if so, whether a change to that medication is required. Here, we summarize recommendations for early optimized treatment of depressive symptoms and functional impairment in MDD (published previously in detail⁷¹), and consider pros and cons of pain medication options for patients with MDD, should they be needed in addition to the treatment used for management of depression. Our recommendations for managing pharmacotherapy in patients with MDD and pain are provided in Table 2. For patients with depression who are already prescribed medication for chronic pain, a treatment plan should be developed in consultation with the pain care provider.

Measurement based care: screening and assessment

Screening for depression in patients with pain can reduce the duration of untreated illness in those not primarily reporting mood symptoms. Screening may be of particular importance for patients with chronic pain and/or sleep disturbance, as patients with depression may actually be more likely to report somatic pain and sleep problems than depression itself.⁴⁰ Table 3 provides examples of tools for screening for depression and pain, as well as sleep disturbance and anxiety, which are likely to co-occur with depression.^{5,21} These same assessments can, and should, be administered regularly during treatment to monitor for improvement in symptoms and function, as previously described in detail.⁷¹ The 9-item Patient Health Questionnaire (PHQ-9)⁷⁶ can be used to screen for and diagnose depression; a PHQ-9 score of 5 is the threshold for mild depression; a score of ≥ 10 , which has a sensitivity of 88% and a specificity of 88% for major depression, is recommended as a screening cut point for moderate/severe MDD.⁷⁷ The PHQ-9 and a function scale such as the Sheehan Disability Scale⁷⁸ can also be used for assessing severity of symptoms and functional impairment, respectively, to inform the treatment plan and monitor early improvement. Several pain scales are useful for initial assessment and monitoring during treatment: the Pain Quality Assessment Scale differentiates nociceptive from neuropathic pain on screening,^{79,80} the Brief Pain Inventory—short form⁸¹ measures pain severity and degree of interference with function.⁸⁰ The Pain Disability Index assesses the level of impairment in a range of functional domains.⁸²⁻⁸⁴

Pharmacotherapy for MDD

First line treatments for MDD include most second-generation antidepressants (serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitor [SNRIs], agomelatine, bupropion, mirtazapine, and vortioxetine; Table 1)²¹; more recent head-to-head trials and network meta-analyses indicate that levomilnacipran and vilazodone also have similar efficacy to these second-generation antidepressants.⁸⁵ Based on CANMAT guidelines and our clinical experience, our recommendation is to initiate treatment with an SNRI such as duloxetine or venlafaxine for patients with comorbid pain.²¹ In systematic reviews, duloxetine has demonstrated efficacy for treating multiple chronic pain conditions, including neuropathic pain, fibromyalgia, and painful physical symptoms in depression.^{86,87} Venlafaxine significantly improved pain vs placebo in clinical trials of painful diabetic

Table 1. Recommended Medications for Depression and Pain Based on Treatment Guidelines.

| Parameter | Major depressive disorder ²¹ | Chronic noncancer pain ³¹ | Chronic neuropathic pain ^{8,32,95} | Low back pain ³³ | Chronic low back pain ³⁴ |
|-------------|---|--------------------------------------|---|-------------------------------------|---|
| First line | SSRIs, SNRIs, agomelatine, bupropion, mirtazapine, mianserin, and vortioxetine | NSAIDs (nonpharmacological options) | Gabapentinoids, TCAs, and SNRIs (duloxetine) | NSAIDs (nonpharmacological options) | Acetaminophen |
| Second line | TCAs, levomilnacipran, moclobemide, quetiapine, selegiline, trazodone, and vilazodone | | Tramadol and opioid analgesics | Tramadol or duloxetine | NSAIDs (ibuprofen and diclofenac) |
| Third line | Phenelzine, tranylcypromine, and reboxetine | | Cannabinoids | | Weak opioids (codeine) |
| Fourth line | | | SSRIs, topical lidocaine, methadone, lamotrigine, lacosamide, tapentadol, and botulinum toxin | | Tramadol |
| Fifth line | | | | | Strong opioids (morphine, hydromorphone, oxycodone, and fentanyl patch) |

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

^aConsider adding additional agents sequentially if partial or inadequate pain relief.

Table 2. Recommendations for Pharmacotherapy in Patients with Depression and Chronic Pain.^a

| Treatment step | Medication | Considerations |
|----------------------|--|--|
| First-line | SNRI, duloxetine | SNRIs are a first-line antidepressant with an analgesic benefit that may be a class effect. Duloxetine has multiple pain indications |
| Optimization | Dose adjustment or switch within class | If ~20% improvement in symptoms is not apparent after 2 wk, a dose increase should be considered |
| Adjunctive treatment | Low dose TCA nortriptyline <50 mg amitriptyline <50 mg | TCAs should only be used as an adjunctive treatment at a low dose and with caution due to safety and tolerability concerns Monitor blood pressure in patients prescribed TCAs Monitor for effects on sleep: nortriptyline may have stimulatory side effects whereas amitriptyline may cause sedation |
| | Gabapentinoid pregabalin | Consider adding a gabapentinoid for neuropathic pain Consider adding pregabalin for neuropathic pain with anxiety; pregabalin has indications for neuropathic pain and fibromyalgia |

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

^aNSAIDs are recommended for pain while treatment for depression is optimized.

neuropathy.^{88,89} It could be presumed that this analgesic benefit may be a class effect of SNRIs.

Early and ongoing monitoring of depression symptoms and function, treatment adherence, and tolerability is critical for making adjustments to treatment when an adequate trial does not yield clinically significant improvement.^{21,71} Approximately 20% improvement in symptoms is expected after 2 to 4 weeks of treatment⁷⁰; if early improvement is not apparent after 2 weeks, a dose increase should be considered.^{21,71} If symptoms are still not improving after dose optimization, an adjunctive treatment or a switch to another monotherapy in the same or different antidepressant class may be needed.^{21,71}

The CANMAT guideline recommends atypical antipsychotic drugs such as aripiprazole as first-line adjunctive treatment for nonresponse or partial response to an antidepressant monotherapy

for symptoms of MDD.²¹ If trials of 2 different SNRIs fail, adding a low-dose tricyclic antidepressant (TCA), such as amitriptyline, nortriptyline, or desipramine should also be considered for patients with MDD and pain. TCAs have a poor safety and tolerability profile at standard doses for treating MDD (≥ 100 mg/d), but may have similar efficacy for treating depression at lower doses,⁹⁰ and several TCAs have also demonstrated efficacy for treating painful conditions.⁹¹⁻⁹⁴ Nonetheless, due to their high side effects burden, TCAs are not recommended as a first-line treatment and they should only be used as an adjunctive treatment with caution.²¹

Pharmacotherapy for chronic pain in patients with MDD

After depressive symptoms have been stabilized and function has improved, the clinician can assess whether additional treatment for

Table 3. Assessment Tools for Measurement-Based Care in Patients with Depression and Pain.

| Assessment tool | Areas assessed | Scoring range/interpretation | Reference |
|--|---|--|-----------------------------------|
| Patient Health Questionnaire (PHQ-9) | Depression; diagnostic and severity rating scale | 1-27; PHQ-9 score ≥ 10 indicates major depression ^a | Kroenke and Spitzer ⁷⁷ |
| Sheehan Disability Scale (SDS) | Functional impairment | 0-30 (total score); SDS total score ≥ 5 strongly predicts impairment, ≥ 21 indicates extreme or marked impairment ^b | Sheehan ¹⁶⁰ |
| Pain Quality Assessment Scale | Changes in pain quality with treatment; differentiation of nociceptive and neuropathic pain | 20 items describing different pain qualities, each scored 0-10 Single temporal descriptor (intermittent, variable, or stable) | Jensen et al ⁷⁹ |
| Brief Pain Inventory—short form (BPI) | Pain intensity, quality, location, interference with function, and relief | Worst, least, average, and current pain intensity each scored 0 (no pain) to 10 (pain as bad as you can imagine) Interference in 7 domains scored 0 (does not interfere) to 10 (completely interferes) Pain relief by treatments or medication scored 0% (no relief) to 100% (completely relief) | Cleeland and Ryan ¹⁶¹ |
| Pain Disability Index | Level of disability related to pain | 0-70 (general disability score), based on the sum of scores for 7 areas of activity, rated 0 (no disability) to 10 (total disability) | Tait et al ⁸² |
| Numeric Rating Scale for Pain (NRS-P) | Pain intensity | 0 (no pain) to 10 (worst possible pain) on a single 11-point numeric scale; evaluates pain intensity only | Farrar et al ¹⁶² |
| Visual Analog Scale (VAS) for pain | Pain intensity | Single continuous scale, usually 10 cm in length, scored 0 (no pain) to 100 (worst imaginable pain) | Hawker et al ¹⁶³ |
| 7-item anxiety scale (GAD-7) | Anxiety; diagnostic and severity rating scale | 0-21; Cut points of 5, 10, and 15 interpreted as mild, moderate, and severe anxiety ^c | Spitzer et al ¹⁶⁴ |
| Insomnia Severity Index (ISI) | Patient perceived insomnia | 0-28 (Total score) based on sum of 7 items scored 0-4 Higher score suggests more severe insomnia | Bastien et al ¹⁶⁵ |
| Snoring, Tired during daytime, Observed apnea, high blood Pressure- BMI, age, neck circumference, and gender (STOP Bang) | Obstructive sleep apnea | 8 yes/no questions | Chung et al ¹⁶⁶ |

^aPHQ-9 score ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression.⁷⁷

^bBased on Sheehan¹⁶⁰ and Sheehan and Sheehan.¹⁶⁷

^cBased on Spitzer.¹⁶⁴

pain is required. Possible benefits and harms of available options should be considered for each individual patient. Published guidelines for the treatment of chronic pain focus on different pain conditions, including chronic noncancer pain,³¹ chronic neuropathic pain,^{32,95} and low back pain.³³ Consequently, recommendations for pain pharmacotherapies differ among the various organizations that provide them (Table 1). It is important to note that nonpharmacological therapies are considered first-line options or essential to the enhancement of pharmacotherapy in all of those guidelines. Guideline recommendations for nonpharmacological therapies for chronic pain include exercise therapy, physiotherapy, cognitive behavioral therapy-based psychological treatment, mindfulness-based stress reduction, acupuncture, and multidisciplinary rehabilitation.³¹⁻³³

Nonsteroidal anti-inflammatory drugs

In guidelines from the National Opioid Use Guideline Group³¹ and the American College of Physicians,³³ NSAIDs are recommended as first-line pharmacotherapy for chronic noncancer pain and low back pain.^{31,33} Clinical trial evidence suggests that there is a small to moderate effect of NSAIDs on reducing low back pain.⁹⁶ A meta-analysis of randomized controlled trials comparing NSAID therapy vs opioids showed no difference in pain control (9 trials) or functioning (7 trials) for the 2 therapies in patients with chronic

noncancer pain, with a significant risk for opioid treatment over NSAIDs.⁹⁷ Ibuprofen may be more effective than acetaminophen in acute pain conditions, but there are limited data comparing these for chronic pain.⁹⁸ NSAIDs have not demonstrated efficacy vs placebo in patients with neuropathic pain,⁹⁹ and the Canadian Pain Society does not recommend for that condition.³²

Clinicians should counsel patients with contraindications for NSAIDs. Gastrointestinal bleeding, kidney damage, and increased cardiac adverse events have been associated with NSAID use, and these medications are potentially hazardous for elderly patients, who are at particular risk for these conditions.¹⁰⁰ Bleeding risk is additive when other medications associated with gastrointestinal (GI) bleeding, such as selective SSRIs, are taken concurrently with NSAIDs.^{101,102} Due to GI bleeding and renal risks, American College of Physicians guidelines for low back pain recommend that when NSAIDs are used, the lowest effective doses should be taken for the shortest periods necessary.³³ The risk of gastrointestinal bleeding may be reduced using acid-suppressing drugs concurrently.¹⁰²

Antidepressant medications

The Canadian Pain Society recommends TCAs, SNRIs, and gabapentinoids as first-line therapy for neuropathic pain⁹⁵; the SNRI duloxetine is a second-line recommendation from the American

College of Physicians for low back pain.³³ TCAs, including amitriptyline, have confirmed efficacy in various neuropathic pain conditions (number needed to treat [NNT] for a 50% pain reduction \approx 4).^{103,104} In clinical practice, amitriptyline is used at low doses for management of neuropathic pain (5–10 mg/d for >70% of 281 doctors surveyed)¹⁰⁵ due to its poor tolerability profile at higher doses.^{106,107} Several studies support the use of nortriptyline for neuropathic pain, although most of those are also limited by small study size.¹⁰⁸ TCAs in general have a very high burden of side effects, including somnolence, anticholinergic effects, weight gain,¹⁰³ and possible cardiac conduction block and orthostatic hypotension.¹⁰⁹ Before prescribing a TCA, patient symptoms and possible effect on sleep should be carefully considered. If the patient presents with significant insomnia, it may be beneficial to initiate treatment with a TCA with hypnotic effects, such as amitriptyline, doxepin, or trimipramine.¹¹⁰ However, the ratio of next day sedation to pain control and overall functional improvement needs to be kept in mind.

SNRIs such as duloxetine and venlafaxine have demonstrated efficacy in neuropathic pain with a NNT for a 50% reduction in neuropathic pain of 6.4 for duloxetine¹⁰³ and 3.1 for venlafaxine.¹¹¹ Duloxetine has also demonstrated efficacy vs placebo for treating painful diabetic neuropathy (duloxetine 60 mg, NNT = 5), fibromyalgia (NNT = 8), and painful physical symptoms in depression (NNT = 8) in a Cochrane Review.⁸⁷ In an indirect meta-analysis, no difference in efficacy was observed between duloxetine and SSRIs, Cox-2 inhibitors, glucosamine, or nonscheduled opioids.¹¹² Desvenlafaxine treatment significantly reduced pain associated with diabetic peripheral neuropathy in a single study, at high doses only (200 and 400 mg/d).¹¹³ Some SNRIs may be associated with weight gain or sexual dysfunction, both of which may reduce adherence to treatment.^{114–117} Other possible adverse events include nausea, abdominal pain, constipation, hypertension (dose related with venlafaxine¹⁰³), loss of appetite, sedation, dry mouth, hyperhidrosis, and anxiety¹⁰⁹; these effects can vary from agent to agent within the SNRI class.¹¹⁸ Patients should also be monitored for suicidal thoughts or behavior, as treatment with TCAs, SNRIs, and other antidepressant medications are also associated with an increased risk for suicidal behavior.¹¹⁹

Gabapentinoids

Gabapentinoids are used for neuropathic pain with U.S. indications for fibromyalgia, postherpetic neuralgia, and neuropathic pain associated with diabetic peripheral neuropathy or spinal cord injury; pregabalin, but not gabapentin, has indications for neuropathic pain and fibromyalgia in Canada.^{120–123} Pregabalin also has demonstrated efficacy vs placebo for treating anxiety in clinical trials; clinical response was comparable for pregabalin and benzodiazepines in a meta-analysis.¹²⁴ The NNT to achieve 50% pain relief with gabapentin is 6.3 to 8.3; for pregabalin, the NNT is 5.6 to 7.7 in neuropathic pain.^{103,125} The safety profile of gabapentinoids includes risk of sedation, dizziness, peripheral edema, weight gain,¹⁰³ and blurred vision.¹⁰⁹ Effects on cognition, including disturbance in attention, abnormal thinking, and confusion, are also reported for pregabalin.¹²⁶

Opioid analgesics

Tramadol is recommended as a second-line medication in guidelines for both low back pain³³ and chronic neuropathic pain^{32,95}; the guideline for chronic neuropathic pain includes other opioid analgesics in that recommendation as well.^{32,33,95} However, caution is warranted when using tramadol with serotonergic drugs such as

SSRIs,^{32,95} and the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain includes a strong recommendation for optimization of nonopioid pharmacotherapy and nonpharmacologic therapy rather than a trial of opioids for patients with chronic, noncancer pain.³¹ For chronic pain patients with a comorbid psychiatric disorder, the 2017 guideline recommends stabilization of the psychiatric disorder before a trial of opioids is considered; opioid therapy is not recommended for patients with chronic noncancer pain and a history of substance use disorder.³¹ The reported NNT for 50% neuropathic pain relief is 4.7 for tramadol.¹⁰³ However, a recent meta-analysis of 96 randomized controlled trials for chronic noncancer pain found that opioids provided only small advantages vs placebo, possibly due to the development of opioid tolerance or opioid-induced hyperalgesia.⁹⁷

Opioid analgesics are associated with nausea, vomiting, constipation, dizziness, somnolence, and the potential for abuse and addiction.^{103,127} Up to a quarter of all U.S. patients on long-term opioid therapy may develop dependence and addiction.¹²⁸ The prevalence of opioid use disorder in people who received chronic opioid therapy may be up to 20% to 25% or more.^{128–131} Tramadol (like the structurally related tapentadol) is a partial μ opioid receptor agonist with an upper bound on analgesic activity, but it also has central GABA, catecholamine, serotonergic, and noradrenergic activities, which may reduce its abuse potential compared with full antagonists such as morphine, hydromorphone, and fentanyl.^{132–135} Nonetheless, abuse of tramadol and tapentadol remains a risk, particularly with oral administration.¹³⁴ Most critically, however, opioids can double the risk of depression recurrence potentially in a dose-dependent manner.^{136,137}

In accordance with the guideline for opioid therapy and chronic noncancer pain, nonopioid treatment options should be considered over opioid analgesics because of abuse potential, the significantly increased risk of serious adverse events, and the increased risk of depression recurrence.^{31,127,136} Although a partial agonist such as tramadol may have a lower (but not negligible) potential for abuse and for respiratory depression,^{132–135} tramadol can result in drug–drug interactions with an increased risk for serotonergic syndrome in patients also prescribed SSRIs or SNRIs.¹³⁸

Emerging therapies

The Canadian Pain Society currently recommends cannabinoids as third-line agents for neuropathic pain due to a lack of evidence from high quality trials supporting their efficacy.^{32,95} Despite evidence of moderate improvement in neuropathic pain with cannabinoid treatment, the NNT for benefit was high (24) and the NNT for harm was low (6) in a recent meta-analysis.¹³⁹ Selective cannabinoids demonstrated a small but statistically significant analgesic effect as an adjunct treatment for neuropathic pain in a second meta-analysis.¹⁴⁰ Based on a more recent review of the evidence, the International Association for the Study of Pain released a position statement that did not endorse the use of cannabinoids for the treatment of pain, due to lack of high-quality clinical evidence.¹⁴¹ The value of these therapies in pain is uncertain, with little or no evidence in patients with depression.¹⁴²

Other potential therapies worth future consideration include anti-inflammatory drugs with antidepressant effects, such as infliximab.^{143,144} Ketamine, which was originally developed as an anesthetic and has short-term analgesic effects, may be of particular interest as a future therapy, as it has emerged as a treatment for treatment-resistant depression, with evidence supporting its use in MDD.^{145–148} Long-term analgesic effects of ketamine have not yet been rigorously examined.¹⁴⁵

Table 4. A Summary of Potential Drug–Drug Interactions Among Compounds Likely to be Used to Treat Concomitant MDD and Chronic Pain.¹⁴⁹⁻¹⁵⁵

| Primary drug | Major CYP elimination pathways | Interacting drug | Possible effect(s) |
|--|-------------------------------------|---|--|
| SSRIs | CYP2C19, CYP2D6, CYP1A2, and CYP2B6 | Warfarin and NSAIDs including aspirin | • Increased risk of GI bleeding |
| | | MAOIs | • Hypertensive crisis, serotonin syndrome |
| | | Tramadol | • Serotonin syndrome reported with concurrent use |
| | | TCAs | • Increased plasma TCA and increased adverse effects • Increases are variable but can be in the order of up to 4-fold. • Risk of serotonin syndrome especially with clomipramine |
| Agomelatine (melatonergic, 5-HT ₂ antagonist) | CYP1A2 | Fluvoxamine, ciprofloxacin, amiodarone, mexiletine, or zileuton | • Up to 60-fold increase of agomelatine concentrations with fluvoxamine and possible occurrence of adverse effects |
| Duloxetine (SNRI) | CYP2D6 | TCAs | • 270% increase in C _{max} and ≤290% increase in AUC of desipramine • Possible serotonin syndrome |
| | | MAOIs, SSRIs, and other serotonergic agents | • Possible serotonin syndrome |
| | | NSAIDs | • Possible risk of GI bleeding |
| Venlafaxine (SNRI) | CYP2D6 | TCAs | • Possible serotonin syndrome • Increased plasma imipramine (27%) or desipramine (40%) |
| | | NSAIDs | • Increased risk of GI bleeding |
| Desvenlafaxine (SNRI) | N/A | TCAs | • Increased plasma desipramine (17%-36%) • Possible serotonin syndrome |
| | | NSAIDs | • Increased risk of GI bleeding |
| Levomilnacipran (SNRI) | CYP3A4 | TCAs | • Possible serotonin syndrome |
| | | NSAIDs | • Increased risk of GI bleeding |
| Vilazodone (SSRI and 5-HT _{1A} antagonist) | CYP3A4 | TCAs | • Possible serotonin syndrome |
| | | NSAIDs | • Increased risk of GI bleeding |
| Bupropion (aminoketone) | CYP2B6 | Carbamazepine | • Reduced AUC of bupropion (90%) |
| | | Desipramine, nortriptyline, and venlafaxine | • Increased plasma concentrations of the interacting drug and potential toxicity/adverse effects |
| Mirtazapine (tetracyclic) | CYP2D6 | Fluvoxamine, carbamazepine, and tramadol | • Increase of mirtazapine concentrations • Possible serotonin syndrome • Risk of restless leg syndrome |
| Vortioxetine (multimodal) | CYP2D6 | N/A | • Little to no effect on various CYP isoforms and therefore is not expected to significantly affect the PK of CYP substrates |
| Gabapentin (anticonvulsant) | N/A | Tramadol | • May work synergistically to alleviate pain |
| TCAs | CYP2C19, CYP2D6, and CYP1A2 | SSRIs and SNRIs | • Increased plasma TCA leading to increased adverse effects. • Serotonin syndrome possible |
| | | Opiates and benzodiazepines | • Decrease respiratory drive and lethality |

Abbreviations: AUC, area under the curve; CNS, central nervous system; CYP, cytochrome P450; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetics; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

If the approach to the treatment of comorbid MDD with chronic pain involves the use of multiple medications, the potential for drug–drug interactions must be considered (Table 4).¹⁴⁹⁻¹⁵⁵ Many medications used in the treatment of MDD are metabolized via the hepatic cytochrome P450 (CYP) enzyme system and can inhibit or induce the activity of those enzymes.¹⁵⁶ Such drug interactions alter plasma drug concentrations, which can result in reduced efficacy and/or increased adverse effects.^{156,157} Careful appraisal of drug–drug interactions listed in drug labeling is essential for safely prescribing multiple drugs for the treatment of MDD and pain. Online resources, such as SwitchRx,¹⁵⁸ are also available

to provide clinicians with current information on combined drug strategies for psychotropic medications.

Response to pain therapy may be best measured by monitoring patients' sleep and functioning.^{95,159} For patients who fail to achieve functional improvement with the pain management plan, consultation with a pain specialist or referral to multimodal pain clinic should be considered. In addition to regular assessment of improvement in both pain and depressive symptoms and function, monitoring for adverse side effects is essential, as tolerability will ultimately contribute to patient adherence and efficacy of the treatment.

Conclusions

The incidence of comorbid chronic pain is high in patients with depression, as pain and depression exacerbate symptoms and influence treatment outcomes in a bidirectional manner. In addition, the presence of comorbid pain in depression can complicate the diagnosis and management of both conditions. Early diagnosis, rapid optimization of treatment, and addressing residual symptoms are key to successful management of MDD. For patients with MDD who have chronic pain, we provide recommendations (Table 2) for aggressively managing depression, focusing on anti-depressant medications with analgesic properties and addressing pain with first-line pharmacotherapy as treatment for depression is optimized, before considering additional drugs to address residual pain symptoms. Potential benefits and harms of pharmacotherapy options for treating pain should be carefully weighed for each individual patient. Careful consideration should be given to potential adverse effects and potential drug–drug interactions when multiple drugs are prescribed.

Acknowledgments. Medical writing support was provided by Kathleen Dorries, PhD, Peloton Advantage, LLC, an OPEN Health company, and was funded in part by Pfizer Canada ULC and in part by the authors. Authors are entirely responsible for the scientific content of the paper.

Author contributions. Data interpretation: all authors; Manuscript preparation: all authors; Manuscript review and revisions: all authors; Final approval of manuscript: all authors.

Disclosures. O.J.O.: Speakers bureau/honoraria: Lundbeck, Otsuka, Pfizer, Janssen, Sunovion, Shire, Purdue, and Allergan; clinical trials: Otsuka/Lundbeck; M.A.K.: Ownership/partnership: START Clinic for Mood and Anxiety Disorders; employment: START Clinic for Mood and Anxiety Disorders, Adler Graduate Professional School, Northern Ontario School of Medicine (NOSM) (Laurentian and Lakehead University); advisory board (or similar committee): AbbVie Eisai, Empower Pharma, Jansen, Otsuka, Pfizer, Purdue, Sante Cannabis, Shire, Takeda, Tilray; clinical trials: Lundbeck; Honoraria or other fees (eg, travel support): Allergan, Jansen, Lundbeck Otsuka, Pfizer, Purdue, Shire, Takeda, and Tilray; research grants: Pfizer; J.H.: Pfizer, Allergan, Amgen, Aralez, Astra-Zeneca, Bausch, Bayer, BMS, Boehringer, Eli-Lilly, Janssen, Lundbeck, Novartis, Novo-Nordisk, Purdue, Servier, Roche, and Otsuka; D.M. has received honoraria for ad hoc speaking or advising/consulting from Abbvie, Allergan, Bausch Health, BC Children's and Women's Hospital, Canadian Network for Mood and Anxiety Treatments, Eisai, Janssen, Lundbeck, Otsuka, Pfizer, PsychedUp CME, Purdue, Save-On-Foods, Shire, Sunovion, Takeda, Western University and the University of Ottawa. D.M. is the co-director of PsychedUp CME and Chief Neuroscience Officer at Telus Communications; A.K. has received honoraria /or is member of advisory board for Allergan, Bausch Health, Eisai, Janssen, Lundbeck, Otsuka, Pfizer, Purdue, Sunovion, Spectrum, Tilray, and Takeda; R.S.M. has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. R.S.M. is a CEO of Braxia Scientific Corp; C.N.S. has received honoraria as a consultant for Lundbeck, Otsuka, and Sunovion and research grants from the AFP Innovation Fund, Ontario Research Fund, Canadian Menopause Society, and Ontario Brain Institute; M.A.O. has received honoraria /or is member of advisory board for Allergan, AbbVie, Eisai, Elvium, Janssen, Lundbeck Otsuka, Pfizer, Purdue, Shire, Sunovion, Takeda, and Wyeth; R.W.L. has received honoraria for ad hoc speaking or advising/consulting, or received research funds, from Akili, Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association, CME Institute, Hansoh, Healthy Minds Canada, Janssen, Lundbeck, Lundbeck Institute, Medscape, MITACS, Movember Foundation, Ontario Brain Institute, Otsuka, Pfizer,

St. Jude Medical, University Health Network Foundation, and VGH-UBCH Foundation; L.J.K. has received honoraria and/or is a member of advisory board for Allergan, CADDRA, Canadian Psychiatric Association, CINP, European Psychiatric Association, Janssen, Lundbeck, Otsuka, Pfizer, Purdue, Sunovion, Takeda, and Tilray; R.T.: Unrestricted conference grants from Allergan, Canopy, Janssen, Lundbeck, Otsuka, Pfizer, Purdue, Shire, and Sunovion; previous speaker honoraria from Allergan, Canopy, Indivior, Lundbeck, Otsuka, and Pfizer; previous member of advisory boards for Allergan, Canopy, and Tilray; clinical trial funding from Sundial Growers and Olds SoftGels; research grants from Canadian Institutes of Health Research, Health Canada's Substance Use and Addiction Program, CAN Health Network, and Alberta Innovates; and speaker's bureau/honoraria with Master Clinician Alliance. He was appointed to a government review committee, the Supervised Consumption Services Review Committee, for which he received remuneration for his time away from his workplace and reimbursement for travel, living, or other expenses reasonably incurred while away from his place of residence according to the Public Service Relocation and Employment Expenses Regulation and the Government of Alberta Travel Meal and Hospitality Expenses Directive.

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