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Musculoskeletal Disorders: Fibromyalgia

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Fibromyalgia is characterized by chronic widespread pain, increased tenderness at specific sites known as "tender points," unrefreshing sleep, fatigue and cognitive dysfunction not attributable to other disease states. Fibromyalgia affects 2–4% of the general population and of those affected, 80–90% are female. In general, symptom onset occurs between the ages of 30 and 60. Central and peripheral system changes in terms of hypothalamic–pituitary–adrenal axis dysfunction, central sensitization, wind-up (a progressive increase in sensitivity over time, i.e., lower stimuli result in increased pain), elevated excitatory neurotransmitters, vasoconstriction, ischemia and adrenergic receptor sensitivity have been described, although none have been identified as clear causative factors.

While the etiology of fibromyalgia is not entirely clear, associations with trauma, adverse life events, impaired mood (e.g., depression), anxiety, irritable bowel syndrome, irritable bladder syndrome, cold intolerance, paresthesias and other medical conditions have been described.[1] Accordingly, the diagnosis of fibromyalgia is an evolving one. See Figure 1 - Investigation of Diffuse Aches and Pains and Figure 3 - Preliminary Diagnostic Criteria for Fibromyalgia for more information regarding associated conditions.

Goals of Therapy

- Reduce pain, fatigue, psychological distress and sleep problems
- Improve physical and emotional well-being, functioning and quality of life
- Address associated conditions on an individual basis
- Promote self-management via individual and group education

Investigations

Figure 1 - Investigation of Diffuse Aches and Pains presents suggested investigations and Figure 2 - Tender Point Examination[a] , the tender point examination.

The American College of Rheumatologists has published provisional diagnostic criteria which provide a case definition for fibromyalgia (Figure 3 - Preliminary Diagnostic Criteria for Fibromyalgia) based on the widespread pain index (WPI) and the symptom severity (SS) scale.[2] The Canadian Rheumatology Association and Canadian Pain Society recently endorsed similar diagnostic criteria indicating that "examination for tender points is not required to confirm the diagnosis".[3] These criteria have not yet been widely adopted by physicians and there will likely be a need for further discussion in this regard. All clinicians seem to agree that the diagnosis, pathogenesis and treatment are complex and require greater understanding.

Therapeutic Choices

Nonpharmacologic Choices

Nonpharmacologic treatment of fibromyalgia should be first-line therapy, especially due to a lack of strong data to support the use of medications.

- Empathy and acknowledgment of suffering from health care providers is fundamental.
- A comprehensive, multidisciplinary program of education, self-management, nonpharmacologic pain reduction techniques, graded aerobic exercises, sleep hygiene, stress management and cognitive behavioural therapy is believed to be beneficial,[4] but a Cochrane review indicated too few high-quality randomized controlled trials to support this common viewpoint.[5] A "person-centred" approach to care has been advocated.[6]
- Ongoing cognitive behavioural therapy (CBT) sessions are one component of the multidisciplinary treatment of fibromyalgia. CBT has been shown to improve the number of tender points, Visual Analogue Scale (VAS) pain scores, pain coping, pain behaviours, depression and physical function.[7]
- Supervised aerobic exercise, walking programs, pool exercises, graded exercise programs, strength training and tai chi can improve function, symptoms and well-being.[8] , [9] , [10] , [11] , [12]

- Nonpharmacologic pain reduction techniques include cold, heat, transcutaneous electrical nerve stimulation (TENS), massage and relaxation techniques such as biofeedback, meditation and hypnosis.[13] Electroacupuncture has also been shown to reduce pain and analgesic requirements in patients with fibromyalgia,[14] while another study concluded that acupuncture could not be recommended for fibromyalgia.[15] A Cochrane systematic review also found that electroacupuncture is probably more effective than acupuncture for pain and stiffness in fibromyalgia.[16]
- Patient education, e.g., the Arthritis Society's Arthritis Self-Management Program, can improve pain, sleep, fatigue, quality of life and the 6-minute walk test. Improvement can last at least 3–12 months.[4]
- Specific identification and subsequent therapy for a particular life event such as history of sexual,[17] physical or emotional abuse, deprivation, post-traumatic stress disorder or any other psychologically distressing event can be efficacious as part of the overall treatment approach, in the clinical experience of the author.

Pharmacologic Choices (Table 1)

Because the etiology of fibromyalgia remains unknown, drug treatments are largely empiric. Studies have been of short duration and varying quality. Note, duloxetine and pregabalin are the only 2 prescription medications with official Health Canada indications for the treatment of fibromyalgia.

Antidepressants

A wide range of antidepressants may be useful in the management of fibromyalgia, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). They may be considered equally for initial therapy and are discussed below.[18] , [19]

Low doses of **tricyclic antidepressants** at bedtime (e.g., amitriptyline starting at 5 mg and progressing slowly, every 2–3 weeks, to a maximum of 50 mg) can improve sleep and reduce pain and fatigue.[20] Only short-term efficacy has been shown. A Cochrane review suggests that although it is an appropriate initial treatment, only a minority of patients will achieve satisfactory pain relief with amitriptyline.[21] If taken 1–2 hours before bedtime the effect will start at bedtime, and morning hangover will be lessened.

A "muscle relaxant" that is somewhat effective is **cyclobenzaprine**, perhaps because it too is a tricyclic molecule.[22]

The SNRI duloxetine provides a small but significant reduction in fibromyalgia pain but does not improve fatigue, quality of life or sleep disturbances.[23][SORT B] Duloxetine is generally well tolerated but some patients may discontinue its use due to nausea, dry mouth, constipation, or headache. Duloxetine may be considered as first-line drug therapy in fibromyalgia patients with concomitant depression. Venlafaxine has not been studied in patients with fibromyalgia. Useful Info? However, **milnacipran**, an SNRI not available in Canada, was shown to be beneficial in treating fibromyalgia symptoms.[24]

SSRIs are not as helpful as tricyclics but are usually better tolerated. **Fluoxetine** has been shown to improve pain and function.[25] Results for other SSRIs have been variable: a controlled-release **paroxetine** formulation improved Fibromyalgia Impact Questionnaire (FIQ) scores in a trial of 116 patients,[26] but **citalopram** was not effective in treating fibromyalgia symptoms.[27] Fluoxetine in the morning with evening amitriptyline was more effective than either agent alone in a double-blind controlled trial in fibromyalgia sufferers.[28]

GABA Derivatives

In clinical trials, **pregabalin** demonstrated variable but statistically significant improvement in painful symptoms[29] , [30] and time to loss of therapeutic response.[31] A meta-analysis of randomized controlled trials determined that pregabalin reduced pain and improved sleep and health-related quality of life indices for patients with fibromyalgia.[32] A Cochrane review of pregabalin use in chronic pain concluded that it was beneficial at doses of 300–450 mg/day; higher doses did not produce greater symptom improvement than 450 mg/day, while lower doses (150 mg/day) were not different from placebo.[33] However, doses of pregabalin should be titrated slowly upward, beginning with 25– 50 mg at bedtime, to minimize adverse effects (drowsiness, dizziness). There is also evidence that **gabapentin** may improve pain scores and sleep in patients with fibromyalgia,[34] although it has not been studied as extensively as pregabalin in this patient population.

Other Drugs

Analgesics such as **acetaminophen** and **nonsteroidal anti-inflammatory drugs (NSAIDs)** may be tried but help very few patients. These drugs may not be useful for fibromyalgia because the pain is probably a result of central sensitization rather than peripheral pain or inflammation.
There is no good evidence to suggest that **opioid** analgesics (other than tramadol) are effective for the relief of pain in fibromyalgia.[35] Additionally, several fibromyalgia guidelines recommend against the use of opioids as part of therapy.[36] Of particular concern is the risk of opioid-induced hyperalgesia since fibromyalgia patients may already have central sensitization (hyperalgesia). Despite the lack of evidence and guidance, inappropriate and widespread use of opioids exists in this patient population.

Tramadol (with or without acetaminophen) has been reported to reduce pain and to improve health-related quality of life in individuals with fibromyalgia.[37] , [38] , [39] , [40] This effect, however, is likely due to the fact that it reduces reuptake of serotonin and norepinephrine[37] , [39] rather than to its narcotic action. The use of tramadol with serotonergic antidepressants may cause serotonin syndrome.

Sedatives may benefit those with severe sleep dysfunction but do not provide effective reduction of pain. Dependency and adverse effects are also concerns. **Zopiclone** might be useful intermittently but evidence is lacking.[41] Antidepressants with sedative properties, such as amitriptyline and trazodone, are commonly used in fibromyalgia patients to improve sleep.[42]

Human growth hormone improved symptoms in a placebo-controlled trial, although further investigation is required.[43] It may help only those with low growth hormone levels. Expense and availability limit its use.

Treatment of peripheral pain generators by local injection (e.g., usually **lidocaine** 1% with or without a depot form of **corticosteroid**) to myofascial trigger points may reduce the total pain burden and the perpetuation of central pain sensitization.[44]

Choices During Pregnancy and Breastfeeding

Considerations Before and During Pregnancy

Before conception, women with fibromyalgia and comorbid myofascial face pain may have reduced fertility.[45]

There is little published evidence regarding the effects of pregnancy on women with fibromyalgia. Theoretically, elevated levels of cortisol and relaxin during pregnancy may ease symptoms in some patients. An analysis of 1178 women determined that fibromyalgia did not affect pregnancy outcomes or newborn health, but almost all patients reported worsening symptoms during pregnancy, especially during the last trimester.[46] Symptoms were worse postpartum in many patients (but eventually returned to previous levels); anxiety and depression also increased after delivery.
Nonpharmacologic approaches to pain control, stress management and energy conservation should be encouraged during pregnancy. A reminder that many fibromyalgia symptoms (generalized pain, fatigue, back pain, muscle weakness, depression and stiffness) are similar to those that also occur in healthy women during pregnancy may help women cope better. Adequate support is important throughout pregnancy and afterwards.

If nonpharmacologic options are insufficient to manage symptoms and drug treatment is deemed necessary, the following information may serve as a guide in making an informed decision. **Acetaminophen** is an appropriate analgesic for use in pregnancy. Short-term **NSAID** use may also be considered in the second trimester; first-trimester use has been associated with spontaneous abortions and a small risk of structural defects and third trimester use is generally contraindicated due to increased risk of premature closure of the ductus arteriosus and neonatal pulmonary hypertension.[47] Use of **tramadol** during pregnancy is not advised; neonatal withdrawal has been reported after long-term tramadol treatment in the pregnant mother.[48] , [49]

There is limited evidence on the effects of **gabapentin** or **pregabalin** in pregnancy or during breastfeeding. A preliminary study suggests gabapentin does not increase risk of major malformations, although it may be associated with other complications including low birth weight and preterm birth.[50] Until more information is available regarding their safety in pregnancy, use of gabapentin or pregabalin during pregnancy cannot be recommended.

If there is co-existing depression with fibromyalgia, the risk/benefit ratio may favour continuing treatment with antidepressants during pregnancy (see Psychiatric Disorders: Depression).

Tricyclic antidepressants, e.g., **amitriptyline** appear relatively safe during pregnancy. The SNRIs, e.g., **duloxetine**, while not associated with increased risk of congenital malformations, have been associated with short-

term agitation, jitteriness and poor feeding in the neonate. Newborns exposed to **SSRIs** in utero had an increased incidence of preterm birth, low Apgar scores, increased admission to neonatal intensive care[51] and seizures; fetal death has been reported.[52] Maternal use of **fluoxetine** and other SSRIs has also been associated with neonatal persistent pulmonary hypertension[53] and septal heart defects.[54] Neonatal withdrawal syndrome may occur.[55]

Considerations During Breastfeeding

After delivery, lack of sleep and stress may aggravate fibromyalgia symptoms. Muscle pain, stiffness and fatigue may result in discomfort and interfere with the breastfeeding process. Proper positioning during feeding, feeding while lying down, use of pillows or other supports and adequate rest periods may assist breastfeeding by the mother with fibromyalgia. Referral to a lactation consultant may be useful.

Acetaminophen and **ibuprofen** are considered compatible with breastfeeding. Most other NSAIDs are also considered compatible; choose agents with shorter half-lives when possible. Small amounts of **tramadol** and its metabolites are excreted into breast milk, but published data of the effects on infants is lacking.[56]

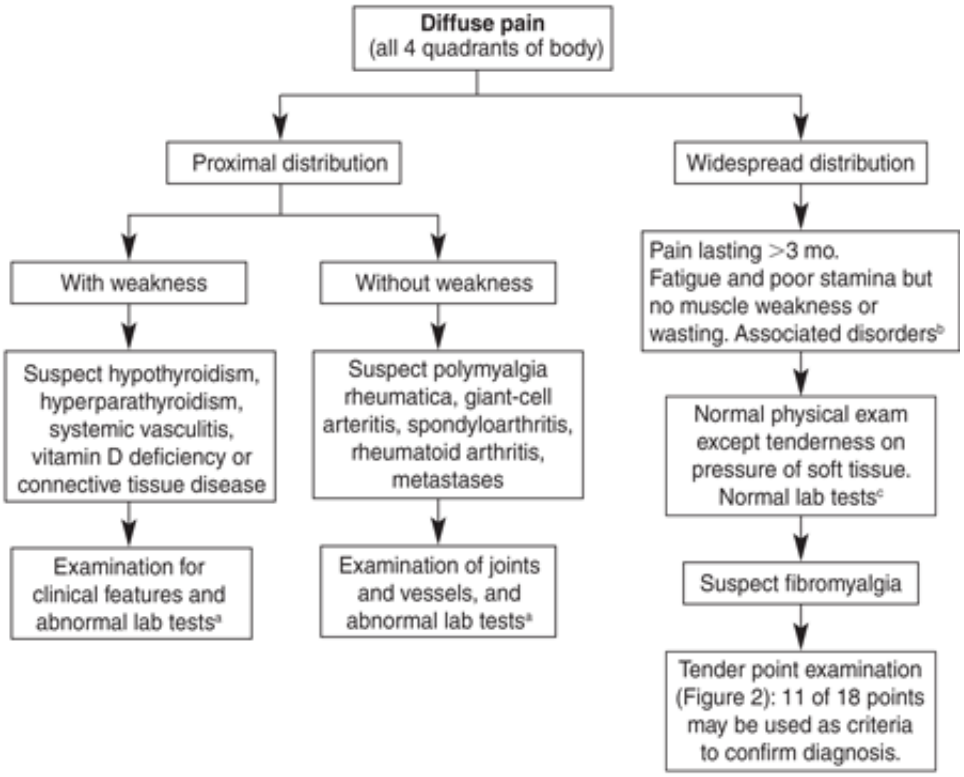
Tricyclic antidepressants can cause sedation in the newborn if used in the antenatal period or during lactation. SSRIs and SNRIs are excreted into breast milk. Although some studies report no adverse effects from **fluoxetine** on breastfed infants,[57] poor weight gain, irritability, colic, vomiting, diarrhea, and/or decreased sleep have been noted in others.[58] , [59] The effects of **duloxetine** [60] on the infant are unknown. Until more data are available, **pregabalin** use is not advised for nursing mothers.[47]

A discussion of general principles on the use of medications in these special populations can be found in Appendix: Drug Use During Pregnancy and Appendix: Drug Use During Breastfeeding. Other specialized reference sources are also provided in these appendices.

Therapeutic Tips

- The treatment of arthritis, hypothyroidism, peripheral neuropathy and other medical conditions may be complicated by concomitant fibromyalgia.
- Pharmacologic agents work best when combined with nonpharmacologic modalities, ideally as part of a multidisciplinary treatment program.[4]
- Patients may also require a combination of drugs with different mechanisms of action.
- It is important to document not only reduced pain but also improved function.
- In the experience of the author and other clinicians, patients with fibromyalgia may be unduly sensitive to drug side effects; a rational approach is to start medications at low doses and increase slowly by small increments.
- The initial improvement of fibromyalgia with pharmacotherapy fades with time. Patients may experience remission not necessarily attributed to any specific therapy. Conversely, there are subsets of patients who are intolerant of and/or unresponsive to all pharmacologic therapy.
- Sleep problems may need further study in a sleep disorder clinic.
- Concomitant mood disorders require higher doses of antidepressants than are used for fibromyalgia. For more information regarding antidepressants, see Psychiatric Disorders: Depression.
- Counselling the patient to recognize the roles of various social, psychological and/or environmental factors in the exacerbation or aggravation of his/her pain can lead to rewarding reductions in pain intensity. Emphasizing that the pain is "not in your head" but that life events and occurrences may be playing various roles in the syndrome's expression can be clinically beneficial.

Figure 1 - Investigation of Diffuse Aches and Pains



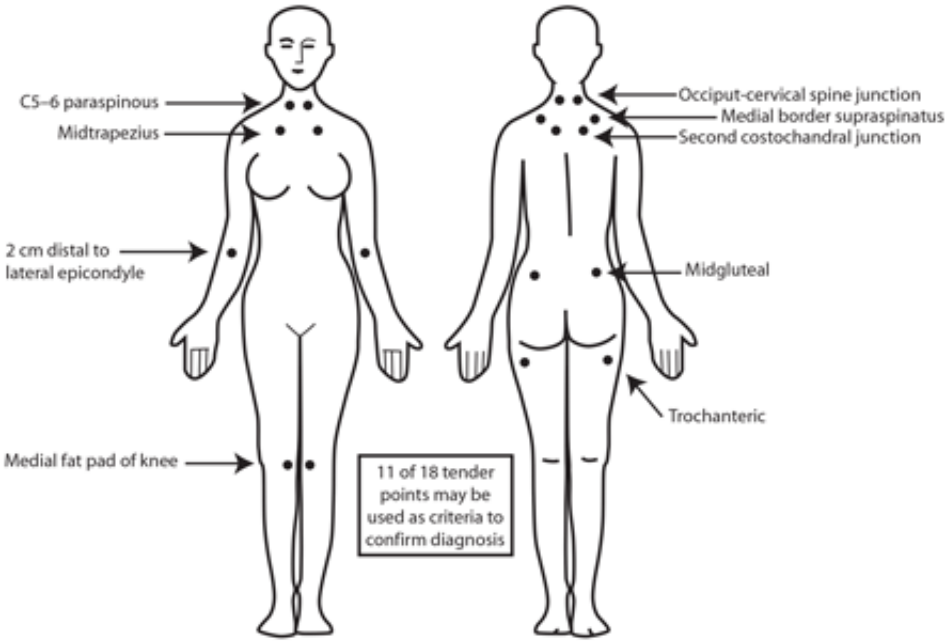
a. AST, alkaline phosphatase, calcium, CBC, creatine kinase, creatinine, CRP, ESR, TSH and 25-hydroxyvitamin D.

b. Associated disorders include mood disturbances, cognitive dysfunction, irritable bowel syndrome, irritable bladder syndrome, dizziness, cold intolerance, subjective swelling, paresthesiae, migraine, severe menstrual pain, myofascial facial pain, sexual dysfunction and temporomandibular joint syndrome.

c. CBC, creatine kinase, ESR, CRP and TSH.

Abbreviations: AST=aspartate transaminase; CBC=complete blood count; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; TSH=thyroid-stimulating hormone

Figure 2 - Tender Point Examination[a]



a. Using thumb pressure sufficient to blanch fingernail.

Figure 3 - Preliminary Diagnostic Criteria for Fibromyalgia

Widespread Pain Index (WPI)

Check the number of areas in which the patient has had pain over the last week.

Shoulder girdle	left ☐	right ☐	Upper back ☐	Abdomen ☐
Upper arm	left ☐	right ☐	Lower back ☐	Neck ☐
Lower arm	left ☐	right ☐	Chest ☐	
Hip (buttock, trochanter)	left ☐	right ☐		
Upper leg	left ☐	right ☐	Score will be between 0 and 19.	
Lower leg	left ☐	right ☐		
Jaw	left ☐	right ☐	**WPI =** _____	

Symptom Severity (SS) Scale

A. Indicate the level of severity of each of the 3 symptoms listed below over the past week using the following scale:

0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems

Fatigue ____ Waking unrefreshed ____ Cognitive symptoms ____ **= TOTAL A** _____

B. Considering somatic symptoms in general,[a] indicate whether the patient has:

0 = no symptoms; **1** = few symptoms; **2** = a moderate number of symptoms; **3** = a great deal of symptoms

= TOTAL B _____

Score (A + B) will be between 0 and 12.

SS SCALE SCORE = _____

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.
2. Symptoms have been present at a similar level for at least 3 months.
3. The patient does not have a disorder that would otherwise explain the pain.

a. Consider: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of or change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, bladder spasms.

Adapted with permission from Wolfe F, Clauw D, Fitzcharles MA et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 2010;62(5):600-10.

Table 1: Drugs Used in Fibromyalgia

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
Tricyclic Agents [b]	*amitriptyline* [c] Elavil, generics	5– 50 mg 2–3 h before bedtime (start low and titrate slowly)	Anticholinergic (dry mouth, blurred vision, constipation, urinary hesitancy, tachycardia, delirium), antihistaminergic (sedation, weight gain), orthostatic hypotension, lowered seizure threshold; sexual dysfunction.	Combination with MAOIs may result in mania, excitation, hyperpyrexia; barbiturates, carbamazepine and rifampin may ↓ effect; cimetidine and antipsychotics may ↑ effect and toxicity; possible interaction with antiarrhythmics (may lead to ↑ effect of either drug); may ↓ antihypertensive effect of clonidine; may ↑ hypotensive effect of thiazides.	$
Tricyclic		10 mg at	Anticholinergic	Combination with MAOIs may	$

Tricyclic Agents[b]	*cyclobenzaprine* [c] generics	10 mg at bedtime. May titrate up to 40 mg/day taken in 2–4 divided doses. Lower doses (<5 mg) may also be effective.[61]	Anticholinergic (dry mouth, blurred vision, constipation, urinary hesitancy, tachycardia, delirium), antihistaminergic (sedation, weight gain), orthostatic hypotension, lowered seizure threshold; sexual dysfunction.	Combination with MAOIs may result in mania, excitation, hyperpyrexia; barbiturates, carbamazepine and rifampin may ↓ effect; cimetidine and antipsychotics may ↑ effect and toxicity; possible interaction with antiarrhythmics (may lead to ↑ effect of either drug); may ↓ antihypertensive effect of clonidine; may ↑ hypotensive effect of thiazides.	$
Selective Serotonin Reuptake Inhibitors	*fluoxetine* [c] Prozac, generics	10–20 mg QAM (better efficacy in 1 trial when combined with amitriptyline in the evening)[28]	Nausea, dry mouth, somnolence, sweating, sexual dysfunction. ↑ risk of GI bleeding.	MAOIs may cause severe reaction—tremor, agitation, hypomania, hypertension. Drugs that inhibit CYP enzymes (e.g., cimetidine, clarithromycin, erythromycin, fluconazole, indinavir, isoniazid, itraconazole, ketoconazole, quinidine, ritonavir) may ↑ SSRI levels. All SSRIs inhibit certain CYP isoenzymes and can ↓ the clearance of other drugs (e.g., clozapine, methadone, mexiletine, phenytoin, pimozide, propafenone). Inducers of CYP enzymes (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) can ↑ the clearance of SSRIs. ↑ risk of GI bleeding with NSAIDs.	$
Serotonin-Norepinephrine Reuptake Inhibitors	*duloxetine* Cymbalta	30– 60 mg once daily. Maximum: 120 mg/day (divided BID)	Nausea, headache, drowsiness, insomnia, dizziness, dry mouth. Do not use in patients with severe renal impairment (CrCl <30 mL/min).	Alcohol, CNS depressants. MAOIs may cause serotonin syndrome (severe reaction—tremor, agitation, hypomania, hypertension). Tramadol may also ↑ risk of serotonin syndrome. Do not use with potent CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine, ketoconazole). CYP2D6 inhibitors (e.g., SSRIs) may ↑ duloxetine levels.	$$$$$
GABA Derivatives	*gabapentin* [c] Neurontin, GD-gabapentin, other generics	Starting dose: 100 mg QHS. Titrate slowly upward as tolerated to 1200–2400 mg/day (in 2–3 divided doses).	Sedation, ataxia, tremor; less commonly, GI upset, peripheral edema, vision changes, weight gain.	Administration with aluminum/magnesium-containing antacids may ↓ bioavailability. May have enhanced CNS depressant effects when coadministered with other CNS depressants.	$$
GABA Derivatives	*pregabalin* [c] Lyrica, generics	Starting dose: 25–50 mg QHS.	Sedation, dizziness,	May have enhanced CNS depressant effects when	$$

	Lyrica, generics	Titrate slowly upward as tolerated to 300–450 mg/day (in 2 divided doses).	cognitive impairment, dry mouth, peripheral edema.	coadministered with other CNS depressants. May cause peripheral edema/weight gain when coadministered with thiazolidinediones (pioglitazone, rosiglitazone).	
Analgesics	*acetaminophen* c Tylenol, Atasol Preparations, generics	325 –1000 mg Q4H Maximum dose 4 g/day	Hepatotoxicity with chronic high doses or in acute overdose.	Excessive alcohol intake may ↑ the risk of hepatotoxicity. Warfarin: ↑ anticoagulant effect particularly with use of >1.3 g/day for longer than 1 wk.	$
Analgesics	*tramadol extended-release* c Durela, Ralivia, Tridural, Zytram XL	Durela, Ralivia or Tridural: Start with 100 mg once daily po; may increase at weekly intervals to maximum 300 mg daily Zytram XL: Start with 150 mg once daily po; may increase at weekly intervals to maximum 400 mg daily	Somnolence, dizziness, flushing, constipation, nausea, pruritus, seizures, anaphylactoid reactions, dependence, withdrawal syndrome.	Possible ↑ risk of seizure with SSRIs, MAOIs, tricyclic antidepressants and other tricyclic compounds, antipsychotics, amphetamines, linezolid, opioids or drugs that reduce the seizure threshold. Use with SSRIs or MAOIs may also ↑ risk of serotonin syndrome. Use with CNS depressants may ↑ the risk of CNS and respiratory depression. Carbamazepine may ↑ the metabolism of tramadol. Also, tramadol may ↑ the risk of seizures in patients taking anticonvulsants.	$$$$
Analgesics	*tramadol with acetaminophen* c Tramacet, generics	Use lowest dose possible to achieve pain control. 1–2 tablets Q4–6H PRN Maximum 8 tablets (300 mg tramadol + 2600 mg acetaminophen) daily	Somnolence, dizziness, flushing, constipation, nausea, pruritus, seizures, anaphylactoid reactions, dependence, withdrawal syndrome.	Excessive alcohol intake may ↑ the risk of hepatotoxicity. Warfarin: ↑ anticoagulant effect particularly with use of >1.3 g/day for longer than 1 wk. Possible ↑ risk of seizure with SSRIs, MAOIs, tricyclic antidepressants and other tricyclic compounds, antipsychotics, amphetamines, linezolid, opioids or drugs that reduce the seizure threshold. Use with SSRIs or MAOIs may also ↑ risk of serotonin syndrome. Use with CNS depressants may ↑ the risk of CNS and respiratory depression. Carbamazepine may ↑ the metabolism of tramadol. Also, tramadol may ↑ the risk of seizures in patients taking anticonvulsants.	$$$
Nonsteroidal Anti-inflammatory Drugs b	*ibuprofen* c Advil, Motrin IB, generics	200–600 mg Q6H	Peptic ulcer, dyspepsia, hypersensitivity, fluid retention, hypertension, renal toxicity.	Warfarin: ↑ anticoagulant effect. Antihypertensives: possible ↓ in hypertensive effect. Lithium: may interfere with sodium/water balance. Monitor lithium levels when NSAID added.	$

				↑ risk of GI bleeding when used with SSRIs.	

a. Cost of 30-day supply of mean dose; includes drug cost only.
b. Listed drugs are examples of medications in this class.
c. Not a Health Canada-approved indication.

Dosage adjustment may be required in renal impairment; see Appendices: Dosage Adjustment in Renal Impairment.

Abbreviations: CNS=central nervous system; CYP=cytochrome P450; MAOI=monoamine oxidase inhibitor; NSAID=nonsteroidal anti-inflammatory drug; SSRI=selective serotonin reuptake inhibitor

Legend: $ <$25 $$ $25–50 $$$ $50–75 $$$$ $75–100 $$$$$ $100–125

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