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Neurologic Disorders: Restless Legs Syndrome

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Restless legs syndrome (RLS), also known as Willis-Ekbom disorder, is a neurologic disorder characterized by an unpleasant sensation in the legs accompanied by an urge to move the legs, especially at bedtime.[1] The cause of primary RLS is not definitively known but is believed to involve a genetic component as well as dysfunctional dopaminergic transmission and low brain iron stores. Secondary RLS is associated with many conditions such as diabetes mellitus, end-stage renal disease (anemia may play a role), iron deficiency, multiple sclerosis, Parkinson's disease, pregnancy and venous insufficiency. Drugs such as alcohol, antidepressants, antipsychotics, caffeine, metoclopramide and nicotine can aggravate symptoms.

Symptoms of RLS occur when the limbs are at rest, and are relieved by movement. In severe cases, symptoms may extend to the arms and trunk. Symptoms are commonly bilateral and symmetrical, but on occasion can be unilateral. The prevalence of RLS is estimated to be 5–15% in the general population,[1,2] is higher in women and increases with age. Patients often use the following terms to describe the symptoms of RLS: a "creepy-crawly", "burning", "nagging", "aching", "painful", "itching-bones" or "electric-current" sensation. These unpleasant sensations may last hours and may persist throughout the night causing sleep disturbance in some patients.

All of the following 4 criteria are required for a diagnosis of RLS:[3]

- An urge to move the legs, usually accompanied or caused by unpleasant sensations in the legs.
- Symptoms begin or worsen during periods of rest or inactivity such as lying or sitting.
- Symptoms are partially or totally relieved by movement, such as walking or stretching, for at least as long as the activity continues.
- Symptoms are worse in the evening or at night, or may occur only in the evening or at night.

Supportive clinical features include a positive family history, response to dopaminergic therapy and periodic limb movements during wakefulness (PLM) or during sleep (PLMS).[3]

Intermittent RLS is defined as symptoms that occur on average less than twice a week but are troublesome enough to require treatment less often than daily. In *chronic persistent* RLS, symptoms cause moderate to severe distress and are frequent and bothersome enough to require daily therapy.[4] Symptoms occur on average at least twice a week. Patients with *refractory* RLS are those who experience inadequate response and/or intolerable side effects and/or "augmentation" (see Goals of Therapy) not responding to more frequent dosing, while receiving first-line therapy for daily symptoms.

Goals of Therapy

- Improve the symptoms of motor restlessness and discomfort
- Improve sleep
- Improve function in patients experiencing daytime symptoms
- Reduce the PLMS, if disruptive
- Reduce the potential for "rebound" or "augmentation" with drug therapy
  - "rebound" is the recurrence of symptoms during the night or early morning coinciding with the end-of-dose wearing off of effectiveness.[5]
  - "augmentation" is the occurrence of symptoms earlier in the day than they occurred prior to treatment, a shorter latency time to symptom onset when at rest, an increase in the severity of symptoms with shorter treatment effect and/or spread of symptoms to involve the upper extremities and trunk.[6]

Investigations

- History from patient and partner regarding sleep and PLMS
- CBC, electrolytes, BUN, creatinine, fasting glucose, serum iron, ferritin and iron saturation
- Nerve conduction studies can be performed if peripheral neuropathy is suspected
- Polysomnography should be performed if there is a clinical suspicion of sleep apnea or concurrent sleep disorder
- Consider vascular insufficiency, e.g., varicose veins, as potential contributing factor

Therapeutic Choices

Nonpharmacologic Choices

While pharmacologic therapy is needed for moderate to severe symptoms, nonpharmacologic measures may be useful in milder cases:

- Engage in mental alertness activities (playing cards, video games or doing crossword puzzles) to reduce symptoms during times of boredom.[7]
- Abstain from alcohol, caffeine and nicotine.[7]
- Take hot baths, stretch and exercise moderately.[8]
- Discontinue medications that may be contributing to symptoms, e.g., antidepressants, antipsychotics, dopamine-blocking antiemetics and sedating antihistamines.[7]
- Minimize aggravating factors such as sleep deprivation
- In patients with RLS and varicose veins, consider sclerotherapy to improve RLS symptoms.[9]

In patients who do not respond to pharmacotherapy or experience intolerable side effects, consider a trial of pneumatic compression devices (PCDs), garments that are intermittently inflated and deflated with compressed air using an electrical pneumatic pump. In a small randomized sham-controlled study of one month's duration, patients who wore PCDs on their legs for at least 1 hour daily prior to the usual onset time of moderate to severe RLS symptoms had improvement in quality of life scores and clinically significant improvement in RLS symptoms.[10]

Pharmacologic Choices

Studies have shown that 25–30% of patients with RLS are iron deficient.[11] The incidence of secondary RLS is increased in patients with conditions associated with iron deficiency such as pregnancy and end-stage renal disease. Furthermore, RLS may be the only clinical indicator of iron deficiency and can be more severe in patients with serum ferritin less than 50 µg/L (normal range is 40–200 µg/L).[4] **When patients present with RLS symptoms, investigate for the possible presence and cause of iron deficiency. Although a systematic review concluded there was insufficient evidence to determine whether iron would benefit any or all patients with RLS,[12] a trial of oral iron therapy should be considered for patients in whom a deficiency is detected [SORT C].**[13] Useful Info? For more information about treatment of iron deficiency anemia, see Blood Disorders: Common Anemias.

See Table 1 for a detailed list of drug therapy options. The choice of pharmacologic agent depends on the severity of RLS symptoms.

Levodopa preparations, benzodiazepines or low-potency opioids are good options for treatment of intermittent RLS.[4] In chronic persistent RLS, dopamine agonists or GABA derivatives are the preferred agents. Both are associated with a lower risk of augmentation compared to levodopa.[4], [14] Figure 1 - Management of Intermittent and Chronic Persistent Restless Legs Syndrome[4] illustrates the clinical management of intermittent and chronic persistent RLS.

In patients with refractory RLS, lower doses of single-agent therapy are not effective. Consider combining treatment from different drug classes, i.e., dopamine agonists, GABA derivatives, benzodiazepines or opioids.[4], [14] Figure 2 - Management of Refractory Restless Legs Syndrome[4] illustrates clinical management of refractory RLS.

Pharmacotherapy for Intermittent RLS

Levodopa Preparations

Many clinical trials have shown **levodopa/carbidopa** to be effective for the treatment of RLS.[15] While levodopa may be suitable for patients with intermittent symptoms, its short half-life increases the potential for rebound and/or augmentation and makes it a poor choice for patients with daily symptoms.

Benzodiazepines

Benzodiazepines do not improve the core symptoms of RLS, but are appropriate for improving sleep quality in patients with intermittent RLS, or as an adjunct to first-line agents in refractory RLS. The main limitation of this drug class is the potential for dependence and the risk of falls in elderly patients. Clinical trials have shown that **clonazepam** significantly improves

objective sleep efficiency and subjective sleep quality in both RLS and PLMS.[16] Clonazepam has a long half-life and a potential to cause morning sedation and dizziness. Consider using agents with short or intermediate duration of action, such as **temazepam**, in the elderly population.

Opioids

Opioids have been used to treat RLS since its earliest description and their clinical efficacy has been demonstrated in a several controlled and open clinical trials.[17] The strong sedating properties of opioids may be responsible for their effectiveness rather than any effect on leg movements. Due to the potential for dependence, low-potency opioids such as **codeine** are a better choice for intermittent RLS. More potent agents such as **oxycodone** or **methadone** are reserved for RLS that is refractory to other treatments. Patients who experience constipation as an adverse effect may benefit from **oxycodone-naloxone** controlled-release tablets.[18] Evaluate the patient for sleep apnea before prescribing opioids.[19]

Although **tramadol** has shown some benefit in the treatment of RLS[20], there are case reports of RLS augmentation[21] and RLS as an adverse effect with this agent.[22]

Pharmacotherapy for Chronic Persistent RLS

Dopamine Agonists

Dopamine agonists have a long-half-life and are associated with a lower incidence of augmentation compared to levodopa, making them a better choice for long-term treatment of RLS.[19] Initiate treatment with a dopamine agonist in patients who have severe symptoms, excessive weight, comorbid depression, cognitive impairment or are at increased risk for falling.[19] The efficacy of bromocriptine,[23] pergolide,[24] , [25] pramipexole,[26] ropinirole[27] and rotigotine[28] in the treatment of RLS has been established in controlled clinical trials. These agents improve sleep efficiency and decrease the frequency of periodic limb movements during sleep. Side effects of dopamine agonists include nausea, sedation and lightheadedness and these generally decrease after the first few months of therapy.[19] Clinicians should inform patients that dopamine agonists are associated with a high risk (6–17%) of developing a compulsive behaviour such as pathological gambling and hypersexuality.[19] , [29] These disorders may occur more frequently in women and may be associated with higher doses of drugs. Monitor for these behaviours at each patient visit and discontinue or decrease the dosage of the dopamine agonist if the adverse effect is significant.[19] When discontinuing dopamine agonist treatment, taper the dose gradually to minimize withdrawal symptoms.[19]

Bromocriptine and **pergolide** are ergoline derivatives that are associated with a higher frequency of adverse effects. Pergolide is no longer available in Canada. It was withdrawn from the market in 2007 due to reports of cardiac valvulopathy.[30]

Pramipexole and **ropinirole** are nonergoline derivatives and have a more favourable side effect profile in patients with RLS. When used at higher doses in the treatment of Parkinson's disease they have been associated with a higher incidence of sudden sleep attacks. For RLS, pramipexole is started at 0.125 mg po taken 2 hours before the onset of symptoms and the dose is increased every 4–5 days until it is effective.[19] The average dose is 0.5 mg but some patients may require up to 2 mg daily. The starting dose of ropinirole is 0.25 mg/day with an average effective dose being in the 1–4 mg/day range. Some patients may require an additional dose given in the late afternoon if symptoms arise earlier in the day.

Rotigotine is a nonergolinic dopamine agonist that is officially approved to treat symptoms of moderate to severe idiopathic RLS in patients 18 years or older. The transdermal system is formulated to deliver rotigotine over a 24-hour period. To minimize skin irritation, advise patients to apply the patch only on intact, undamaged skin and not to use the same application site for at least 14 days. The patches should not be cut. Avoid the use of external heat to the area where the patch is applied as this would increase the release of the drug from the patch.

GABA Derivatives

GABA derivatives are alternatives to dopamine agonists in the treatment of chronic persistent RLS. Consider these agents first in patients who have severe sleep disturbance, comorbid insomnia or anxiety, painful RLS, or a history of compulsive behaviour or anxiety.[19] **Gabapentin** and **pregabalin** are administered once or twice daily later in the day (afternoon, evening or before sleep). Gabapentin was shown to be effective in open[31] and double-blind, randomized controlled trials.[32] Initiate gabapentin at 300 mg po daily and titrate to effect; typical doses range from 900–1800 mg/day.[4] Consider pregabalin in patients who develop augmentation with a dopamine agonist. In a year-long double-blind trial, 719 patients with RLS were randomized to once daily doses of pregabalin 300 mg, pramipexole 0.25 mg, pramipexole 0.5 mg or 12 weeks of placebo

followed by 40 weeks of one of the active treatments.[33] Pregabalin was shown to significantly improve RLS symptom scores compared to placebo, and significantly lower augmentation rates compared to pramipexole 0.5 mg. To minimize adverse effects, start pregabalin at 100 mg po daily and increase every 2–3 days to an effective dose usually in the range of 150–450 mg/day.[4] (See Goals of Therapy.) Major side effects of these agents include drowsiness and unsteady gait, especially in the elderly. Suicide-related events have been reported with GABA derivatives; monitor patients for signs of suicidal ideation and behaviours.

Gabapentin enacarbil is a novel prodrug of gabapentin that is not currently available in Canada. This agent was developed to address the pharmacokinetic limitations of gabapentin and can be administered once daily. Its effectiveness in the treatment of RLS has been shown in several randomized, controlled trials.[34]

Other Agents

Antiepileptic drugs such as carbamazepine and valproic acid have not been as rigorously studied as the GABA derivatives.[35], [36] There is some evidence for improved RLS symptoms with other agents such as amantadine,[37] baclofen[38] and clonidine.[39] These drugs should be reserved for patients who develop tolerance to recommended first-line agents.

Choices during Pregnancy and Breastfeeding

RLS and Pregnancy

RLS symptoms are common during pregnancy with an estimated prevalence of 10–20%.[40] The exact cause is not known but deficiency of iron and vitamins may be involved. Symptoms of RLS are most often a feature of the third trimester and are usually temporary, with most symptoms disappearing soon after childbirth.

None of the drugs used to treat RLS are known to be safe in pregnancy. Nonpharmacologic choices are therefore the safest treatments for women who experience RLS during pregnancy. It is important to rule out iron, magnesium or folate deficiency, as appropriate supplementation may be helpful. RLS typically becomes more severe as the pregnancy progresses. If pharmacologic therapy is deemed necessary, waiting until the third trimester will reduce the risk of adverse pregnancy outcomes. **Dopamine agonists** are not recommended. **Opioids** can be used but should be avoided near term because of the risk of respiratory depression in the newborn. For most pregnant women, RLS is temporary and the symptoms will typically resolve postpartum. Educating pregnant women about the self-limiting nature of symptoms may allay fears.

RLS and Breastfeeding

As in pregnancy, nonpharmacologic choices are the safest option for women experiencing RLS when breastfeeding. There is no available information on the use of **pramipexole**, **ropinirole** and **rotigotine** in breastfeeding women, but these drugs suppress serum prolactin and may interfere with lactation.[41] Limited information indicates that maternal doses of **gabapentin** and **pregabalin** may produce relatively low levels in infant serum.[41] Limited data indicate that **levodopa** is poorly excreted into breast milk and that sustained-release formulations may result in a smaller amount of drug transferred to the breastfed infant than immediate-release products.[42] Several studies indicate that levodopa can decrease serum prolactin during lactation, but a reduced prolactin level may not affect breastfeeding in a mother with established lactation.[43], [44] The effect of long-term use of levodopa on breastfeeding has not been adequately evaluated.

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

Therapeutic Tips

- Always consider nonpharmacologic management.
- When possible, discontinue drugs that may be contributing to symptoms.
- Drugs should be started at the lowest dose, administered 1–2 hours before bedtime, and gradually titrated to the lowest effective dose.
- Optimizing long-term therapy may be difficult; if one drug loses its effectiveness, switching to another drug in the same or a different class may be effective.
- For symptoms beginning earlier in the day, a second daily dose can be prescribed in the afternoon, and if needed, in the morning.
- Intractable RLS may require the use of polytherapy.
- Levodopa is associated with a higher incidence of rebound. Restrict its use to the treatment of intermittent RLS.

- Augmentation occurs less frequently with dopamine agonists than with levodopa. Manage augmentation by alternating medications, i.e., switch between drug classes every few months as needed.
- For patients taking dopamine agonists, monitor at each visit for the emergence of compulsive behaviours.
- The Willis-Ekbom Disease Foundation website (www.willis-ekbom.org) is a good resource for healthcare providers and patients.

Algorithms

Figure 1 - Management of Intermittent and Chronic Persistent Restless Legs Syndrome[4]

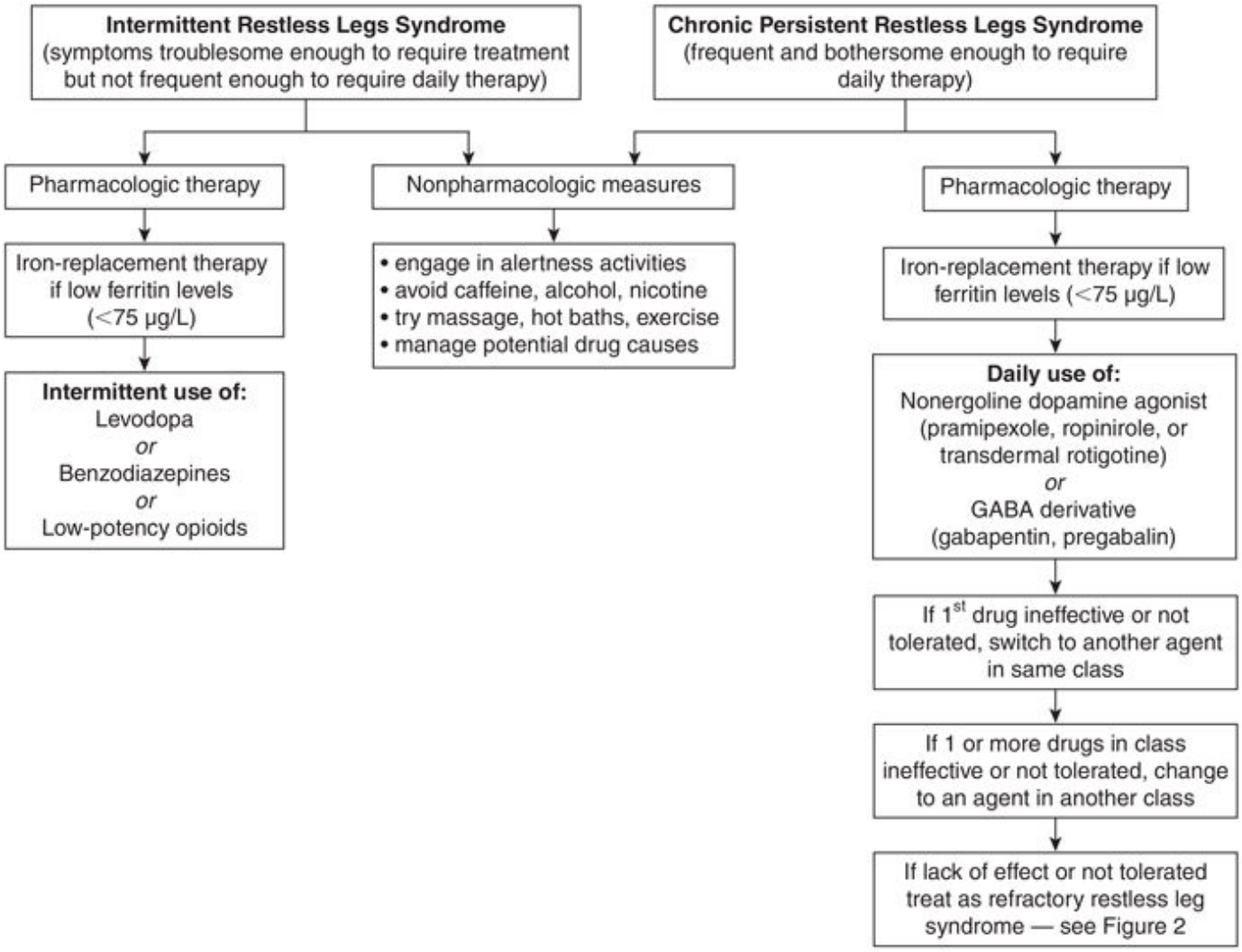
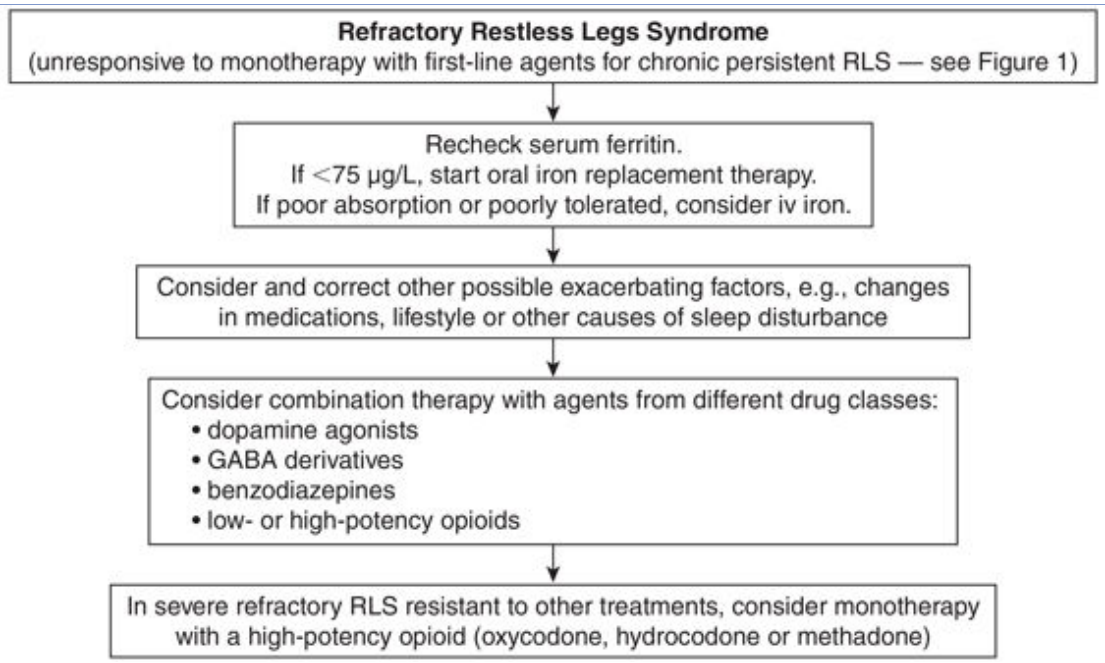


Figure 2 - Management of Refractory Restless Legs Syndrome[4]



Abbreviations:
RLS=
restless legs syndrome

Drug Table

Table 1: Drug Therapy for Restless Legs Syndrome

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
Benzodiazepines	*clonazepam* Rivotril, generics	0.25–2 mg QHS po	Sedation, dizziness, dependence.	Additive sedation with other CNS depressants such as alcohol.	$
Benzodiazepines	*temazepam* Restoril, generics	15–30 mg QHS po	Sedation, dizziness, dependence.	Additive sedation with other CNS depressants such as alcohol.	$
Benzodiazepines	*triazolam* generics	0.125–0.25 mg QHS po	Sedation, dizziness, dependence.	Additive sedation with other CNS depressants such as alcohol.	$
Dopamine Agonists	*bromocriptine* generics	7.5 mg QHS po	Nausea, vomiting, lightheadedness, hallucinations, psychosis, erythromelalgia (burning pain, warmth and redness of the extremities), pleural fibrosis. Risk of parkinsonism-hyperpyrexia syndrome with abrupt discontinuation; taper gradually. Drug holidays not recommended.	First-generation antipsychotics decrease effect of dopamine agonists.	$$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
Dopamine Agonists	*pramipexole* Mirapex, generics	0.125–0.75 mg/day po; at least 2 hours before usual time of symptom onset May need up to 2 mg/day.	Orthostatic hypotension, somnolence, confusion, hallucinations, nausea, vomiting, insomnia, sudden sleep attacks. Caution patients about potential compulsive behaviours such as pathologic gambling or hypersexual behaviour. Caution patients about driving or operating dangerous machinery. Risk of parkinsonism-hyperpyrexia syndrome with abrupt discontinuation; taper gradually. Drug holidays not recommended.	First-generation antipsychotics decrease effect of dopamine agonists.	$
Dopamine Agonists	*ropinirole* ReQuip, generics	0.25–4 mg/day po May be given in 2–3 divided doses if needed.	Orthostatic hypotension, somnolence, confusion, hallucinations, nausea, vomiting, insomnia, sudden sleep attacks. Caution patients about potential compulsive behaviours such as pathologic gambling or hypersexual behaviour. Caution patients about driving or operating dangerous machinery. Risk of parkinsonism-hyperpyrexia syndrome with abrupt discontinuation; taper gradually. Drug holidays not recommended.	First-generation antipsychotics decrease effect of dopamine agonists.	$
Dopamine Agonists	*rotigotine* Neupro	1–3 mg/24 h patch once daily Apply to clean, dry intact skin on abdomen, thigh, hip, flank, shoulder or upper arm. Avoid using the	Lightheadedness, confusion, hallucinations, nausea, vomiting, sedation, fatigue, headache. Caution patients about potential compulsive behaviours such as pathologic gambling or	First-generation antipsychotics decrease effect of dopamine agonists.	$100–200

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
		same site twice within 14 days.	hypersexual behaviour. Risk of parkinsonism-hyperpyrexia syndrome with abrupt discontinuation; taper gradually. Drug holidays not recommended. Application site reactions can occur.		
GABA Derivatives	*gabapentin* Neurontin, generics	300–2400 mg daily po May be given in 2–3 divided doses if needed. Not a Health Canada-approved indication.	Sedation, dizziness, ataxia, tremor, vision changes, weight gain.	May enhance CNS depressant effects when coadministered with other CNS depressants. May cause peripheral edema/weight gain when coadministered with thiazolidinediones (pioglitazone, rosiglitazone).	$$$$
GABA Derivatives	*pregabalin* Lyrica, generics	100–450 mg/day May be given in 2 divided doses if needed. Not a Health Canada-approved indication.	Sedation, dizziness, ataxia, tremor, vision changes, weight gain.	May enhance CNS depressant effects when coadministered with other CNS depressants. May cause peripheral edema/weight gain when coadministered with thiazolidinediones (pioglitazone, rosiglitazone).	$$$
Levodopa Preparations	*levodopa/carbidopa* Sinemet, Sinemet CR, generics	50/12.5–200/50 mg QHS po	Nausea, vomiting, lightheadedness, dry mouth, "rebound" and "augmentation".	First-generation antipsychotics decrease effect of levodopa. Antihypertensives, diuretics, tricyclic antidepressants may increase hypotensive action. Reduced absorption with high-protein meals.	$
Opioids	*codeine immediate-release* generics	30–180 mg/day po May be given in 2–3 divided doses if needed.	Sedation, constipation, dependence.	Additive sedation with other CNS depressants such as alcohol.	$
Opioids	*codeine sustained-release* Codeine Contin	50–150 mg daily po divided Q12H	Sedation, constipation, dependence.	Additive sedation with other CNS depressants such as alcohol.	$$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
Opioids	*methadone* Metadol, generics	5–40 mg/day po May be given in 2 divided doses if needed.	Sedation, constipation, dependence. May prolong QT_C interval.	Additive sedation with other CNS depressants such as alcohol. Caution with other drugs that can cause QT_C interval prolongation such as amiodarone, erythromycin, quinidine.	$$$
Opioids	*oxycodone immediate-release* Oxy-IR, Supeudol, generics	5–30 mg daily po May be given in 2–3 divided doses if needed.	Sedation, constipation, dependence.	Additive sedation with other CNS depressants such as alcohol.	$$
Opioids	*oxycodone sustained-release* OxyNEO, generics	10–20 mg HS po	Sedation, constipation, dependence.	Additive sedation with other CNS depressants such as alcohol.	$$
Opioids	*oxycodone/naloxone controlled-release* Targin	10–20 mg (oxycodone component) HS po	Sedation, constipation, dependence. Role of naloxone is to relieve opioid-induced constipation.	Additive sedation with other CNS depressants such as alcohol.	$$$

a. Cost of 30-day supply of mean dose; includes drug cost only.

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

Legend: $ < $15 $$ $15–30 $$$ $30–45 $$$$ $45–60

Suggested Readings

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