



BC Epilepsy Society

New Antiepileptic Medication

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Epilepsy is unpredictable. The development of new antiepileptic medications has been increasing over the last two decades as a result of refractory epilepsy and unmet needs, and while many people with epilepsy respond well to their medications, some continue to have seizures or experience intolerable side effects. The growing number of antiepileptic medications provides more available treatment options which may be particularly beneficial for those who need better seizure control. But with the increase in number of options, does choosing an antiepileptic medication become more difficult?

It is not just a guessing game!

The selection of antiepileptic medications is based on many different considerations. Treatment is highly individualized and decisions are often based on a person's specific situation including their age, gender, allergies, genetics, current medications, and insurance coverage. Antiepileptic medications are also considered in detail with respect to their mechanism of action, effectiveness, side effects, drug interactions, available formulations, and cost. Combining all of this information helps with making a rational decision on treatment for an individual.

When a new antiepileptic medication is approved

New antiepileptic medications that are approved in Canada have undergone several phases of clinical trials that include laboratory testing and human trials from small to large groups of participants for evaluation. To obtain relevant details as to what has been studied about a medication and its subsequent role in treatment, some good questions to ask may include the following:

- Do the trials demonstrate effectiveness?
- Which individuals is the medication best suited for?
- Are there any side effects?
- Are there any drug interactions?
- What is available in Canada?
- How much does it cost?

Let's use these questions and take a look at three antiepileptic medications recently approved in Canada.

Brivaracetam (Brivlera™)

Brivaracetam was approved by Health Canada in 2016 as an add-on therapy for adult patients with uncontrolled focal (partial) epilepsy. The chemical structure is related to the commonly used antiepileptic medication levetiracetam and similarly appears to work on a protein in the brain called SV2A (synaptic vesicle protein 2A), but has shown to be up to 30 times more likely to bind to the site of action when compared to levetiracetam. ^{1,2}

Do the trials demonstrate effectiveness? Four clinical trials^{3,4,5,6} on brivaracetam demonstrated significant reduction in frequency of focal (partial) seizures from baseline when compared with placebo. The treatment dose ranged from 50mg to 200 mg divided twice daily. Thus far, there are no trials that directly compare brivaracetam to other antiepileptic medications.

Which individuals is the medication best suited for? The major trials that demonstrated effectiveness included individuals age ≥ 16 years old with uncontrolled focal (partial) seizures. The study participants were on at least one other antiepileptic medications and brivaracetam was added on to be used in combination. The use in children is currently being investigated.

Are there any side effects?^a When taken within the recommended dose range, brivaracetam was well tolerated.^{3,4,5} The most common reported side effects of brivaracetam include drowsiness, fatigue, dizziness, headache, mood changes, and irritability.^{7,8}

Are there any drug interactions?^a Carbamazepine, phenobarbital, phenytoin, and rifampin can REDUCE the amount brivaracetam in the body, while brivaracetam appears to ELEVATE the amount of both carbamazepine and phenytoin in the body.⁹ Dosage adjustments may be required.

What is available in Canada? Tablets are currently available in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg. The 10 mg/mL oral solution and 10 mg/mL injectable are approved, but not yet marketed.^b

How much does it cost? The tablet cost is the same regardless of dosage strength and is approximately \$300 per month.^c

Eslicarbazepine (Aptiom®)

Eslicarbazepine was approved by Health Canada in 2014 as an add-on therapy for adult patients with uncontrolled focal (partial) epilepsy. The chemical structure is related to oxcarbazepine and carbamazepine and likewise works on blocking sodium channels in the brain that are responsible for generating seizures. An advantage of eslicarbazepine compared with its related medications is the ease of administration with once daily dosing.

Do the trials demonstrate effectiveness? Four clinical trials,^{10, 11, 12,13} on eslicarbazepine demonstrated significant reduction in frequency of focal (partial) seizures at doses of 800 to 1200 mg once daily when compared with placebo. Thus far, there are no trials that directly compare eslicarbazepine to other antiepileptic medications.

Which individuals if the medication best suited for? The major trials that demonstrated effectiveness included individuals age ≥ 16 years old with uncontrolled focal (partial) seizures. The study participants were on at least one other antiepileptic medications and eslicarbazepine was added on to be used in combination. The use in children is currently being investigated.

Are there any side effects?^a Most common reported side effects include nausea, dizziness, double vision, headache, and fatigue. Other observed serious side effects include low sodium levels (hyponatremia) and skin rash including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and toxic epidermal necrolysis (TEN).¹⁴

Are there any drug interactions?^a The use of eslicarbazepine and oxcarbazepine in combination should be avoided due to concern for increased side effects. Carbamazepine may be used; however, lower doses may be required based on tolerability. Eslicarbazepine may ELEVATE the amount of phenytoin in the body which will require close monitoring of phenytoin levels. Carbamazepine, phenobarbital, and phenytoin may

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^b Current at the time of publication

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REDUCE the amount of eslicarbazepine in the body. A higher dose of eslicarbazepine may be required. Other drug interactions include oral contraceptives, warfarin, and simvastatin.¹⁴

What is available in Canada?^b Tablets are currently available in 200 mg, 400 mg, 600 mg, and 800 mg.

How much does it cost? The tablet cost is the same regardless of dosage strength and is approximately \$330 per month.^c The medication may be eligible for Pharmacare Special Authority coverage when used as add-on therapy focal seizures and after the failure of four other antiepileptic medications.¹⁵

Perampanel (Fycompa™)

Perampanel was approved by Health Canada in 2013 as an add-on therapy for adult patients with uncontrolled focal (partial) seizures. In 2016, the approval was extended to include add-on therapy for adult patients with primary generalized tonic-clonic seizures. Perampanel is unique in that it is the first antiepileptic medication to target the AMPA receptor in the brain, thus reducing the effect of glutamate, a neurotransmitter that is associated with seizures.

Do the trials demonstrate effectiveness? Three clinical trials^{16,17,18} on focal (partial) seizures and one clinical trial¹⁹ on generalized tonic-clonic seizures have demonstrated significant reduction in frequency when compared with placebo. The effective treatment dose ranged from 4 mg to 12 mg once daily. Thus far, there are no trials that directly compare perampanel to other antiepileptic medications.

Which individuals is the medication best suited for? The major trials that demonstrated effectiveness included individuals age ≥ 12 years old with either uncontrolled focal (partial) seizures or primary generalized tonic-clonic seizures. The study participants were on at least one other antiepileptic medication and perampanel was added on to be used in combination.

Are there any side effects? The most common reported side effects include dizziness, fatigue, nausea, loss of balance, and irritability. Aggressive behaviour may also be seen and could potentially be related to previous history of behavioural problems with other antiepileptic medications or pre-existing behavioural conditions.^{20,21}

Are there any drug interactions?^a Carbamazepine, oxcarbazepine and phenytoin may REDUCE the amount of perampanel in the body. A higher dose of perampanel may be required.²⁰

What is available in Canada? Tablets are currently available in 2 mg, 4 mg, 8 mg, 10 mg, and 12 mg. An oral suspension in 0.5 mg/mL is approved, but not yet marketed.^b

How much does it cost? The tablet cost is the same regardless of dosage strength and is approximately \$320 per month.^c The medication may be eligible for Pharmacare Special Authority coverage when used as add-on therapy focal seizures and after the failure of four other antiepileptic medications.²²

Conclusion

Asking the same set of questions in reviewing each of these new medications helps with a practical comparison between them. In this review of three new antiepileptic medications, it is evident that these medications all have a different mechanism of action but seem to have a very similar role in treatment as add-on therapy when an individual is uncontrolled on at least one medication. On the other hand, the side effects and drug interactions are different and applying these differences can help with individualized treatment. For

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example, if a person is on warfarin or simvastatin, the choice of brivaracetam or perampanel may be better than eslicarbazepine to avoid any potential drug interactions. Or if a person has a history of behavioural issues, eslicarbazepine may be better than brivaracetam or perampanel to avoid these potential side effects.

Overall, a better understanding of the details of a medication helps rationalize decisions on whether or not it is appropriate to use in an individual. If the antiepileptic medication is new, there are usually ongoing long-term follow up studies in order to continually evaluate the effectiveness and safety of the medication. As more results are published, the role of an antiepileptic medication may change thus, further affecting the decisions on individualized treatments. People with epilepsy are encouraged to continually work with their health care team to understand the application of newly approved antiepileptic medications as well as subsequent published information regarding them.

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