Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

TITLE: Pharmacological Treatments in Patients with Epilepsy: Guidelines

DATE: 01 April 2011

RESEARCH QUESTION

What are the evidence-based guidelines for pharmacological treatments in patients with epilepsy?

KEY MESSAGE

Pharmacological monotherapy should be used as first line treatment for epilepsy. Polytherapy should be initiated only if different monotherapy options have failed.

METHODS

A focused search (with main concepts appearing in title, subject heading or major subject heading) was conducted using key health technology assessment resources, including PubMed and The Cochrane Library (2011, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and March 22, 2011. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by evidence-based guidelines.

Two health technology assessments, 23 systematic reviews and meta-analyses, and nine evidence-based guidelines were identified regarding the pharmacological treatments for patients with epilepsy.

OVERALL SUMMARY OF FINDINGS

The results of the identified health technology assessments,[1,2] systematic reviews and meta-analyses[2-25] are summarized in Table 1. Nine guidelines[26-34] were identified from the literature search results.

Table 1: Pharmacological Interventions for Treatment of Epilepsy

Authors	Study type	Interventions	Conclusions or recommendations
All patients			
Beavis et al.[3]	SR	Antiepileptic drug interventions in people with epilepsy and intellectual disabilities	The authors concluded the evidence supports the use of these drugs in patients with intellectual disability and epilepsy. The evidence suggests that side effects are similar to those observed in the general population.
Geng et al.[4]	SR	IVIg as add-on therapy	One study was identified comparing add-on treatment with IVIg to placebo add-on in patients with refractory epilepsy. No conclusions could be drawn from the results.
Shi et al.[5]	SR	Felbamate as add-on therapy for refractory partial-onset epilepsy	The authors were not able to combine the results of the studies included in the review. None demonstrated a 50% or greater reduction in seizure frequency. Adverse events with felbamate were higher than with placebo. The authors conclude there is insufficient evidence to support the use of felbamate as add-on therapy
Chaisewikul et al.[6]	SR	Levetiracetam as add-on therapy for drug-resistant localization related (partial) epilepsy	The authors concluded there was a reduction in seizure frequency when levetiracetam was used an add-on treatment. No long term efficacy information was available.
Maguire et al.[8]	SR	Vigabatrin for patients with partial epilepsy	Visual field loss was experienced by 44% of patients in the vigabatrin group compared to 7% in the control group. The authors conclude this treatment should be reserved for those patients who have no other treatment options.
Pereira et al.[9]	SR	Tiagabine as add-on treatment for drug-resistant partial epilepsy	Tiagabine was associated with a reduction in seizure frequency and an increase in some adverse effects.
Posner et al.[10]	SR	Ethosuximide, sodium valproate or lamotrigine for absence seizures	The authors determined there was not enough evidence to determine which drug was superior for treatment of absence seizures.
Powell et al.[11]	SR	IR carbamazepine versus CR carbamazepine for patients with newly diagnosed epilepsy	One trial reported a statistically significant decrease in seizures for patients receiving CR carbamazepine. The authors were unable to determine one formulation to be superior to the other.
Ramaratnam	SR	Lamotrigine as add-on	Lamotrigine was significantly more effective

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et al.[12]		treatment for drug-resistant partial epilepsy	than placebo for seizure reduction. The authors concluded lamotrigine was effective for seizure reduction when used as an add-on therapy.
Castillo et al.[14]	SR	Oxcarbazepine as add-on treatment for drug-resistant partial epilepsy	Efficacy was demonstrated in both adults and children. The authors concluded there was insufficient evidence to determine long term outcomes.
Koch et al.[15]	SR	Oxcarbazepine vs carbamazepine monotherapy for partial onset seizures	The two drugs demonstrated similar efficacy. Significantly fewer patients receiving carbamazepine experienced nausea and vomiting.
Marson et al.[16]	SR	Gabapentin as add-on treatment for drug-resistant partial epilepsy	The authors concluded gabapentin was effective as an add-on treatment but no evidence was available to determine long-term efficacy.
Saconato et al.[17]	SR	Oxcarbazepine for refractory partial or generalized epilepsy	For adults, chance of 50% seizure reduction was greatest with 600 mg, 1200 mg, and 2400 mg doses. For children, 1200 mg and 2400 mg doses were effective.
Hemming et al.[18]	SR	Vigabatrin for treatment of refractory epilepsy	Included studies of doses between 1000 mg and 6000 mg per day. Vigabatrin was more effective for 50% or greater seizure reduction than placebo. Vigabatrin patients were significantly more likely to experience adverse effects.
Jette et al.[19]	SR	Topiramate as add-on therapy for drug-resistant partial epilepsy	The authors concluded topiramate was effective as an add-on therapy. Seizure reduction of 50% or more was greater in treatment groups than placebo.
Lozsadi et al.[20]	SR	Pregabalin as add-on treatment for drug-resistant partial epilepsy	Included studies of 50 mg to 600 mg per day. Seizure reduction of 50% or greater was significantly higher with pregabalin than with placebo. Some adverse effects were significantly associated with pregabalin use.
Michael et al.[21]	SR	Clobazam as add-on treatment for management of refractory epilepsy	The outcomes measures of the included studies were too different to be combined in the review. The authors concluded clobazam may reduce frequency of seizures and may be most effective for partial onset seizures however more evidence is needed.
Rheims et al.[22]	SR and MA	Placebo response in treatment of drug-resistant partial epilepsy	Children in the included studies responded to placebo treatment more frequently than adults. There was no significant difference between the adults and children when comparing active treatment groups.
Chadwick et al.[23]	SR	Zonisamide as add-on treatment for drug-resistant partial epilepsy	Included studies of 300 mg to 500 mg per day. The authors concluded zonisamide was effective as an add-on treatment. They were not able to determine optimal dosing based on the information available.
Adults			

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Authors	Study type	Interventions	Conclusions or recommendations
Wilbey et al.[2]	HTA	Newer antiepileptic drugs (including: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin)	Newer drugs were effective as adjunctive therapy when compared to placebo, but long term data was lacking. Limited, poor quality evidence suggests a significant improvement in cognition with lamotrigine and oxcarbazepine compared with older drugs. One study suggested gabapentin and lamotrigine had some benefit for people with learning disabilities. Little good-quality evidence to support the use of one newer drug over another, or in place of older drugs.
Delahoy et al.[7]	MA	Pregabalin vs gabapentin for patients with refractory partial epilepsy	All doses of pregabalin were more effective than corresponding doses of gabapentin in terms of symptom free days.
Otoul et al.[24]	MA and indirect comparison	Levetiracetam vs other second-generation antiepileptic drugs for patients with partial epilepsy	At tested doses levetiracetam was more effective than gabapentin and lamotrigine and had a significantly lower withdrawal rates and comparable efficacy to topiramate and oxcarbazepine.
Adab et al.[25]	SR	Common antiepileptic drugs in pregnancy in women with epilepsy	The authors found little evidence regarding risk of in utero exposure to the different drugs. The authors recommend pregnant women continue monotherapy at the lowest effective dose to maintain seizure control.
Children and Adolescents			
Connock et al.[1]	HTA	Newer antiepileptic drugs (including: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin)	Limited evidence available does not show a difference in effectiveness between newer and older drugs, but suggests that the newer drugs may be better tolerated. There is not enough data to support a development of a comprehensive prescribing strategy. More evidence is required.
Weijenberg et al.[13]	SR	Monotherapy with antiepileptic drugs	No difference in safety or efficacy was reported between first and second-generation drugs. The authors concluded the results of this review are not sufficient to support decisions regarding treatment options.

CR = controlled release; HTA = health technology assessment; IR = immediate release; IVIg = intravenous immunoglobulin; MA = meta-analysis; SR = systematic review

The main recommendations regarding pharmacological treatment of epilepsy are as follows:

All populations

- Gabapentin, lamotrigine, topiramate, and oxycarbazepine have shown efficacy as monotherapy for adults and adolescents with newly diagnosed partial or mixed seizure disorders[31]
- The most commonly prescribed, and most widely used, antiepileptic drugs in the United Kingdom are sodium valproate, carbamazepine and phenytoin[32]
- Changing the formulation or brand of antiepileptic drug is not recommended due to possible differences bioavailability[34]

Adults

- Antiepileptic drug treatment should be individualized based on each patient's needs (seizure type, epilepsy type) and lifestyle.[28,32,34]
- Patients should be started on monotherapy. If monotherapy with the initial drug fails or is not well tolerated, monotherapy with a second drug should be attempted.[28,32,34]
- All drugs licensed for monotherapy have similar efficacy in newly diagnosed patients. The decision of which drug to prescribe should be left to the discretion of the treating physician.[28]
- Combination (add-on) therapy should only be initiated after attempts to control seizures with monotherapy have failed[32]
- Carbamazepine, phenytoin and sodium valproate can be considered first line treatments for newly diagnosed partial and generalized tonic-clonic seizures[28]
- Sodium valproate, lamotrigine and clonazepam may be prescribed for absence and myoclonic seizures[28]
- Carbamazepine, phenytoin, and valproic acid may be appropriate for initial monotherapy for partial-onset seizures[29]
- Gabapentin and lamotrigine may be appropriate for initial monotherapy for elderly adults with partial-onset seizures[29]
- Newer antiepileptic medications (gabapentin, lamotrigine, topiramate, levetiracetam, tiagabine, zonisamide, oxcarbazepine) are recommended as add-on medications for the treatment of individuals who have suboptimal treatment response to the older medications (phenytoin, carbamazepine, sodium valproate, phenobarbitone, clonazepam, clobazam) or as monotherapy (lamotrigine, topiramate) in individuals for whom the older medications are unsuitable (adverse drug reactions, intolerable side effects, multiple drug interactions to concomitant medications)[28, 32,34]

Pregnant women

- Women should be counseled and informed that freedom from seizures, with antiepileptic drugs, for at least nine months before pregnancy is likely associated with a high rate of remaining seizure free during pregnancy[26,28]
- Women with epilepsy have an increased risk of premature contractions and premature labor and delivery[26,34]
- Valproate and antiepileptic drug polytherapy should be avoided during the first trimester, if possible, to help decrease risk of major congenital maformations[27,32,34]
- Valproate, phenytoin, phenobarbital, and antiepileptic drug polytherapy should be avoided during pregnancy to help decrease risk of reduced cognitive outcomes[27,32,34]
- Folate supplementation is recommended for women of childbearing age taking antiepileptic drugs to help prevent neural tube defects. Folic acid, 5 mg per day, should be given in these women from pre-conception through the first trimester[28,34]

Children

- The choice of first antiepileptic drug should be determined based on the type of epilepsy diagnosed and the potential adverse effects of the drug[30]
- Drug monotherapy should be first line treatment. Combination therapy should be considered if monotherapy is insufficient to reduce seizure frequency[30,33,34]
- The newer antiepileptic drugs (gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin) are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable[33,34]

- Oxcarbazepine may be appropriate for initial monotherapy for children with partial-onset seizures[29]
- Lamotrigine is effective for children with newly diagnosed absence seizures[31]
- Febrile seizures should not be treated prophylactically with antiepileptic drugs[30]
- Withdrawal of drug therapy should be considered for children who have been symptom free for two or more years[30]

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