Perampanel (Fycompa) and Pregnancy

Evidence Summary:
Due to limited data on outcomes in human pregnancy, Perampanel (Fycompa) is not currently recommended for use in pregnant or women of childbearing potential. Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk, as such a risk to breastfeeding infants cannot be excluded.

Source: Electronic Medicines Compendium:

2. Perampanel (Fycompa): A review of clinical efficacy and safety in epilepsy
Author(s): Greenwood J.; Valdes J.
Source: P and T; Nov 2016; vol. 41 (no. 11); p. 683-688
Publication Date: Nov 2016
Publication Type(s): Review
Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5083075/
Database: EMBASE
2. New antiepileptic drugs and women

Author(s): Reimers A.

Source: Seizure; Sep 2014; vol. 23 (no. 8); p. 585-591

Publication Date: Sep 2014

Publication Type(s): Review

PubMedID: 24908139

Available at Seizure - from Unpaywall

Abstract: Since 1990, sixteen new antiepileptic drugs (AEDs) have been introduced. Most of these new AEDs have only been insufficiently studied with respect to women-specific aspects such as endogenous sex hormones, hormonal contraception, pregnancy, breastfeeding, or menopause. This is of concern because it has been shown for some of the new AEDs that these factors may have a clinically significant impact on their pharmacokinetics and seizure control. Also, new AEDs may affect hormone homeostasis and pass over into breast milk. The best studied of the new AEDs are lamotrigine, levetiracetam and oxcarbazepine. Although gabapentin and pregabalin are even more frequently used (due to their therapeutic effects in nonepileptic conditions), our understanding of these two drugs in relation to women's issues is surprisingly poor. Little to nothing is known about zonisamide, retigabine/ezogabine, lacosamide, perampanel and the other new AEDs. Nevertheless, many small studies and case series have been published on new AEDs and women-specific aspects. This review gives an overview on what is known today. © 2014 British Epilepsy Association.

Database: EMBASE

3. Predictions of the pharmacokinetic profile of perampanel during pregnancy using physiologically based pharmacokinetic (PBPK) modeling

Author(s): Schuck E.; Rege B.; Laurenza A.; Williams B.; Ferry J.; Hussein Z.

Source: Neurology; Apr 2017; vol. 88 (no. 16)

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Abstract: Objective: To predict perampanel exposure when administered during pregnancy.

Background: Perampanel is a selective, non-competitive AMPA receptor antagonist, approved for adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures, and for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged >12 years. Perampanel is eliminated primarily via CYP3A metabolism, and concomitant enzyme-inducing antiepileptic drugs (EIAEDs; eg carbamazepine) reduce exposure 2-3-fold. Perampanel is also characterized by high protein binding (95-96%). Induction of CYP3A activity and changes in plasma protein concentrations that have been reported to occur during pregnancy could potentially impact perampanel exposure and warrant dose adjustments. Design/Methods: A PBPK model, developed using Simcyp version 15.1, was used to assess three prediction scenarios: (1) single oral doses of perampanel 8 mg administered during pregnancy Weeks 0, 10, 19, 28, and 36; (2) once-daily doses of oral perampanel 8 mg administered over a 270-day pregnancy; and (3) single oral doses of perampanel 8 mg administered on Day 8 after start of twice-daily carbamazepine 300 mg administration, on pregnancy Weeks 10 and 36. Results: Single-dose simulations predicted that total perampanel exposures are 2.6-fold lower at the end of pregnancy (Week 36) compared with non-pregnant women; exposures for unbound (free) perampanel were predicted to be 1.9-fold lower. Multiple-dose simulations predicted that total perampanel exposures are up to 4-fold lower towards the end of pregnancy compared with non-pregnant women; exposures for unbound perampanel were predicted to be 3-fold lower. Total perampanel exposures were predicted to be 2-fold lower in pregnant women receiving concomitant carbamazepine than in pregnant women not receiving
Carbamazepine. Conclusions: In addition to the known effect of EIAEDs on perampanel exposure, these simulations predict that perampanel exposure may decline by 2-4-fold during pregnancy. It is suggested that pregnant women should be carefully monitored.

**Database:** EMBASE

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**4. Practice Update: Review of Anticonvulsant Therapy.**

**Author(s):** Chong, Derek J; Lerman, Andrew M

**Source:** Current neurology and neuroscience reports; Apr 2016; vol. 16 (no. 4); p. 39

**Publication Date:** Apr 2016

**Publication Type(s):** Journal Article Review

**PubMedID:** 26984292

Available at [Current neurology and neuroscience reports - from ProQuest (Hospital Premium Collection) - NHS Version](#)

Available at [Current neurology and neuroscience reports - from SpringerLink](#)

**Abstract:** Since 2010, the Food and Drug Administration has approved the use of four new anti-epilepsy drugs (AEDs) for the treatment of epilepsy in the USA: clobazam (Onfi), ezogabine (Potiga), perampanel (Fycompa), and eslicarbazepine (Aptiom) as well as two extended release formulations, topiramate ER (Qudexy XR and Trokendi) and oxcarbazepine ER (Oxtellar). This not only provides practitioners ample choice to match medication profiles to their patients' preferences and comorbidities better, but also challenges us to be proficient in the use of all. In addition to providing a brief overview of these new medications and of the current medical management of epilepsy, this review discusses new data regarding vitamin D and AED-related osteoporosis, pregnancy registries, suicidality, marijuana-related compounds for epilepsy, and the recently published guidelines on the approach and management of a first unprovoked seizure in adults and guidelines for when to stop AEDs.

**Database:** Medline
5. Novel treatment and new drugs in epilepsy treatment

Author(s): Eskioglou E.; Perrenoud M.P.; Ryvlin P.; Novy J.
Source: Current Pharmaceutical Design; 2017; vol. 23 (no. 42); p. 6389-6398
Publication Date: 2017
Publication Type(s): Article

Abstract: We now get benefit from more than 20 antiepileptic drugs (AEDs) in the care of people with epilepsy. Newer generation of AED is associated with a more favourable tolerability profile than older generation AEDs which makes them easier to use, despite similar efficacy. In order to define the place of newer generation AEDs in the therapy, we review here the main current guidelines about their use for a special issue concerning antiepileptic drugs in neurosurgical practice. We also discuss how to tailor the treatment with newer generation AEDs according to the patient's needs and comorbid conditions. We review different common setting that may require specific therapeutic considerations, i.e. elderly, pregnancy, HIV infection, tumours and hospital/critical care use. We also discuss the current evidence regarding the use of newer generation AEDs in the neurosurgical practice. We present the most recent commercially available newer AEDs (ezogabine, perampanel, brivacetam, everolimus), describing their mechanism of action, adverse effects and indication according to the type of seizure. We finally describe the promising AEDs that are currently under development or testing. This article is a special issue concerning antiepileptic drugs in neurosurgical practice. Copyright © 2017 Bentham Science Publishers.

Database: EMBASE

6. An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs

Author(s): Jacob S.; Nair A.B.
Source: Drugs in R and D; Dec 2016; vol. 16 (no. 4); p. 303-316
Publication Date: Dec 2016
Publication Type(s): Review
PubMedID: 27766590
Available at Drugs in R&D - from Europe PubMed Central - Open Access

Abstract: Given the distinctive characteristics of both epilepsy and antiepileptic drugs (AEDs), therapeutic drug monitoring (TDM) can make a significant contribution to the field of epilepsy. The measurement and interpretation of serum drug concentrations can be of benefit in the treatment of uncontrollable seizures and in cases of clinical toxicity; it can aid in the individualization of therapy and in adjusting for variable or nonlinear pharmacokinetics; and can be useful in special populations such as pregnancy. This review examines the potential for TDM of newer AEDs such as eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, perampanel, pregabalin, rufinamide, retigabine, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide. We describe the relationships between serum drug concentration, clinical effect, and adverse drug reactions for each AED as well as the different analytical methods used for serum drug quantification. We discuss retrospective studies and prospective data on the serum drug concentration-efficacy of these drugs and present the pharmacokinetic parameters, oral bioavailability, reference concentration range, and active metabolites of newer AEDs. Limited data are available for recent AEDs, and we discuss the connection between drug concentrations in terms of clinical efficacy and nonresponse. Although we do not propose routine TDM, serum drug measurement can play a beneficial role in patient management and treatment individualization. Standardized studies designed to assess, in particular, concentration-efficacy-toxicity relationships for recent AEDs are urgently required. Copyright © 2016, The Author(s).

Database: EMBASE
7. Perampanel for the treatment of primary generalized tonic-clonic seizures in idiopathic generalized epilepsy

**Author(s):** Rohracher A.; Hofler J.; Kalss G.; Neuray C.; Dobesberger J.; Kuchukhidze G.; Leitinger M.; Trinka E.; Brigo F.

**Source:** Expert Opinion on Pharmacotherapy; Jul 2016; vol. 17 (no. 10); p. 1403-1411

**Publication Date:** Jul 2016

**Publication Type(s):** Article

**Abstract:** Introduction: The non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) - receptor antagonist perampanel (PER) was approved in 2015 for treatment of primary generalized tonic-clonic seizures (pGTCS). The aim of this narrative review is to summarize available data on pharmacological properties, efficacy and tolerability of PER in pGTCs.

Areas covered: Data sources included MEDLINE, EMBASE, Google Scholar and ClinicalTrials.gov, conference proceedings of the ILAE congresses and the most recent conference proceedings of the American Epilepsy Society (2013 to 2015). Expert opinion: A placebo-controlled clinical phase III study including 164 patients (≥ 12 years) with pGTCS in idiopathic generalized epilepsies (IGE) demonstrated efficacy of PER in reducing pGTCS with good tolerability profile, and without aggravating absence seizures or myoclonic seizures. Dizziness, the main adverse event (AE), can be avoided by bedtime administration. Psychiatric AEs ranging from mild depression to aggression and suicidal attempts should be especially monitored in patients with a history of psychiatric disorders. Co-administration of enzyme inducing antiepileptic drugs (AEDs) might decrease PER plasma levels and make dose adjustment necessary. A reduced efficacy of progesterone-containing oral contraceptives should be considered when administering PER to young women. There is lack of evidence on PER treatment in pregnancy. Although no teratogenic effects were observed in animal models, PER is not recommended for women of childbearing age without contraception. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

**Database:** EMBASE
8. The long-term safety of antiepileptic drugs

Author(s): Gaitatzis A.; Sander J.W.
Source: CNS Drugs; Jun 2013; vol. 27 (no. 6); p. 435-455
Publication Date: Jun 2013
Publication Type(s): Review

Abstract: Antiepileptic drugs (AEDs) are used by millions of people worldwide for the treatment of epilepsy, as well as in many other neurological and psychiatric conditions. They are frequently associated with adverse effects (AEs), which have an impact on the tolerability and success of treatment. Half the people who develop intolerable AEs discontinue treatment early on after initiation, while the majority of people will continue to be exposed to their effects for long periods of time. The long-term safety of AEDs reflects their potential for chronic, cumulative dose effects; rare, but potentially serious late idiosyncratic effects; late, dose-related effects; and delayed, teratogenic or neurodevelopmental effects. These AEs can affect every body system and are usually insidious. With the exception of delayed effects, most other late or chronic AEs are reversible. To date, there is no clear evidence of a carcinogenic effect of AEDs in humans. While physicians are aware of the long-term AEs of old AEDs (the traditional liver enzyme-inducing AEDs and valproate), information about AEs of new AEDs (such as lamotrigine, levetiracetam, oxcarbazepine, topiramate or zonisamide), particularly of their teratogenic effects, has emerged over the years. Sporadic publications have raised issues about AEs of the newer AEDs eslicarbazepine, retigabine, rufinamide, lacosamide and perampanel but their long-term safety profiles may take years to be fully appreciated. Physicians should not only be aware of the late and chronic AEs of AEDs but should systematically enquire and screen for these according to the individual AED AE profile. Care should be taken for individuals with comorbid conditions that may render them more susceptible to specific AEs. Prevention and appropriate management of long-term AED AEs is expected to improve adherence to treatment, quality of life and control of epilepsy. © 2013 Springer International Publishing Switzerland.

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