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Brodie, M., and Kwan, P. (2012) *Newer drugs for focal epilepsy in adults*. British Medical Journal, 344 . e345. ISSN 0959-8138

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Deposited on: 13th December 2012

PRACTICE

THERAPEUTICS

Newer drugs for focal epilepsy in adults

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

A 28 year old woman sees her general practitioner after experiencing what sounds like a convulsion without any apparent provoking factor. Over the past month she has also had “blank spells” during which her husband noticed her to be unresponsive. Her general practitioner suspects she may have developed focal epilepsy and refers her to an epilepsy specialist. The specialist elicits from the patient and her husband additional features in the history that are highly compatible with seizures arising from the temporal lobe (lip smacking, ipsilateral motor automatism, and contralateral dystonia) and confirms the diagnosis by finding focal epileptiform discharges on electroencephalography and cortical dysplasia in the left temporal lobe on brain imaging. To prevent further seizures the specialist advises treatment with antiepileptic drugs (AEDs). The patient is reluctant to start treatment because she has read that AEDs have many adverse effects, could interact with her oral contraception, and are harmful for babies. She wonders if there are newer AEDs that for her might be better than the traditional ones.

What are the newer antiepileptic drugs?

Epilepsy is resistant to drug treatment in a third of patients.¹ Driven by this high prevalence of drug resistance, 12 agents have been developed to treat adult epilepsy since the late 1980s. These are often referred to collectively as the “newer” antiepileptic drugs—that is, newer than the established drugs, such as phenobarbital, phenytoin, carbamazepine, sodium valproate, and several benzodiazepines, with phenobarbital having been around for 100 years.² In this article we will review the clinical use of (in chronological order of approval in the United Kingdom) lamotrigine, gabapentin, topiramate, oxcarbazepine, levetiracetam, pregabalin, zonisamide, and lacosamide (table 1⇓). We will not discuss the other newer AEDs tiagabine and vigabatrin because they are rarely used for

focal epilepsy in adults (owing to efficacy and safety concerns respectively) or eslicarbazepine acetate and retigabine, which have only recently been approved and for which clinical experience is therefore limited.

How well do the newer antiepileptic drugs work?

Add-on therapy

To obtain licensing approval as add-on therapy, all AEDs have to show superior efficacy compared with placebo in double blind randomised controlled trials. In regulatory studies for AEDs, the primary efficacy measure is statistical significance against placebo for responder rate in Europe (defined as a $\geq 50\%$ reduction in seizure frequency) and median reduction in seizure frequency in the United States.⁴ A recent meta-analysis that evaluated the clinical effectiveness and tolerability of the newer AEDs included 62 placebo controlled studies in children and adults in terms of responder and withdrawal rates (table 2⇓).⁵ Owing to methodological heterogeneity—such as in the range of dosages tested and of treatment durations (8–26 weeks)—and the small differences found, caution is needed in drawing comparisons between these drugs. In addition, the clinical relevance of the responder rate as a useful clinical end point remains questionable. The recent consensus from the International League Against Epilepsy⁶ proposes that a treatment’s success should be defined by sustained freedom from seizures, as that is the only efficacy outcome consistently associated with improved quality of life (and in the UK the only efficacy outcome that allows a patient to drive legally). Using this measure, another meta-analysis showed that the overall weighted pooled-risk difference in favour of the newer AEDs compared with placebo for freedom from seizures during the limited study periods was only 6% (95% confidence interval 4% to 8%; number needed to treat in terms of freedom from seizures, 16).⁷

Monotherapy

Several of the newer AEDs have shown efficacy similar to that of the older drugs (mostly carbamazepine), and sometimes similar to that of each other, for the treatment of new onset focal epilepsy in adults in head to head monotherapy trials and have been approved for this indication in the UK and other European countries.⁸ These approved drugs include levetiracetam, lamotrigine, oxcarbazepine, and topiramate and in some countries gabapentin. Seizure-free rates for a year in this highly selective population have increased to about 60% as the design of the studies has evolved.⁹

However, although there is evidence of efficacy under controlled research conditions for these drugs, their clinical effectiveness and cost effectiveness have been poorly studied. The greater overall effectiveness for focal seizures (mostly in terms of better tolerability) of lamotrigine compared with carbamazepine, oxcarbazepine, and gabapentin in the randomised open-label Standard and New Antiepileptic Drugs (SANAD) study of 1721 patients arguably makes it the drug of first choice in this clinical setting.¹⁰ The SANAD study found that gabapentin had significantly inferior efficacy compared with carbamazepine, and most experts do not recommend gabapentin as initial monotherapy.

How safe are the newer antiepileptic drugs?

All AEDs are associated with a range of adverse effects, the main reason for withdrawal in regulatory trials.⁵ Many adverse effects were detected only during postmarketing surveillance, and their long term adverse effects (such as on bone health) are unknown.

Idiosyncratic reactions

Such reactions are unpredictable adverse effects independent of dosage.¹¹ The most common of these is rash, which develops in 3-5% of patients taking lamotrigine, zonisamide, or oxcarbazepine but in <1% of those taking topiramate, levetiracetam, gabapentin, or pregabalin.¹² Lamotrigine and oxcarbazepine can rarely lead to Stevens-Johnson syndrome or toxic epidermal necrolysis. Other rare idiosyncratic reactions include hepatitis, pancreatitis, and blood dyscrasias.

Ophthalmic effects

Rare cases of acute angle-closure glaucoma and myopia have been reported with topiramate.

Neurotoxicity

Typical dose related symptoms including nausea, diplopia, dizziness, headache, tiredness, somnolence, sedation, and ataxia can occur with all AEDs.¹³

Renal calculi

Topiramate and zonisamide carry a small (1%) risk of symptomatic renal calculi as both drugs inhibit carbonic anhydrase.

Cardiac effects

Minor prolongation in the PR interval has been observed in clinical studies with lacosamide.

Psychiatric effects

Topiramate is associated with anorexia, weight loss, word finding difficulties, and neuropsychiatric complications. Behavioural problems, such as agitation, aggression, hostility, psychosis, anxiety, and depression, have been reported in patients treated with levetiracetam. Zonisamide can also produce or exacerbate psychiatric comorbidities, particularly depression.¹⁴ The US Food and Drug Administration analysed data from 199 placebo controlled trials of 11 AEDs and found an increase in risk of suicidal behaviour or ideation among patients receiving them (0.43%) compared with those receiving placebo (0.22%).¹⁵ A community based case-control study in treated epilepsy documented increased risk of suicidal behaviour associated with some newer AEDs (such as topiramate, levetiracetam) only in patients with a high risk of depression.¹⁶

Teratogenicity

Recent data from EURAP, the largest international prospective cohort study of 3909 pregnancies, reported that in utero exposure to lamotrigine monotherapy was associated with an overall, dose dependent rate of major fetal malformation at 1 year of age that ranged from 2% (<300 mg/day) to 4.5% (≥300 mg/day). This was less than that with carbamazepine (3.4% to 8.7%), phenobarbital, (5.4% to 13.7%) and particularly sodium valproate (5.6% to 24.2%).¹⁷ The UK pregnancy register reported a rate of major fetal malformation for untreated women with epilepsy (n=239) of 3.5% (95% confidence interval 1.8% to 6.8%).¹⁸ Children exposed to lamotrigine in utero had similar IQs at age 3 years to those exposed to phenytoin and carbamazepine, which was around 10 percentage points higher than those taking high dose sodium valproate.¹⁹ Data from the US and UK pregnancy registries indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester.²⁰ Sufficient data for other newer AEDs are lacking, although preliminary experience from the UK pregnancy registry has suggested a low risk of teratogenicity with levetiracetam.²¹

What are the precautions?

Precautions relate to potential adverse effects as discussed above. Examples are outlined as follows.

Rash

Closely monitor patients with a history of allergic rash when introducing an AED as they have an approximate fivefold increased risk of developing another rash.¹² Avoid oxcarbazepine in patients with a history of rash induced by carbamazepine because of a cross sensitivity rate between these drugs of 25-31%.

Cardiac problems

For patients with a history of cardiac problems, including conduction block, taking drugs known to prolong the PR interval, and for those aged over 65, use lacosamide cautiously and perform electrocardiography before starting treatment and after titration to optimal dosage.

History of psychiatric illness

Avoid topiramate, levetiracetam, and zonisamide, or, if essential, use these cautiously.

History of renal calculi

Avoid topiramate and zonisamide as they inhibit carbonic anhydrase; advise all patients taking these drugs to avoid dehydration.

Renal impairment

For patients with renal impairment prescribe lower doses of gabapentin, levetiracetam, and pregabalin as these are predominantly excreted unchanged in the urine.

Interaction with oral contraceptives

As oxcarbazepine and topiramate (at daily doses above 200 mg) selectively induce the breakdown of the oestrogenic component of oral contraception,¹³ patients taking oral contraception need formulations with higher doses (50 µg) of oestrogen, with subsequent adjustment of hormones depending on any breakthrough bleeding; other contraceptive measures must be taken until the menstrual pattern has been stable for at least three months. As the oestrogenic component of oral contraception significantly increases the metabolism of lamotrigine, the dosage of lamotrigine may need adjustment when starting combined oral contraception (to maintain seizure control) and when stopping the pill (to minimise adverse effects of lamotrigine).²²

Pregnancy

Limited data are available on the teratogenic risk of the newer AEDs. Counsel women of childbearing potential on pregnancy matters early.²³ Advise them to plan pregnancy, so that any changes to their regimen of AED treatment can be made before conception (because teratogenesis may occur early in the first trimester). Treatment with AEDs should be continued during pregnancy on the basis that seizures, especially convulsive seizures, are more harmful to the mother and fetus than are the drugs themselves; however, treatment should be tapered to a minimal effective dose before pregnancy, if possible to a single AED. Supplemental folic acid is advised (≥ 400 µg daily) before conception and during pregnancy to reduce the risk of major congenital malformation.²⁴ Offer prenatal diagnosis using targeted fetal ultrasonography to detect any major structural abnormalities. After delivery, encourage all mothers to breast feed their babies. If the AED dose, particularly that of lamotrigine, has been increased during pregnancy, consider a reduction in dosage after delivery.

Breast feeding

Lamotrigine can accumulate in the breastfed baby because of slow elimination. However, few data relate to the other newer AEDs. As a general rule, if the baby is noted to be drowsy or sedated, breast feeding should be alternated with bottle feeding or discontinued.

How are the newer antiepileptic drugs taken and monitored?

All the newer AEDs discussed in this article are taken orally. Oxcarbazepine and levetiracetam are available in liquid formulations. Lacosamide is also available as a syrup and by intravenous injection. An intravenous formulation of levetiracetam has been licensed in Europe for patients aged ≥ 4 years when oral administration is temporarily not feasible.

In general, start newer AEDs at low dosage, with increments over several weeks to establish an effective and tolerable

regimen.¹³ Some agents, such as gabapentin and levetiracetam, can be started at effective doses with or without rapid titration, whereas others, such as lamotrigine and topiramate, require slow titration to reduce the risk of rash and cognitive impairment, respectively. Slow titration will also facilitate the development of tolerance to sedation and will ensure early detection of potentially serious idiosyncratic reactions.

Once the target dosage has been reached, adjust the dose further on the basis of seizure control and tolerability. Routine measurement of serum concentrations of the newer AEDs is not recommended (and not available in most clinical settings), as they do not correlate well with efficacy or side effects.²⁵

However, serum concentrations of lamotrigine fall dramatically during pregnancy, in patients who have recently started taking an oral contraceptive containing oestrogen, and in women just before the onset of the menses. Lamotrigine monitoring is particularly helpful in guiding dosing during pregnancy.²⁴ Such monitoring is not available routinely across the UK and is best performed with advice from an epilepsy specialist. Arguably, however, lamotrigine concentrations should be measured before conception, regularly throughout pregnancy, and in the puerperium.²⁵

How cost effective are the newer antiepileptic drugs?

Whether the better tolerability and interaction profile of newer AEDs are worth the higher price has been much debated. High quality cost effectiveness studies are lacking. The guidelines from the National Institute for Health and Clinical Excellence (NICE) included cost utility analyses of AEDs and found lamotrigine to be the most cost effective monotherapy (although carbamazepine may be as cost effective).²⁶ However, such cost utility analyses often do not adequately account for indirect or "hidden" costs such as interactions between drugs and long term adverse effects. Moreover, generic formulations are becoming available for many of the newer AEDs, thus driving down prescription costs.

How do the newer antiepileptic drugs compare with the established ones?

Given the limited number of comparative studies, AED treatment for the individual patient is not based entirely on these and depends also on the patient's age, weight, sex, comorbidities, and perceived differences in adverse effects, propensity for interactions, and cost. Owing to the absence of adequate evidence, judgments about treatment choice (in an attempt to be rational) are based on what we think we know about these other factors. Table 3↓ lists some advantages and disadvantages of the established and newer AEDs.

Choice of drug in newly diagnosed epilepsy

Based on a systematic review and consideration of clinical benefits, harms, and cost effectiveness, the updated NICE guidelines recommend offering carbamazepine or lamotrigine as first line treatment to children, young people, and adults with newly diagnosed focal seizures; if these are unsuitable or not tolerated, NICE recommends levetiracetam (if its acquisition cost falls to at least 50% of the value at June 2011), oxcarbazepine, or sodium valproate.²⁶ The American Academy of Neurology supports starting treatment with the older AEDs and lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patients' characteristics.²⁷ The International League against Epilepsy adopts a stricter

classification of evidence, supporting only carbamazepine, phenytoin, and valproic acid as initial monotherapy for partial onset seizures in adults and lamotrigine and gabapentin for older people.²⁸ On the basis of the double blind, randomised monotherapy study of levetiracetam versus extended release carbamazepine in newly diagnosed epilepsy, which fulfilled the strict criteria of the International League against Epilepsy, levetiracetam can also be recommended for this indication.⁹ These differing recommendations may reflect fundamental differences in the purposes of the various guidelines and in the approaches adopted by the groups developing them.

Choice of drug in uncontrolled epilepsy

As very few head to head comparisons of new AEDs exist for the treatment of drug resistant epilepsy, choice remains largely empirical. The increasing number of available agents has encouraged consideration of their different mechanisms of action (table 1↓) in optimising their efficacy in combination. The broad spectrum AEDs levetiracetam, topiramate, and zonisamide, which have multiple mechanisms of action, are often chosen in drug resistant epilepsy.²⁹

Our case scenario

Treatment with AEDs is indicated for our patient with recurrent focal seizures, the latest of which seem to have developed into a secondarily generalised seizure (epileptic seizure with focal onset and subsequent bilateral convulsion). On the basis of this review and in line with NICE guidance, given the patient's childbearing potential, the drug of choice would be lamotrigine, preferably maintained at <300 mg/day. Ideally, monitor the concentration before conception, during pregnancy, and in the puerperium. We do not recommend carbamazepine for her because of its comparatively higher risk of fetal malformation (when the dose is ≥400 mg/day) and enzyme induction of the oestrogenic component of her oral contraception. Levetiracetam can also be considered because it is effective as controlled release carbamazepine and preliminary data suggest a low risk of teratogenicity, although NICE asserts that it is not as cost effective as lamotrigine at June 2011 unit costs.

Contributors: Both authors contributed equally to this manuscript. PK is the guarantor.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; MJB has received consulting fees from Eisai; lecture fees from GlaxoSmithKline, UCB Pharma, Eisai, Novartis, SanofiAventis, and Medtronic; funding for travel and accommodation from UCB Pharma; and grant support to his institution from UCB Pharma, Eisai, and GlaxoSmithKline. PK has received consulting fees from Pfizer and UCB Pharma and lecture fees from Eisai and UCB Pharma; he also holds a patent related to a rapid HLA typing method (PCT/CN2009/074891), and his institution has received grant support from Eisai, Johnson & Johnson, Pfizer, and UCB Pharma; the authors declare no other relationships or activities that could appear to have influenced the submitted work.

Patient consent not required (patient anonymised, dead, or hypothetical).

Provenance and peer review: Commissioned; externally peer reviewed.

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Cite this as: *BMJ* 2012;344:e345

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Tips for patients

- Drug treatment aims at preventing the development and spread of seizures (the electrical consequence of an underlying process in the brain) but does not affect the underlying cause of the epilepsy
- Keep a diary of any seizures and side effects you have experienced and discuss the record with your general practitioner or epilepsy specialist during consultations
- Discuss the common problems associated with your treatment with your general practitioner before starting any new drug
- If you think you are experiencing a side effect with your epilepsy treatment, discuss this as soon as possible with your general practitioner or epilepsy specialist
- If you are a woman you should seek advice on contraception to ensure that the epilepsy treatment does not interfere with your oral contraception and request referral to an epilepsy specialist if you are planning a pregnancy
- Health problems that arise months or years after taking an unchanged treatment schedule are unlikely to be the result of the antiepileptic drugs but should be discussed with your doctor as they may affect your epilepsy treatment
- Adding another medicine can sometimes interfere with the epilepsy drugs, producing side effects or reducing the efficacy of these drugs and thus worsening seizure control. Check this specifically with your doctor when he or she recommends starting you on any new drug
- Very rarely an epileptic seizure can affect the function of the heart, lungs, or brain, resulting in sudden death, and so taking the antiepileptic drugs is essential

Tips for general practitioners

- Refer patients with suspected epilepsy to a specialist in epilepsy care for diagnosis, investigation, and treatment
- If problems arise, seek advice from the appropriate neurologist or local epilepsy specialist nurse
- Refer patients planning a pregnancy to an epilepsy specialist for advice, optimisation of the antiepileptic drug regimen, and initiation of folic acid
- When introducing adjunctive treatment in a patient with drug resistant epilepsy it may be necessary to reduce the dose of one of the other drugs, particularly if this is being taken at a high dose, to facilitate optimal tolerability
- If a clinical problem occurs after an antiepileptic drug monotherapy or multidrug regimen has been stable for some years, the problem is unlikely to be caused by the antiepileptic drugs
- Routine therapeutic drug monitoring of antiepileptic drugs is not necessary. Use monitoring only to ask a clinical question, such as whether the patient is complying with the treatment
- If a patient is considering stopping treatment, advise him or her to discuss the risks with an epilepsy specialist before finalising the decision

Tables**Table 1 | Mechanisms of action, year first licensed, and approved indications for newer antiepileptic drugs discussed in this review for use in adults in the United Kingdom**

| Antiepileptic drug (year first licensed) | Mechanism of action | Indications | | |
|--|---|--------------------|----------------|-------------|
| | | Seizure type* | Add-on therapy | Monotherapy |
| Lamotrigine (1991) | Blocks fast-inactivated state of sodium channel | Focal, generalised | Yes | Yes |
| Oxcarbazepine (2000) | Blocks fast-inactivated state of sodium channel | Focal | Yes | Yes |
| Lacosamide (2008) | Blocks slow-inactivated state of sodium channel | Focal | Yes | |
| Gabapentin (1993) | Blocks high voltage-activated calcium channel | Focal | Yes | |
| Pregabalin (2004) | Blocks high voltage-activated calcium channel | Focal | Yes | |
| Levetiracetam (2000) | Modulates synaptic vesicle protein 2A | Focal, generalised | Yes | Yes |
| Topiramate (1995) | Various actions on multiple targets | Focal, generalised | Yes | Yes |
| Zonisamide (2005) | Various actions on multiple targets | Focal | Yes | |

*Seizures are broadly classified into focal or generalised on the basis of the mode of onset.³ Focal (partial) epileptic seizures are conceptualised as originating within networks limited to one hemisphere and may be discretely localised or more widely distributed. Focal seizures may or may not lead to impairment of consciousness or awareness and may evolve to bilateral convulsive seizures (secondarily generalised tonic-clonic seizure). Generalised epileptic seizures are conceptualised as originating at some point within, and rapidly engaging, bilaterally distributed networks. Examples include (primarily) generalised tonic-clonic, absence, myoclonic seizures.

Table 2| Meta-analysis of responder rate and withdrawal rate for newer antiepileptic drugs as add-on therapy for uncontrolled focal epilepsy in randomised controlled trials (modified from Costa et al, 20115)

| | Gabapentin | Lacosamide | Levetiracetam | Lamotrigine | Oxcarbazepine | Pregabalin | Topiramate | Zonisamide |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Data for responder rate* | | | | | | | | |
| Trials/patients (n/n) | 6/1187 | 3/1092 | 10/1693 | 12/1314 | 2/961 | 6/1867 | 10/1312 | 4/850 |
| Responder rates for drug/placebo (%) | 19.9/10.9 | 37.7/22.6 | 40.1/17.0 | 28.3/15.1 | 39.5/16.6 | 37.2/15.2 | 44.8/15.2 | 32.6/13.1 |
| Odds ratio (95% CI) | 2.08 (1.47 to 2.96) | 2.06 (1.54 to 2.76) | 3.75 (2.71 to 5.20) | 2.34 (1.66 to 3.30) | 3.30 (1.80 to 6.08) | 3.61 (2.21 to 5.89) | 4.31 (3.07 to 6.06) | 2.99 (2.07 to 4.32) |
| Number needed to treat | 19 (14-31) | 10 (8-15) | 8 (8-10) | 12 (10-18) | 9 (7-15) | 10 (8-13) | 9 (8-10) | 12 (10-16) |
| Data for withdrawal rate† | | | | | | | | |
| Trials/patients (n/n) | 6/1206 | 3/1105 | 10/1721 | 13/1767 | 2/961 | 6/1867 | 10/1312 | 4/850 |
| Withdrawal rates for drug/placebo (%) | 8.8/10.0 | 21.2/12.9 | 11.7/11.6 | 16.5/14.1 | 41.1/19.9 | 23.2/17.1 | 16.5/6.9 | 20.6/12.9 |
| Odds ratio (95% CI) | 0.99 (0.66 to 1.5) | 1.8 (1.26 to 2.56) | 0.97 (0.69 to 1.36) | 1.19 (0.90 to 1.57) | 2.27 (1.62 to 3.17) | 1.52 (1.17 to 1.98) | 2.38 (1.54 to 3.65) | 1.59 (1.08 to 2.34) |
| Number needed to harm | NA | 19 (13-42) | NA | NA | 10 (8-15) | 19 (13-47) | 26 (20-43) | 23 (9-119) |

CI=confidence interval; NA=not applicable.

*Responders had at least a 50% reduction in seizure frequency.

†Withdrawals were mostly because of adverse events.

Table 3| Advantages and disadvantages of the established and newer antiepileptic drugs

| | Advantages | Disadvantages |
|----------------------------------|--|---|
| Older antiepileptic drugs | | |
| Carbamazepine | Cost effective for new onset focal seizures | Dizziness, headache, drowsiness, diplopia, rash, hyponatraemia, osteoporosis, enzyme induction, blood dyscrasias |
| Phenobarbital | Broad spectrum of activity; once daily; cheap | Sedation, behavioural disturbances, hyperactivity, rash, teratogenesis, osteoporosis, folate deficiency, enzyme induction, Dupuytren's contracture |
| Phenytoin | Once daily; rapid titration; intravenous formulation available; cheap | Headache, dizziness, ataxia, rash, gum hyperplasia, hirsutism, acne, osteoporosis, peripheral neuropathy, enzyme induction, saturation kinetics, cerebellar atrophy |
| Sodium valproate | Cost effective for new onset generalised seizures; broad spectrum of activity; rapid titration; few interactions | Nausea, diarrhoea, lethargy, drowsiness, weight gain, thrombocytopenia, alopecia, tremor, extrapyramidal symptoms, enzyme inhibition, teratogenesis |
| Newer antiepileptic drugs | | |
| Gabapentin | Low risk of allergic reactions; low risk of drug interaction | Drowsiness, dizziness, ataxia, weight gain, diarrhoea, dose adjustment needed in renal impairment |
| Lacosamide | Low risk of drug interaction; intravenous formulation available | Dizziness, headache, diplopia, nausea, vomiting, tremor, rash, minor prolongation in the PR interval |
| Lamotrigine | Cost effective for new onset focal seizures; broad spectrum; few interactions; better tolerated than older drugs; low risk of teratogenicity | Headache, insomnia, diplopia, dizziness, ataxia, rash, interacts with combined contraception pill |
| Levetiracetam | Broad spectrum of activity; intravenous formulation available; low risk of drug interaction | Somnolence, headache, neuropsychiatric and behavioural effects such as aggression, depression, dose adjustment needed in renal impairment |
| Oxcarbazepine | Better tolerated than older drugs | Dizziness, nausea, vomiting, headache, drowsiness, rash, hyponatraemia, interacts with combined contraception pill |
| Pregabalin | Low risk of allergic reactions; low risk of drug interaction | Dizziness, somnolence, headache, ataxia, weight gain, peripheral oedema, sexual dysfunction, dose adjustment needed in renal impairment |
| Topiramate | Broad spectrum; weight loss in obesity | Dizziness, paraesthesia, somnolence, confusion, fatigue, weight loss, renal stones, neuropsychiatric effects, interacts with combined contraception pill |
| Zonisamide | Broad spectrum; once daily; weight loss in obesity; low risk of drug interaction | Anorexia, dizziness, fatigue, nausea, vomiting, weight loss, renal stones, rash, neuropsychiatric effects especially depression |