Oxcarbazepine
An Update of its Efficacy in the Management of Epilepsy

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Data Selection
Sources: Medical literature published in any language since 1992 on oxcarbazepine, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'oxcarbazepine'. EMBASE search terms were ‘oxcarbazepine’. AdisBase search terms were ‘oxcarbazepine’ or ‘GP-47779’. Searches were last updated 15 Jan 2001.

Selection: Studies in patients with epilepsy who received oxcarbazepine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: oxcarbazepine, epilepsy, pharmacodynamics, pharmacokinetics, therapeutic use.

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Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenzo[b,f]azepine-5-carboxamide) is a 10-keto analogue of carbamazepine with anticonvulsant activity.

In newly diagnosed adult patients, oxcarbazepine monotherapy is as effective as phenytoin and valproic acid at reducing generalised tonic-clonic and partial seizure frequency. Furthermore, oxcarbazepine 2400 mg/day as monotherapy has also proved effective in the treatment of refractory partial seizures in adult patients. Oxcarbazepine 600, 1200 and 2400 mg/day as adjunctive therapy significantly reduced seizure frequency compared with placebo in 692 patients with refractory partial seizures.

The efficacy of oxcarbazepine monotherapy is similar to that of phenytoin in the treatment of children and adolescents with newly diagnosed partial or generalised tonic-clonic seizures. Additionally, adjunctive therapy with oxcarbazepine was significantly more effective than placebo at reducing seizure frequency in children and adolescents with refractory partial seizures.

The most commonly reported adverse events associated with oxcarbazepine monotherapy and/or adjunctive therapy in adults and/or children are somnolence, dizziness, headache, nausea and vomiting.

Oxcarbazepine monotherapy is better tolerated than phenytoin (in both adults and children) and valproic acid (in adults), and although 75 to 90% of adult patients in 5 recent monotherapy studies reported adverse events while receiving oxcarbazepine, <8% withdrew from treatment because of them.

Acute hyponatraemia, although usually asymptomatic, develops in 2.7% of patients treated with oxcarbazepine.

Adverse events most likely to resolve upon switching to oxcarbazepine therapy from treatment with carbamazepine are undetermined skin reactions (rashes, pruritus, eczema), allergic reactions and a combination of malaise, dizziness and headache.

Although oxcarbazepine does have a clinically significant interaction with some drugs (e.g. phenytoin and oral contraceptives), it has a lower propensity for interactions than older antiepileptic drugs (AEDs) because its major metabolic pathway is mediated by noninducible enzymes.

Conclusion: Oxcarbazepine as monotherapy is a viable alternative to established AEDs in the treatment of partial and generalised tonic-clonic seizures in adults and children. Furthermore, it is also effective as adjunctive therapy in the treatment of refractory partial seizures in both age groups. In addition, the drug
Oxcarbazepine is tolerated better than the older, established AEDs, and has a lower potential for drug interactions. These attributes make oxcarbazepine an effective component in the initial treatment of newly diagnosed partial and generalised tonic-clonic seizures, and also as an adjunct for medically intractable partial seizures in both adults and children.

**Pharmacodynamic Properties**

Oxcarbazepine is a 10-keto analogue of carbamazepine which appears to exert its anticonvulsant activity [as its major active metabolite, the monohydroxy derivative (MHD) 10-hydroxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide] by blocking neuronal ion channels. In vitro studies in rodents showed that the drug blocks voltage-sensitive sodium channels, thereby stabilising neural membranes, inhibiting repetitive neuronal firing and reducing synaptic impulse activity. In vitro studies have also shown that MHD reduces high voltage–activated calcium currents in striatal and cortical neurons, thus reducing glutamatergic transmission at corticostriatal synapses.

Cognitive function and saccadic and smooth-pursuit eye movements were minimally affected in newly diagnosed patients with epilepsy undergoing short term oxcarbazepine monotherapy. However, oxcarbazepine was found to stimulate some aspects of psychomotor functioning, such as focused attention and writing speed, in healthy volunteers after 2 weeks.

**Pharmacokinetic Properties**

Oxcarbazepine is rapidly absorbed after oral administration. Maximum plasma concentrations (C max ; 1.05 to 1.74 mg/L) are reached within 2 hours after a single dose of oxcarbazepine 600mg taken after an overnight fast. The C max of MHD (5.44 to 8.85 mg/L) is reached after about 4 to 6 hours and the area under the plasma concentration-time curve ranges from 80 to 220 mg/L h.

Steady-state plasma concentrations of MHD are achieved within 2 to 3 days of implementing a twice daily regimen. Oxcarbazepine pharmacokinetics are linear and show dosage proportionality over the dosage range 300 to 2400 mg/day. Approximately 37 to 43% of MHD and 60 to 67% of oxcarbazepine is bound to plasma proteins.

Once absorbed from the gastrointestinal tract, oxcarbazepine is almost immediately reduced by an hepatic cytosolic aryloketone reductase to form the major active metabolite MHD. Hence, the metabolism of oxcarbazepine is not affected by autoinduction, as is the case with carbamazepine. The plasma elimination half-life of oxcarbazepine is 1 to 2.5 hours, illustrating its rapid conversion to MHD. The elimination half-life of MHD in healthy volunteers averages about 8 to 10 hours. The rate of renal clearance of MHD is 0.71 to 1.26 L/h in healthy volunteers. Plasma concentrations of MHD are higher in patients with renal dysfunction and in the elderly because of reduced renal clearance, and lower in healthy children aged between 2 and 5 years compared with older children and adults because of increased systemic clearance. Dosage adjustments for these 3 patient groups are recommended.

Because the metabolism of oxcarbazepine to its active metabolite is mediated by noninducible enzymes, oxcarbazepine pharmacokinetics are largely unaffected by induction of the microsomal cytochrome P450 (CYP) system. As such, the potential for interactions with antiepileptic drugs (AEDs) that induce CYP isozymes is reduced. However, there are reports of clinically significant interactions between oxcarbazepine, phenytoin and lamotrigine.

The efficacy of oral contraceptives may be reduced by oxcarbazepine because of significant reductions in serum ethinylestradiol and levonorgestrel concentrations.
reported in healthy women receiving oral contraceptives and oxcarbazepine concomitantly.

Furthermore, switching to oxcarbazepine therapy from treatment with carbamazepine resulted in a 47 to 200% increase in plasma concentrations of haloperidol, chlorpromazine and clozapine, most probably due to the removal of the inducing effect of carbamazepine.

**Therapeutic Efficacy**

**Adults.** Early studies showed oxcarbazepine monotherapy to be equivalent in efficacy to carbamazepine in the treatment of generalised tonic-clonic seizures and partial seizures in adults. In a more recent study, oxcarbazepine 1200 mg/day significantly reduced seizure frequency by 89.1 vs 37.4% and increased the time to the first seizure compared with placebo in previously untreated patients.

Two monotherapy trials showed oxcarbazepine to be as effective at reducing generalised tonic-clonic and partial seizure frequency as valproic acid and phenytoin in patients with newly diagnosed epilepsy. About 57 and 60% of patients with newly diagnosed epilepsy treated with oxcarbazepine were seizure-free during a 48-week maintenance treatment period. Furthermore, oxcarbazepine and the other 2 AEDs did not differ significantly in their effects on seizure frequency during the maintenance period, number of patients discontinuing treatment due to lack of efficacy, or overall physician and patient evaluation of treatment.

Oxcarbazepine monotherapy has also proved effective in the treatment of refractory partial seizures. Oxcarbazepine 2400 mg/day significantly reduced seizure frequency and increased the time to the first seizure compared with placebo or a subtherapeutic dosage of the drug (300 mg/day), in patients with intractable seizures.

Oxcarbazepine 600, 1200 and 2400 mg/day as adjunctive therapy significantly reduced seizure frequency compared with placebo in 692 patients with refractory partial seizures.

**Children.** The efficacy of oxcarbazepine monotherapy is similar to that of phenytoin in the treatment of previously untreated children and adolescents with partial or generalised tonic-clonic seizures. In a well designed clinical trial, 60% of evaluable patients treated with oxcarbazepine 150 to 2400 mg/day were seizure-free during the maintenance period. Similarly, 60% of the patients treated with phenytoin 150 to 800 mg/day were also free of seizures. After accounting for baseline seizure frequencies, there was no significant difference in seizure frequency between the 2 treatment groups.

Adjunctive therapy with oxcarbazepine was significantly more effective than placebo at reducing seizure frequency in children and adolescents with refractory partial seizures. Reductions in seizure frequency of 35% from baseline were reported for oxcarbazepine-treated patients compared with 9% for children receiving placebo.

**Tolerability**

**Adults.** The most commonly reported adverse events associated with oxcarbazepine monotherapy in adults (in ≥5% of patients) are somnolence, headache, dizziness, nausea, vomiting, fatigue, rash and diplopia. Although 75 to 90% of patients in 5 recent monotherapy studies who received at least one dose of oxcarbazepine reported adverse events, <8% withdrew from treatment because of them. Reasons for discontinuing treatment prematurely included rash, postictal psychosis, ataxia, oxcarbazepine intoxication, headache and dizziness.

The time to premature discontinuation of treatment due to adverse events was significantly in favour of oxcarbazepine compared with phenytoin in one study,
but there was no significant difference compared with valproic acid in another study. However, oxcarbazepine was better tolerated than phenytoin (particularly with respect to gum hyperplasia, tremor, diplopia and nystagmus), and valproic acid (particularly with respect to tremor, weight gain, alopecia and headache).

The most commonly reported adverse events among adult patients receiving oxcarbazepine adjunctive therapy are dizziness, somnolence, sedation, headache, fatigue, nausea, vomiting, ataxia, nystagmus and abnormal gait.

In 757 patients with severe partial and/or generalised seizures, as few as 110 adverse events were reported and only 1.3% of patients discontinued treatment because of them. The majority of these patients were treated for 2 to 6 years with a dosage of 150 to 3600 mg/day and along with dizziness, headache, nausea and vomiting, hyponatraemia was also a common adverse event.

In 164 patients switched to oxcarbazepine (monotherapy and adjunctive therapy were not differentiated) from carbamazepine therapy because of adverse events and/or intolerability while receiving carbamazepine, 18% became free of adverse events, and in 60% of the patients, symptoms became tolerable. The adverse events most likely to resolve upon switching to oxcarbazepine were undetermined skin reactions (rashes, pruritus, eczema), allergic reactions and a combination of malaise, dizziness and headache.

In a large well designed clinical trial where oxcarbazepine 600, 1200 or 2400 mg/day was administered to patients taking up to 3 concomitant AEDs the highest dosage was associated with >65% of patients discontinuing treatment, mainly because of CNS-related adverse events. However, treatment was well tolerated in patients receiving oxcarbazepine 1200 mg/day.

Children. Common adverse events in previously untreated children receiving oxcarbazepine monotherapy are similar to those in adults: somnolence, headache, dizziness, nausea, apathy and rash. Oxcarbazepine was tolerated better than phenytoin, particularly with respect to nervousness, dizziness, gum hyperplasia, hypertrichosis and ataxia. Furthermore, the time to premature discontinuation of treatment due to adverse events was significantly in favour of oxcarbazepine.

The most common adverse events experienced by children and adolescents receiving oxcarbazepine adjunctive therapy were somnolence, headache, dizziness, vomiting, nausea, diplopia, fever and ataxia.

Hyponatraemia. Acute hyponatraemia (serum sodium level <125 mmol/L), although usually asymptomatic, develops in 2.7% of patients receiving oxcarbazepine treatment. In a large retrospective evaluation of the records of 1966 patients who had been enrolled in 14 controlled monotherapy and adjunctive therapy trials conducted to date, and who were treated for about 20 months with oxcarbazepine 600 to 1800 mg/day, the incidence of acute hyponatraemia was found to be low (2.7%).

In the US and the UK, orally administered oxcarbazepine is approved for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as adjunctive therapy in the treatment of partial seizures in children (aged ≥4 years in the US and ≥6 years in the UK). In the UK, the drug is also approved for use as monotherapy in children ≥6 years of age.

The manufacturer recommends that initiation of monotherapy in adults should begin with a dosage of 600 mg/day and be titrated to 1200 mg/day. However, in practice a lower initial dosage may be better tolerated. Adult patients being switched to oxcarbazepine monotherapy from treatment with other AEDs can
receive ≤2400 mg/day after a 4-week titration period starting at 600 mg/day.

Adjunctive therapy with oxcarbazepine in adults should not exceed the recommended dosage of 1200 mg/day because of intolerability at higher dosages.

Adjunctive therapy in children aged 4 to 16 years can begin with a daily dosage of 8 to 10 mg/kg (but not exceed 600 mg/day). The target maintenance dosage (median =30 mg/kg/day) should be reached within 2 weeks and is dependent upon patient bodyweight. Children <8 years of age have an increased clearance (by about 30 to 40%) compared with older children and adults and, therefore, may need higher maintenance dosages to achieve effective seizure control.

During the titration phase, patients need to be observed closely and plasma concentrations of the concomitant AEDs should be monitored, as they may be altered, especially at oxcarbazepine dosages >1200 mg/day.

The measurement of serum sodium levels should be considered during treatment with oxcarbazepine, especially if the patient is receiving concomitant medication known to decrease serum sodium levels or if the symptoms of hypona
taena appear.

There is a 25 to 30% chance that patients with a history of hypersensitivity to carbamazepine will also experience hypersensitivity reactions to oxcarbazepine. As such, oxcarbazepine treatment must be discontinued immediately if signs of hypersensitivity develop.

1. Introduction

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide) is a 10-keto analogue of carbamazepine with anticonvulsant activity. The pharmacology and clinical use of oxcarbazepine in epilepsy, trigeminal neuralgia and affective disorders were previously discussed by Grant and Faulds in Drugs. This review re-examines the role of oxcarbazepine in the management of epilepsy in the light of more recent data.

2. Pharmacodynamic Properties

There have been few pharmacological studies on oxcarbazepine reported since the earlier review and, therefore, this section is a general overview of the previous data updated with a small number of subsequent reports in animals and humans. Oxcarbazepine showed activity in standard animal models of tonic-clonic and partial seizures but not in a rat model of absence seizures.

2.1 Mechanism of Action

The actual mechanism of action of oxcarbazepine remains unknown but its major active metabolite, the monohydroxy derivative (MHD) 10-hydroxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, appears to affect neuronal ion channels.[2-4] The anticonvulsant profiles of oxcarbazepine and MHD are very similar to that of carbamazepine.[5] Table I summarises in vitro and in vivo pharmacodynamic studies with oxcarbazepine. The 3 major proposed mechanisms of activity for new antiepileptic drugs (AEDs) are the modulation of voltage-dependent ionic conductances, enhancement of inhibitory processes [mainly those mediated by γ-aminobutyric acid (GABA)] and reduction of synaptic excitatory transmission.[6,15] While there have been no direct results from studies in the human brain, in vitro studies in rodents showed that voltage-sensitive sodium channels are blocked by oxcarbazepine, thereby stabilising neural membranes, suppressing repetitive neuronal firing (table I) and reducing synaptic impulse activity.[3] This in vitro activity parallels the ability of the drug to reduce partial and generalised tonic-clonic seizures clinically (see section 4) and, thus, limitation of the firing rate could contribute to blocking the spread of seizure activity from an epileptogenic focus.

There is also in vitro evidence that calcium
channels could be involved in the anticonvulsant mechanism of oxcarbazepine through the ability of the drug to reduce excitatory synaptic transmission (table I). In vitro studies showed that MHD reduces high voltage-activated calcium currents in striatal and cortical neurons, thus reducing glutamatergic transmission at corticostriatal synapses.[4,7]

2.2 Effects on the CNS

Recently, studies in humans have evaluated the effects of oxcarbazepine on the CNS.[16-19] Cognitive function was minimally affected in newly diagnosed patients with epilepsy undergoing oxcarbazepine monotherapy.[17,19] After short term treatment (4 months) with oxcarbazepine 900 to 1200 mg/day, cognitive function was unimpaired in 10 adult patients with partial or generalised seizures.[19] In a study of longer duration, both oxcarbazepine and phenytoin showed minimal impediment of memory, attention and simple motor speed in 29 patients who received oxcarbazepine (n = 14) or phenytoin (n = 15) for 1 year. Dosages were individualised to achieve serum oxcarbazepine or phenytoin concentrations of 30 to 120 µmol/L and 40 to 80 µmol/L, respectively.[17] Similarly, oxcarbazepine 600 mg/day produced negligible effects on saccadic and smooth-pursuit eye movements in healthy volunteers.[16] In another study, oxcarbazepine 600 mg/day was found to stimulate some aspects of psychomotor functioning, such as focused attention and increased writing speed, in healthy volunteers over a 2-week treatment period.[18]

3. Pharmacokinetic Properties

The pharmacokinetic properties of oxcarbazepine in healthy volunteers and in patients with epilepsy have been comprehensively reviewed recently.[20-24] This section provides a brief overview of these data, with additional information from other patient groups and healthy volunteers.

3.1 Absorption and Distribution

Oxcarbazepine is rapidly absorbed after oral administration. In fasting healthy volunteers, maximum plasma concentrations (Cmax) ranging from 1.05 to 1.74 mg/L are reached within 2 hours (tmax) after a single dose of oxcarbazepine 600 mg (table II).[25-28] The area under the plasma concentration-time curve (AUC) ranges from 5.10 to 6.84 mg/L·h (table II). The Cmax of MHD (5.44 to 8.85 mg/L) is reached after about 4 to 6 hours and the AUC is about 16- to 32-fold higher than for the parent drug (table II). Food has no effect on the rate or extent of absorption of oxcarbazepine.[35]

Steady-state plasma concentrations of MHD are achieved within 2 to 3 days of implementing a twice daily regimen. Oxcarbazepine pharmacokinetics are linear and show dose proportionality over the dosage range 300 to 2400 mg/day.[35] MHD is distributed equally between plasma and red blood cells but, at steady state, plasma concentrations of MHD were found to be 3 to 5 times higher than corresponding saliva concentrations, indicating that drug monitoring by saliva sampling is inappropriate.[37] Approximately 37 to 43% of MHD and 60 to 67% of oxcarbazepine is bound to plasma proteins.[29,33] Because only a relatively small
proportion of MHD is protein bound, the potential for clinically relevant competitive plasma protein binding with other AEDs is unlikely.[38]

The ratio between the concentration of MHD in breast milk and that in maternal plasma is 0.5, [39] therefore the active moiety is excreted in breast milk (see section 6).

3.2 Metabolism and Elimination

Once absorbed from the gastrointestinal tract, oxcarbazepine is almost immediately reduced by an hepatic cytosolic arylketone reductase (there is also some evidence of placental metabolism[40,41]) to form the major active metabolite MHD (fig. 1).[21]

This is in contrast to the metabolism of carbamazepine, in which oxidative attack of the double bond at C-10 and C-11 by an epoxidase forms the intermediate carbamazepine-10,11-epoxide (fig. 1). This conversion, unlike that of oxcarbazepine to MHD, requires microsomal cytochrome P450 (CYP) isozymes, which are inducible. Hence, the metabolism of oxcarbazepine is not affected by autoinduction, which is a feature of treatment with carbamazepine.

The metabolic reduction of the 10-keto group of oxcarbazepine results in the formation of an asymmetric carbon and, therefore, a chiral molecule. Hence, MHD is formed as an enantiomeric pair (fig. 1), with both the S- and R-enantiomers (formed in the ratio of 80% to 20%, respectively) demonstrating equivalent potency in several animal models for anticonvulsant activity.[30] Because both enantiomers have equivalent anticonvulsant potency, studies determining the efficacy of oxcarbazepine have been nonstereospecific with regard to MHD, despite both enantiomers having different pharmacokinetic properties (table III).[30]

The majority of the administered dose of oxcarbazepine is excreted by the kidneys as the inactive glucuronide conjugates of MHD (49%) and oxcarbazepine (9%) and unchanged MHD (27%). Less than 1% of the administered dose is excreted as unchanged oxcarbazepine.[32,35] A small proportion (4 to 7%) of MHD undergoes further metabolism to the inactive dihydroxy derivative 10,11-dihydro-10,11-trans-dihydroxycarbamazepine.[32] This is the only conversion that requires inducible CYP isozymes. However, this induction is less pronounced than the induction associated with carbamazepine.[21] This has been shown in studies in patients with epilepsy in whom, upon replacement of carbamazepine treatment with oxcarbazepine, altered levels of serum lipids associated with induction of the CYP system were normalised.[43-46]

The plasma elimination half-life (t_{1/2}β) of oxcarbazepine is 1 to 2.5 hours (table II), illustrating its rapid conversion to MHD.[22] The t_{1/2}β of MHD in healthy volunteers averages about 6.5 to 24.3 hours[25,28-31], although values between 6.5 and 24.3 hours have been reported (table II).[25,28-31]

3.3 Special Patient Populations

The pharmacokinetics of oxcarbazepine have been studied in healthy elderly patients and children, and in patients with impaired renal function. Because 96% of the total administered dose of oxcarbazepine is eliminated renally, hepatic impairment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oxcarbazepine</th>
<th>MHD</th>
</tr>
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<tbody>
<tr>
<td>C_{max} (mg/L)</td>
<td>1.05-1.74[25-28]</td>
<td>5.49-8.85[25-30]</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>1.0-2.2[25]</td>
<td>4.0-6.6[25-30]</td>
</tr>
<tr>
<td>AUC (mg/L • h)</td>
<td>5.10-6.84[25-28]</td>
<td>60-220[25-30]</td>
</tr>
<tr>
<td>Plasma protein binding (%)</td>
<td>60-67[32,33]</td>
<td>37-43[22,23,34]</td>
</tr>
<tr>
<td>V_{dss} (L)</td>
<td>49[31]</td>
<td>49[31]</td>
</tr>
<tr>
<td>V_{dss adjusted for bodyweight (L/kg)}</td>
<td>0.7-0.8[32]</td>
<td></td>
</tr>
<tr>
<td>t_{1/2}β (h)</td>
<td>1.0-2.5[25]</td>
<td>6.5-24.3[25,28-31]</td>
</tr>
<tr>
<td>CL_{R} (L/h)</td>
<td>0.71-1.2[30,36]</td>
<td></td>
</tr>
<tr>
<td>Excretion (% of dose)</td>
<td>&gt;96% in urine; &lt;4% in faeces[36]</td>
<td></td>
</tr>
</tbody>
</table>

AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; CL_{R} = renal clearance; t_{1/2}β = elimination half-life; t_{max} = time to reach C_{max}; V_{dss} = volume of distribution at steady state.

a The majority of the administered dose is excreted as the inactive glucuronide conjugates of MHD (49%) and oxcarbazepine (9%) and unchanged MHD (27%).
has no apparent effect on the pharmacokinetics of oxcarbazepine or its metabolites, although patients with severe hepatic dysfunction have not been studied.\textsuperscript{[22,35]} However, plasma concentrations of MHD are significantly increased in patients with impaired renal function [creatinine clearance (CL\textsubscript{CR}) <1.8 L/h] and dosage reductions are recommended in these patients (section 6).\textsuperscript{[36,47]} The C\textsubscript{max} and AUC of MHD are significantly higher in healthy elderly volunteers (60 to 82 years) than in younger adults, probably because of the effects of aging on renal function. Conversely, plasma concentrations of MHD are lower in healthy children aged between 2 and 5 years than in older children and adults because systemic clearance is higher.\textsuperscript{[22,48]}

3.4 Drug-Drug Interactions

3.4.1 Interactions Between Oxcarbazepine and Antiepileptic Drugs

Patients undergoing adjunctive therapy with carbamazepine and concomitant AEDs may experience complicated pharmacokinetic drug interactions due to the propensity of various drugs to induce CYP isozymes, resulting in important changes in serum concentrations of concomitant AEDs. However, because the metabolism of oxcarbazepine to its active metabolite is mediated by noninducible enzymes, the pharmacokinetic properties of the

![Diagram of metabolic pathway of oxcarbazepine and carbamazepine](image-url)

**Fig. 1.** Metabolic pathway of oxcarbazepine and carbamazepine. MHD (monohydroxy derivative) is formed as a pair of enantiomers in the ratio of 80\% (S+) to 20\% (R–), both of which are active and undergo elimination upon conjugation with a microsomal glucuronyl transferase. A minor amount (4-7\%) is oxidised to an inactive 10,11-trans-dihydroxy derivative common to both oxcarbazepine and carbamazepine.\textsuperscript{[2,42]} CYP = cytochrome P450.
drug are largely unaffected by induction of the CYP system. For this reason, the potential for interactions with AEDs that induce CYP isozymes is reduced during oxcarbazepine therapy compared with carbamazepine therapy.[49]

Carbamazepine reduced the median AUC of MHD by 15 to 35% in 3 double-blind, placebo-controlled studies involving 531 adults and 138 children.[31,50] Serum carbamazepine concentrations were decreased (by ≈15%) by oxcarbazepine, although not to a clinically significant level.[50]

There is no evidence of a significant interaction between oxcarbazepine and valproic acid or felbamate (table IV).[28,31,51] However, there was a statistically significant interaction between oxcarbazepine and phenobarbital (table IV).[28] The AUC of MHD after a single dose of oxcarbazepine 600mg was 25% lower in patients with epilepsy being treated with phenobarbital than in healthy controls receiving oxcarbazepine alone.[28] Plasma phenobarbital concentrations increased by 14% in adults and in children receiving concomitant oxcarbazepine. These changes, however, are unlikely to be of clinical significance.[50]

Oxcarbazepine inhibits the CYP2C19 isozyme which is involved in the human metabolism of phenytoin.[33] This inhibition can lead to an increase in serum phenytoin concentrations. As such, up to a 40% increase in plasma phenytoin concentrations in adult patients receiving a higher dosage of oxcarbazepine (>1200 mg/day) has been reported, suggesting dosage adjustments of phenytoin may be necessary in these patients.[50]

Oxcarbazepine had a significant inducing effect on lamotrigine, although this was smaller than that of carbamazepine. The Cmax of lamotrigine was reduced by 29% with oxcarbazepine (table IV) and 54% with carbamazepine.[52] However, oxcarbazepine in conjunction with valproic acid (a CYP inhibitor) increased serum lamotrigine concentrations by 111%, compared with 211% with valproic acid alone. This implies that the inhibiting effect of valproic acid dominates the inducing effect of oxcarbazepine, and that removal of oxcarbazepine therapy in patients coadministered valproic acid and lamotrigine would cause a 50% increase in serum lamotrigine concentrations.[52]

### 3.4.2 Interactions Between Oxcarbazepine and Other Drugs

Oxcarbazepine induces specific isozymes of the CYP3A group (CYP3A4 and CYP3A5) which are involved in the metabolism of oral contraceptives and dihydropyridine calcium antagonists.[23,57] Oxcarbazepine decreased the AUCs of ethinyl-estradiol and levonorgestrel by about 47 and 36%, respectively, in healthy women receiving an oral contraceptive (table IV).[54,55] Breakthrough bleeding in women taking oxcarbazepine with an oral contraceptive has also been reported.[58] Hence, the efficacy of oral contraceptives may be reduced by oxcarbazepine.

Furthermore, repeated administration of oxcarbazepine 900 mg/day reduced the AUC and Cmax of the calcium antagonist felodipine by 28 and 34%, respectively, in 7 healthy volunteers (table IV).[56] However, this reduction is considerably less than that seen when felodipine is coadministered with carbamazepine, which has been shown to reduce the bioavailability of felodipine by up to 94%,[59] and plasma felodipine concentrations remained within the recommended therapeutic range.[56]

Although viloxazine was shown to moderately increase plasma MHD concentrations in 6 patients with partial seizures stabilised on a mean dosage of

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**Table III.** Mean pharmacokinetic parameters of the R- and S-enantiomers of monohydroxy derivative (MHD), the main active metabolite of oxcarbazepine. Values are calculated from serum data obtained after a single 600mg dose of oxcarbazepine in 12 healthy Chinese volunteers.[30]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S-MHD</th>
<th>R-MHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>4.49</td>
<td>0.99*</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>6.0</td>
<td>5.5</td>
</tr>
<tr>
<td>AUC (mg/L h)</td>
<td>129.8</td>
<td>26.3*</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>13.0</td>
<td>11.9</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>22.9</td>
<td>20.9**</td>
</tr>
</tbody>
</table>

AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; MRT = mean residence time; t1/2 = half life; tmax = time to reach Cmax. *p < 0.001, **p < 0.02 vs S-MHD.
Oxcarbazepine 1500 mg/day (table IV), this interaction is unlikely to be of clinical significance.[53]

Studies have shown a lack of statistically significant interactions between oxcarbazepine 600 mg/day and cimetidine 400 mg/day or erythromycin 500 mg/day (table IV).[26,27] Similarly, oxcarbazepine (600mg once daily and 900mg twice daily) did not affect the anticoagulant activity of warfarin in 7 healthy volunteers.[60]

The disappearance of induction of hepatic metabolism after substitution of oxcarbazepine for carbamazepine can cause an increase in the serum concentration of concomitant medications. Switching to oxcarbazepine therapy from treatment with carbamazepine in 12 patients receiving concomitant clozapine resulted in a 47% increase in plasma clozapine concentrations.[61] Furthermore, serum concentrations of haloperidol, chlorpromazine and clozapine increased by 50 to 200% upon switching to oxcarbazepine from carbamazepine in 7 patients with schizophrenia or organic psychosis.[62] In 2 further case reports, plasma citalopram concentrations increased to usual therapeutic concentrations after replacing carbamazepine with oxcarbazepine in 2 patients with comorbid epilepsy, depression and panic disorder.[63]

4. Therapeutic Efficacy

Previous studies[64-68] found oxcarbazepine to be effective at reducing seizure frequency in patients with generalised tonic-clonic seizures or partial seizures with or without secondary generalisation. Since the earlier review,[1] clinical experience

Table IV. Pharmacokinetic drug interactions involving oxcarbazepine and other drugs

<table>
<thead>
<tr>
<th>Coadministered drug regimen (no. of participants)</th>
<th>Oxcarbazepine dosage (mg/day)</th>
<th>Effect of coadministered drug on MHD pharmacokinetics</th>
<th>Effect of oxcarbazepine on coadministered drug pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>AUC</td>
</tr>
<tr>
<td>In combination with antiepileptic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine 400-2000 mg/day (12)&lt;sup&gt;[51]&lt;/sup&gt;</td>
<td>900</td>
<td>↓35%&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Felbamate 2400 mg/day (16)&lt;sup&gt;[56]&lt;/sup&gt;</td>
<td>1200</td>
<td>↓2%</td>
<td>↑12%</td>
</tr>
<tr>
<td>Lamotrigine 6.5-100 mg/day (14)&lt;sup&gt;[52]&lt;/sup&gt;</td>
<td>2057 (mean)</td>
<td>↓20%</td>
<td>↑25%&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phenytoin 25-500 mg/day (12)&lt;sup&gt;[53]&lt;/sup&gt;</td>
<td>600</td>
<td>↓32%</td>
<td></td>
</tr>
<tr>
<td>Valproic acid 1000-2000 mg/day (8)&lt;sup&gt;[24]&lt;/sup&gt;</td>
<td>600</td>
<td>↓11%</td>
<td></td>
</tr>
<tr>
<td>Valproic acid 400-2800 mg/day (12)&lt;sup&gt;[31]&lt;/sup&gt;</td>
<td>900</td>
<td>↓13%</td>
<td></td>
</tr>
<tr>
<td>In combination with hepatic microsomal enzyme inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine 400 mg/day (8)&lt;sup&gt;[27]&lt;/sup&gt;</td>
<td>600</td>
<td>↑1%</td>
<td>↑6%</td>
</tr>
<tr>
<td>Erythromycin 500 mg/day (8)&lt;sup&gt;[28]&lt;/sup&gt;</td>
<td>600</td>
<td>↓8%</td>
<td>↑2%</td>
</tr>
<tr>
<td>Vilaroxine 200 mg/day (6)&lt;sup&gt;[30]&lt;/sup&gt;</td>
<td>1500 (mean)</td>
<td>↑11%&lt;sup&gt;††&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>In combination with other drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinylestradiol 50 µg/day (22)&lt;sup&gt;[54]&lt;/sup&gt;</td>
<td>1200</td>
<td>↓35%***</td>
<td></td>
</tr>
<tr>
<td>Ethinylestradiol 30-40 µg/day (10)&lt;sup&gt;[55]&lt;/sup&gt;</td>
<td>900</td>
<td>↓25%***</td>
<td></td>
</tr>
<tr>
<td>Felodipine 10 mg/day (7)&lt;sup&gt;[56]&lt;/sup&gt;</td>
<td>900</td>
<td>↓34%**</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel 250 µg/day (22)&lt;sup&gt;[54]&lt;/sup&gt;</td>
<td>1200</td>
<td>↓25%***</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel 50-125 µg/day (10)&lt;sup&gt;[55]&lt;/sup&gt;</td>
<td>900</td>
<td>↓7%</td>
<td></td>
</tr>
</tbody>
</table>

a Patients with epilepsy.
b Healthy volunteers.
c Patients with epilepsy and healthy volunteers as control.

AUC = area under the plasma concentration-time curve; C<sub>max</sub> = maximum plasma concentration; MHD = monohydroxy derivative; ↑ indicates increase; ↓ indicates decrease; ↔↔ indicates no effect; † p < 0.05, †† p < 0.003 vs oxcarbazepine alone; * p < 0.05, ** p < 0.01, *** p < 0.006 vs coadministered drug alone.
with oxcarbazepine in the treatment of epilepsy has increased, both in children and in adults.

4.1 In Adults

4.1.1 Monotherapy

Early studies,\[64,65\] as discussed previously,\[1\] showed oxcarbazepine monotherapy to be equivalent in efficacy to carbamazepine in the treatment of generalised tonic-clonic seizures and partial seizures. Subsequently, 5 well designed clinical trials have been published, 3 of which examined the therapeutic potential of oxcarbazepine in previously untreated patients with partial and/or generalised seizures.\[69-71\] The other 2 investigated the efficacy of oxcarbazepine in patients with refractory partial seizures.\[72,73\] Each trial was of randomised, double-blind, parallel-group design.

In most studies, assessment of efficacy was based on the number of patients who became seizure-free, the reduction in seizure frequency and the number of discontinuations due to unsatisfactory therapeutic effect. Exclusion criteria in the trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients evaluated/randomised</th>
<th>Treatment regimen (mg/day) [duration]</th>
<th>Seizure frequency at baseline (mean/median per week)</th>
<th>Results seizure frequency during maintenance period (mean/median per week, unless otherwise stated)</th>
<th>no. of patients seizure free</th>
<th>no. of patients meeting ≥1 exit criterion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill et al.[70]</td>
<td>118/143</td>
<td>OXC 600-2100 (mean 1028.4) [48wk]</td>
<td>0.98/0.20</td>
<td>0.08/0</td>
<td>70 (59.3%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>119/144</td>
<td>PHT 100-650 (mean 313.4) [48wk]</td>
<td>0.84/0.23</td>
<td>0.06/0</td>
<td>69 (58.0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Christe et al.[71]</td>
<td>106/128</td>
<td>OXC 600-2400 (mean 1052.8) [48wk]</td>
<td>0.53/0.13</td>
<td>0.17/0</td>
<td>60 (56.6%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>106/121</td>
<td>VPA 200-2700 (mean 1146.2) [48wk]</td>
<td>1.09/0.25</td>
<td>0.40/0</td>
<td>57 (53.8%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

In patients with previously untreated partial and/or generalised seizures

- In the study by Beydoun et al.,\[73\] exit criteria included a 2-fold increase in partial seizure frequency in any 28-day period or a 2-fold increase in the highest consecutive 2-day seizure frequency relative to baseline, a new-onset secondarily generalised seizure, worsening of generalised seizure duration or frequency requiring investigator intervention. In the study by Schachter et al.,\[72\] patients exited the treatment phase by experiencing 4 partial seizures, 2 new-onset secondarily generalised seizures, serial seizures or status epilepticus.

- These figures are based on the intent-to-treat population (i.e randomised).

- Existing treatment with antiepileptic drugs was stopped 48 hours prior to randomisation, during which time partial seizure frequency was recorded (i.e. baseline results are mean frequency per 48h).

NA = not assessed; NR = not reported; PHT = phenytoin; PL = placebo; VPA = valproic acid; *p < 0.0001 vs OXC 300 mg/day; **p = 0.0001, ***p ≤ 0.0001 vs PL.
included a history of status epilepticus, progressive neurological disorder and significant organic disease. Among the trials in refractory patients, exclusion criteria also featured the use of barbiturates, benzodiazepines, calcium antagonists or monoamine oxidase inhibitors (MAOIs) and the use of felbamate 30 days prior to randomisation. The study by Schachter et al. also excluded patients with hypersensitivity to carbamazepine or lorazepam.

In Previously Untreated Patients

Oxcarbazepine was as effective as phenytoin and valproic acid at reducing generalised tonic-clonic and partial seizure frequency in 2 large trials of similar design (table V). About 57 and 60% of patients with newly diagnosed epilepsy treated with oxcarbazepine were seizure-free during a 48-week maintenance treatment period, a proportion similar to that observed with phenytoin and valproic acid. Oxcarbazepine and the other 2 AEDs also did not differ significantly in their effects on seizure frequency during the maintenance period (table V), number of patients discontinuing treatment due to lack of efficacy, or overall physician and patient evaluation of treatment (1 trial used a 4-point scale to assess this latter parameter).

Oxcarbazepine was as effective as phenytoin and valproic acid in reducing both partial and generalised seizures (fig. 2); for all drugs there appeared to be a slightly higher efficacy rate in patients with generalised seizures than in those with partial seizures.

Oxcarbazepine significantly reduced seizure frequency, and increased the time to the first seizure, in previously untreated patients compared with placebo in a study reported as an abstract. 67 previously untreated patients with recent-onset partial seizures received either oxcarbazepine 1200 mg/day (600mg twice daily) or placebo for 90 days after a 56-day baseline phase. During the double-blind treatment phase, the median time to the first partial seizure was 12 days in the oxcarbazepine group (n = 32) compared with 3 days in placebo recipients (n = 35; p = 0.0457). The seizure frequency per 28 days was reduced by a median 89.1% from baseline in the oxcarbazepine group compared with 37.4% in the placebo group (p = 0.033).

In Patients with Refractory Seizures

Oxcarbazepine significantly reduced seizure frequency and increased the time to the first seizure in patients with refractory partial seizures compared with patients receiving placebo. In a study of short duration, 102 hospitalised patients (who had undergone evaluation for epilepsy surgery) ranging in age from 11 to 62 years with refractory partial seizures including simple, complex and secondarily generalised seizures, were randomised to receive oxcarbazepine 2400 mg/day or placebo for...
9 days. The primary efficacy variable detailed the time taken for a patient to meet one of the exit criteria. Patients exited the trial after experiencing 4 partial seizures, 2 new-onset secondarily generalised seizures, serial seizures or status epilepticus, whichever came first. Seizure monitoring did not begin until day 2, once the full dosage level was achieved. During the first day, lorazepam 8mg was administered to 45 and 47 patients in the oxcarbazepine and placebo groups, respectively, to maintain an acceptable seizure frequency.\(^{[72]}\)

Within 4.5 days, approximately 25% of the oxcarbazepine-treated patients versus 75% of the patients given placebo, excluding 5 who dropped out, exited from the trial according to the defined criteria. In the 9-day study period, 47% of the oxcarbazepine–treated patients met one of the exit criteria compared with 84% of the placebo group (p < 0.0001; fig. 3). The median seizure frequency for the oxcarbazepine-treated group was also significantly lower than that of the placebo group (table V). Additionally, oxcarbazepine significantly reduced the number of patients experiencing secondarily generalised partial seizures compared with placebo (8% vs 47%, p = 0.0006).\(^{[72]}\)

In a dose comparison study in 87 patients, oxcarbazepine 2400 mg/day, administered in 2 daily doses for 16 weeks (after a 2-week titration period), was significantly more effective (p < 0.0001) at seizure control than a low dosage of oxcarbazepine (300 mg/day) [table V].\(^{[73]}\) Given that the lower dosage of oxcarbazepine is subtherapeutic (see section 6), this result is to be expected.

### 4.1.2 Adjunctive Therapy

Oxcarbazepine 600, 1200 or 2400 mg/day was significantly more effective than placebo as adjunctive therapy in adult patients with refractory partial seizures.\(^{[74,75]}\) 692 randomised patients who had experienced ≥4 partial seizures per month during the baseline period while taking 1, 2 or 3 other AEDs (actual AEDs not reported) in optimum dosages received oxcarbazepine 600, 1200 or 2400 mg/day or placebo for a 26-week double-blind treatment period (including an initial 2-week titration phase). All 3 active treatment groups experienced significant reductions in seizure frequency compared with the placebo group (fig. 4).\(^{[74,75]}\) Furthermore, 22, 10 and 3% of patients in the oxcarbazepine 2400, 1200 and 600 mg/day groups, respectively, were free of seizures during the treatment phase compared with 0.6% of patients in the placebo group.\(^{[74]}\)

---

**Fig. 3.** Efficacy of oxcarbazepine 2400 mg/day versus placebo as monotherapy in 102 adults with refractory partial seizures. The proportion of patients (%) who responded to treatment and, thus, remained in the trial throughout the 9-day randomised, double-blind treatment phase and the percentage of patients who experienced 1 of 4 exit criteria. No patients experienced status epilepticus, the fourth exit criterion.\(^{[72]}\) *p < 0.0001 vs placebo.*
4.2 In Children

Recently, 2 randomised, double-blind, multi-centre trials evaluating the efficacy of oxcarbazepine have been conducted in young patients,[76,77] but the majority of studies performed in children and adolescents with epilepsy are retrospective postmarketing analyses.[11,78-81] All the studies of oxcarbazepine as adjunctive therapy found the drug to be effective in reducing seizure frequency among children under the age of 18 years.[11,78-80] In these studies, children (including those with intellectual disability[78,79]) who had intractable partial or generalised epilepsy received oxcarbazepine in conjunction with at least one other AED. The mean duration of treatment was 18.4 months with dosages ranging from 18 to 123 mg/kg/day. Patient numbers ranged from 40 to 67 among the 4 studies.

There have also been a number of noncomparative retrospective analyses involving patients under the age of 18 years receiving oxcarbazepine as monotherapy, but these did not supply separate results for monotherapy and adjunctive therapy.[11,33,79] In the one retrospective, postmarketing study that specifically investigated monotherapy, 71 of the 100 patients aged 3 months to 4 years (the majority of whom experienced partial seizures) who were treated with oxcarbazepine 20 to 55 mg/kg/day for a mean duration of 35 months, became seizure-free. A further 11 patients had a ≥50% reduction in seizure frequency, and 18 experienced no improvement.[81]

The 2 well designed trials, 1 investigating oxcarbazepine monotherapy[76] and the other adjunctive therapy,[77] included patients under the age of 18 years diagnosed with generalised tonic-clonic seizures without partial onset and/or partial seizures with or without secondary generalisation. Exclusion criteria in both trials included a history of status epilepticus, progressive neurological disorder or significant organic disease. The study involving oxcarbazepine adjunctive therapy excluded patients who had recently used calcium antagonists or MAOIs, who were hypersensitive to carbamazepine or who had used felbamate within 90 days of randomisation.[77]

4.2.1 Monotherapy

The efficacy of oxcarbazepine was similar to that of phenytoin in the treatment of previously untreated children and adolescents with partial seizures with or without secondary generalisation, or generalised tonic-clonic seizures, in a randomised, double-blind, multicentre clinical trial (table VI).[76] After a retrospective baseline phase, 193 children aged 5 to 17 years (mean, 10 years) with newly diagnosed partial seizures (78%) or generalised tonic-clonic seizures (22%) were randomised to receive oxcarbazepine (n = 97) or phenytoin (n = 96) for 56 weeks (starting with an 8-week titration phase).

During the 48-week maintenance phase, 4 patients receiving oxcarbazepine and 3 phenytoin-treated patients withdrew because of lack of efficacy, and 16 patients (2 receiving oxcarbazepine and 14 receiving phenytoin) exited because of adverse events, (see section 5). These patients were, however, included in the efficacy analysis. Among the 158 evaluable patients, the same proportion in each group (60%) were seizure-free during the maintenance period and there were no significant differences in seizure frequency (table VI). 60% of
the oxcarbazepine-treated patients with partial seizures were seizure-free during the maintenance period compared with 62% in the phenytoin group. 59 and 54% of patients with generalised seizures who were treated with oxcarbazepine and phenytoin, respectively, were seizure-free throughout the 48-week period.

### 4.2.2 Adjunctive Therapy

Adjunctive therapy with oxcarbazepine was significantly more effective than placebo at reducing seizure frequency in children and adolescents in a randomised, double-blind, multicentre trial\[77\] and a noncomparative, nonblind extension study.\[82\]

In the well designed study by Glauser et al.,\[77\] 267 patients between the ages of 3 and 17 years with refractory partial seizures (including simple, complex and partial seizures with secondary generalisation) received either oxcarbazepine 30 to 46 mg/kg/day or placebo, administered twice daily, for a period of 14 weeks after a preliminary titration period of 2 weeks in which the initial dosage was 10 mg/kg/day. Children were eligible for randomisation if they had experienced at least 8 partial seizures during the 56-day baseline period, were being treated with 1 or 2 concomitant AEDs and had a serum sodium level ≥130 mmol/L.\[77\]

During the maintenance period, the reduction in median seizure frequency per 28 days (the primary efficacy variable) and the percentage of patients with ≥50% seizure reduction were significantly greater in patients treated with oxcarbazepine than in patients who received placebo (table VI). Furthermore, the median percentage reduction in seizure frequency for the 2 partial seizure subtypes, and also for secondarily generalised seizures, was significantly greater (p = 0.0012) in oxcarbazepine-treated patients than placebo recipients. The median reduction in simple and complex partial seizure frequency among the oxcarbazepine-treated patients was 45 and 42%, respectively, compared with 16 and 10% among the placebo group. The median reduction in secondarily generalised seizure frequency was 78% in the oxcarbazepine group compared with 33% in placebo recipients.\[77\]

### Table VI. Efficacy of oxcarbazepine (OXC) as monotherapy and adjunctive therapy in the treatment of children and adolescents with epilepsy: results of randomised, double-blind, multicentre trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of pts evaluated/randomised</th>
<th>Treatment regimen (mg/day) [duration]</th>
<th>Seizure frequency at baseline (mean/median per week)</th>
<th>Results no. of pts seizure-free</th>
<th>Seizure frequency (mean/median per week)</th>
<th>% reduction from baseline in median seizure frequency/28d</th>
<th>% of pts with ≥50% seizure reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>As monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerreiro et al.[76]</td>
<td>81/97</td>
<td>OXC 450-2400 [48wk]</td>
<td>0.68/0.25</td>
<td>49 (60%)</td>
<td>0.07/0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>77/96</td>
<td>PHT 150-800 [48wk]</td>
<td>0.66/0.33</td>
<td>46 (60%)</td>
<td>0.04/0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>As adjunctive therapy[a]</strong></td>
<td>136/138</td>
<td>OXC 30-46 mg/kg/day [16wk]</td>
<td>Median[b] 12/28d</td>
<td>5</td>
<td>NR</td>
<td>35**</td>
<td>41*</td>
</tr>
<tr>
<td></td>
<td>128/129</td>
<td>PL [16wk]</td>
<td>Median[b] 13/28d</td>
<td>1</td>
<td>NR</td>
<td>9</td>
<td>22</td>
</tr>
</tbody>
</table>

\[a\] Patients were receiving 1 or 2 other antiepileptic drugs concomitantly.

\[b\] Partial seizures.

NR = not reported; PHT = phenytoin; PL = placebo; pts = patients; * p = 0.0005; ** p = 0.0001 vs PL.
monotherapy in 5 children. In the first 28-day period, 1 patient was seizure-free, 4 had a decrease of >50% and 4 patients had an increase in seizure frequency. Seizure control increased in the second treatment phase: 9 patients had a reduction in seizure frequency of >25%; 7 of these had a decrease of >50%, although it was not reported which 5 patients received oxcarbazepine as monotherapy.[82]

5. Tolerability

In the previous review in Drugs,[1] there were limited data from which to draw definitive conclusions about the incidence of adverse events associated with oxcarbazepine therapy compared with other AEDs. However, oxcarbazepine was shown to have a similar tolerability profile to carbamazepine, although oxcarbazepine was associated with a lower incidence of serious adverse events, especially allergic reactions.

In the ensuing years there have been a number of clinical trials examining both the efficacy (see section 4) and the tolerability of oxcarbazepine in comparison with placebo or other active therapies,[70-73,76,77] as well as studies that concentrated solely on tolerability.[18,83-87] There have also been a number of clinician case reports.[88-91]

5.1 In Adults

5.1.1 Monotherapy

The most commonly reported adverse events associated with oxcarbazepine monotherapy in adults (in ≥5% of patients) are somnolence, headache, dizziness, nausea, vomiting, fatigue, rash and diplopia.[11,33,35,70-72,83,87,91] There are also reports of abdominal pain, acne, agitation, alopecia, apathy, ataxia, convulsions, diarrhoea, gum hyperplasia, hyponatraemia, memory complaints, nervousness, respiratory distress, tremor and weight gain.[33,35,70-72,85-87]

Oxcarbazepine was well tolerated in the 5 clinical trials involving oxcarbazepine monotherapy (table VII).[69-73] Although 75 to 90% of the 388 patients who received at least one dose of oxcarbazepine reported adverse events, <8% withdrew from treatment because of them. Reasons for discontinuing treatment prematurely included rash,[69-72] postictal psychosis,[72,73] ataxia,[73] oxcarbazepine intoxication after attempted suicide,[70] headache and dizziness.[71,92] However, in the study by Beydoun et al.[73] all dropouts (15%) occurred during a tapering phase (before monotherapy was reached) in which concomitant AEDs were phased out.

The time to premature discontinuation of treatment due to adverse events was significantly in favour of oxcarbazepine compared with phenytoin (p = 0.02) in one study,[70] but there was no significant difference compared with valproic acid in another.[71] However, oxcarbazepine was better tolerated than phenytoin (particularly with respect to gum hyperplasia, tremor, diplopia and nystagmus; table VII), and valproic acid (particularly with respect to tremor, weight gain, alopecia and headache; table VII).[70,71]

As few as 33% of oxcarbazepine recipients reported adverse events, with 18% discontinuing treatment prematurely, in a retrospective analysis of the records of 947 patients with epilepsy.[11] The majority of patients (93%) were aged ≥15 years and received oxcarbazepine at an average dosage of 18 mg/kg/day as monotherapy (n = 597) or adjunctive therapy (n = 350) for a mean duration of 23 months. Among the patients who received oxcarbazepine as monotherapy, rash (7%), fatigue (5%), dizziness (4%) and sedation (4%) were most prevalent, although half of the patients who experienced rash had previously had allergic reactions to carbamazepine. CNS-related adverse events associated with oxcarbazepine monotherapy were usually moderate in severity and were less frequent than those in patients receiving adjunctive therapy (fig. 5), yet they were more often rated as severe (in 26 vs 15% of patients). However, discontinuation of treatment due to adverse events was similar in both groups.[11]

5.1.2 Adjunctive Therapy

The most commonly reported adverse events among adult patients receiving oxcarbazepine adjunctive therapy are dizziness, somnolence, sedation, headache, fatigue, nausea, vomiting, ataxia, nystagmus and abnormal gait.[31,74,83]
Oxcarbazepine was well tolerated in 2 retrospective studies, reported as an abstract,[83] involving the long term use of oxcarbazepine adjunctive therapy. In 757 patients (aged 7 to 91 years) with severe partial (66%) and/or generalised seizures, as few as 110 adverse events were reported which were severe in 0.9% of patients, and only 10 patients (1.3%) discontinued treatment because of them. The majority of patients were treated for 2 to 6 years with a dosage of 150 to 3600 mg/day. Specific concomitant AED medication was not reported. Along with dizziness, headache, nausea and vomiting, hyponatraemia was also a common adverse event (see section 5.3).

In a long term monitoring study, 164 patients who had previously been treated with carbamazepine were switched to oxcarbazepine therapy (monotherapy and adjunctive therapy were not differentiated in the report) because of adverse events and/or intolerability while receiving carbamazepine. 18% became free of adverse events and in 60% of the patients, symptoms became tolerable. The adverse events most likely to resolve upon switching to oxcarbazepine were undetermined skin reactions (rashes, pruritus, eczema), allergic reactions and a combination of malaise, dizziness and headache.[33]

In a large (n = 692) randomised, double-blind trial,[74] the highest dosage of oxcarbazepine (2400 mg/day) was associated with a high proportion of patients (>65%) discontinuing treatment, mainly because of CNS-related adverse events. However, treatment was well tolerated in patients receiving oxcarbazepine 1200 mg/day.[74]

| Table VII. Tolerability profile [percentage of patients (> 5%) experiencing adverse events] of oxcarbazepine (OXC) monotherapy compared with phenytoin (PHT), valproic acid (VPA) and placebo (PL). Results of randomised, multicentre clinical trials |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Adverse event                  | Reference                        | OXC 2400a | PHTb | OXC 600 to 2400 mg/day or VPA 200 to 2700 mg/day in previously untreated adults with partial seizures. | OXC 2400a | PHTb | OXC 600 to 2400 mg/day or VPA 200 to 2700 mg/day in previously untreated adults with partial seizures. | OXC 2400a | PHTb | OXC 600 to 2400 mg/day or VPA 200 to 2700 mg/day in previously untreated adults with partial seizures. | OXC 2400a | PL |
| somnolence                     | Beydoun et al.[72]               | 29.3      | 30.1 | 28.9 | 14.8 | 19.8 | 25.0 | 29.8 | 16.0 | 0 |
| headache                       | Bill et al.[70]                  | 22.0      | 8.7  | 14.7 | 19.0 | 10.2 | 17.4 | 13.5 | 14.9 | 20.0 | 20.0 |
| dizziness                      | Christe et al.[71]               | 46.3      | 8.7  | 13.2 | 15.5 | 10.2 | 11.6 | 9.4  | 22.3 | 16.0 | 12.0 |
| nausea                         | Guerreiro et al.[76]             | 29.3      | 8.7  | 9.6  | 11.3 | 8.6  | 11.6 | 5.2  | 7.4  | 20.0 | 6.0 |
| vomiting                       | Schachter et al.[72]             | 22.0      | 4.3  | 12.5 | 15.7 | 0    | 5.3  | 10.0 | 4.0  | |
| rash                           |                                 | 39.0      | 8.7  | 8.8  | 11.3 | 4.2  | 5.3  | 18.0 | 8.0  | |
| gum hyperplasia                |                                 | 12.2      | 4.3  | 0    | 7.7  | 2.1  | 5.3  | 12.0 | 0.0  | |
| tremor                         |                                 | 19.5      | 0    | 1.5  | 6.3  | 2.1  | 11.7 | 1.5  | 6.3  | 2.1  | 11.7 |
| dizziness                      |                                 | 12.2      | 4.3  | 0    | 7.7  | 2.1  | 5.3  | 12.0 | 0.0  | |
| nervousness                    |                                 | 19.5      | 0    | 1.5  | 6.3  | 2.1  | 11.7 | 1.5  | 6.3  | 2.1  | 11.7 |
| apathy                         |                                 | 22.0      | 4.3  | 0    | 7.7  | 2.1  | 5.3  | 12.0 | 0.0  | |
| abdominal pain                 |                                 | 1.5       | 6.3  | 2.1  | 11.7 | 1.5  | 6.3  | 2.1  | 11.7 | |
| weight gain                    |                                 | 12.2      | 21.5 | 5.2  | 4.3  | 1.5  | 6.3  | 2.1  | 11.7 | |
| alopecia                       |                                 | 12.2      | 21.5 | 5.2  | 4.3  | 1.5  | 6.3  | 2.1  | 11.7 | |
| abnormal vision                |                                 | 17.1      | 2.2  | 2.2  | 5.6  | 17.1 | 2.2  | 5.6  | |
| nystagmus                       |                                 | 17.1      | 2.2  | 2.2  | 5.6  | 17.1 | 2.2  | 5.6  | |

a OXC 2400 or 300 mg/day in adults with refractory partial and/or generalised seizures.
b OXC 600 to 2100 mg/day or PHT 100 to 650 mg/day in previously untreated adults with partial seizures.
c OXC 600 to 2400 mg/day or VPA 200 to 2700 mg/day in previously untreated adults with partial seizures.
d OXC 450 to 2400 mg/day or PHT 150 to 800 mg/day in previously untreated children with partial and/or generalised seizures.
e OXC 2400 mg/day or PL in patients with refractory partial and/or generalised seizures.
f These patients experienced pruritus.

5.2 In Children

5.2.1 Monotherapy

Common adverse events in previously untreated children receiving oxcarbazepine monotherapy are...
similar to those in adults: somnolence, headache, dizziness, nausea, apathy and rash.\textsuperscript{[35,76,81]} Oxcarbazepine was tolerated better than phenytoin, particularly with respect to nervousness, dizziness, gum hyperplasia (table VII), hypertrichosis (0 vs 8.5%) and ataxia (0 vs 13.8%).\textsuperscript{[76]} Furthermore, the time to premature discontinuation of treatment due to adverse events was significantly in favour of oxcarbazepine (p = 0.002). 82.3% of patients reported adverse events while receiving oxcarbazepine compared with 89.4% of the phenytoin group. Of these patients, 2 receiving oxcarbazepine discontinued treatment because of rash and 14 phenytoin recipients were withdrawn from treatment because of hypertrichosis, gingival hypertrophy or rash.\textsuperscript{[76]}

In a study examining the effects of AEDs on growth and sexual maturation, oxcarbazepine 14.2 to 33.2 mg/kg/day had no effect on pubertal development and linear growth in 18 prepubescent girls with epilepsy.\textsuperscript{[84]}

### 5.2.2 Adjunctive Therapy

The most common adverse events experienced by children (aged 1.2 to 17.9 years) undergoing oxcarbazepine adjunctive therapy were somnolence, headache, dizziness, vomiting, nausea, diplopia, fever and ataxia.\textsuperscript{[35,77,80]} 91 and 82% of patients receiving oxcarbazepine or placebo, respectively, reported adverse events in a trial involving 267 children between the ages of 3 and 17 years with refractory partial seizures on 1 or 2 concomitant AEDs.\textsuperscript{[77]} Figure 6 illustrates the incidence of adverse events that occurred in ≥10% of patients. 14 patients (10%) receiving oxcarbazepine discontinued treatment prematurely (mainly because of nausea, vomiting and rash) compared with 3% of the patients receiving placebo. Rash occurred in 4% of the oxcarbazepine group and in 5% of the placebo group, and of the 4 patients who discontinued oxcarbazepine treatment because of maculopapular and erythematous rash, 2 were receiving carbamazepine as concomitant medication.\textsuperscript{[77]}

### 5.3 Hyponatraemia

Hyponatraemia is usually defined as a serum sodium level <135 mmol/L. The clinical symptoms of acute hyponatraemia (which normally occur when the serum sodium level is <125 mmol/L) include headache, nausea, vomiting, tremors, delirium, seizures and decerebrate posturing, and can lead...
to death. The symptoms of chronic hyponatraemia are more subtle and include anorexia, cramps, personality changes, gait disturbance, stupor, nausea and vomiting. \[87\]

While hyponatraemia has been associated with oxcarbazepine therapy, it is usually asymptomatic and does not lead to discontinuation of the drug. \[87,93,94\] The manufacturer’s prescribing information states that acute hyponatraemia, although usually asymptomatic, developed in 2.7% of oxcarbazepine-treated patients in the 14 controlled monotherapy and adjunctive therapy studies conducted to date, compared with no patients who received placebo or active controls (carbamazepine, phenobarbital, phenytoin or valproic acid). The evaluation included records of 1966 patients with epilepsy aged between 2 and 88 years who had been treated for 20 months with oxcarbazepine 600 to 1800 mg/day. \[35,87\] Serum sodium levels were <135 mmol/L in 423 patients (21.5%) and <125 mmol/L in 54 patients (2.7%). Such low levels were uncommon in patients aged <18 years (0.5%) and absent among patients <6 years of age. Generally, patients with hyponatraemia recovered once oxcarbazepine therapy was stopped. The incidence of symptoms suggestive of hyponatraemia was similar among all patients, irrespective of sodium levels and, therefore, most likely due to the treatment milieu rather than hyponatraemia. \[87\]

Among recent monotherapy trials which evaluated serum sodium levels, \[70-73,76\] the incidence of hyponatraemia was highest in a 10-day study with a 2-day titration period. \[72\] 22% of patients receiving oxcarbazepine 2400 mg/day had serum sodium levels <135 mmol/L, although only one patient (2%) had a sodium level <125 mmol/L. In contrast, one patient receiving placebo had sodium levels <135 mmol/L. One \[70,73,76\] or 2 \[71\] instances of hyponatraemia were reported in other trials, prompting treatment discontinuation in one patient. \[73\] The time and frequency of serum sampling was often not reported. \[70,71,76\]

Although a retrospective study reported serum sodium levels <135 mmol/L in 9 of 48 children who received oxcarbazepine as adjunctive therapy (all were asymptomatic), baseline levels of serum sodium were not measured and neither the age of the children nor the duration of therapy were reported. \[90\]

In a study involving 144 randomly selected patients with epilepsy, females were found to have lower serum sodium levels than males \[(monotherapy: 134 \text{ vs } 137.6 \text{ mmol/L}, p < 0.05; \text{adjunctive therapy: } 131.3 \text{ vs } 137.9 \text{ mmol/L}, p < 0.001).\] \[95\]

Hyponatraemia was reported in 23% of patients in a large retrospective study of oxcarbazepine.
therapy. Friis et al.\textsuperscript{[11]} reported a shift to abnormal (not defined) serum sodium levels in 23% of the 350 patients (from a total population of 947) with available laboratory test data. However, only 4 patients (0.4% of the total population) discontinued treatment because of hyponatraemia.

6. Dosage and Administration

In the US and the UK, oxcarbazepine is approved for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as adjunctive therapy in the treatment of partial seizures in children (aged $\geq$4 years in the US and $\geq$6 years in the UK).\textsuperscript{[35,96]} In the UK, the drug is also approved for use as monotherapy in children $\geq$6 years of age.\textsuperscript{[96]} Oxcarbazepine is administered orally, with or without food, and a twice daily regimen is recommended.

The manufacturer recommends that initiation of monotherapy with oxcarbazepine in adult patients not currently treated with AEDs should begin with a dosage of 600 mg/day (given as a twice daily regimen) and be increased by 300 mg/day every third day to a dosage of 1200 mg/day.\textsuperscript{[35]} However, in practice a lower initial dosage may be better tolerated.\textsuperscript{[97]}

Adult patients already being treated with AEDs can be switched to oxcarbazepine monotherapy by initiating treatment at a dosage of 600 mg/day while simultaneously reducing the dosage of the concomitant AEDs, which should be withdrawn after 3 weeks. Oxcarbazepine should be increased as clinically indicated by a maximum increment of 600 mg/day at weekly intervals to achieve a dosage of $\leq$2400 mg/day.\textsuperscript{[35]}

In adults, adjunctive therapy with oxcarbazepine can begin with a dosage of $\leq$600 mg/day and, if clinically indicated, be increased by a maximum of 600 mg/day at weekly intervals. The manufacturer recommends a daily dosage of 1200 mg/day, as unpublished results have shown that partial dosages above 1200 mg/day, while more efficacious, were intolerable in most patients because of adverse CNS effects.\textsuperscript{[35]} During the titration phase, the patient needs to be observed closely and plasma concentrations of the concomitant AEDs should be monitored, as they may be altered, especially at oxcarbazepine dosages $>$1200 mg/day.

Adjunctive therapy in children aged 4 to 16 years can begin with a daily dosage of 8 to 10 mg/kg (but not exceed 600 mg/day). The target maintenance dose (median $\approx$30 mg/kg/day) should be reached within 2 weeks and is dependent upon patient bodyweight (table VIII).\textsuperscript{[35]}

Monotherapy in children can be initiated with a dosage of 8 to 10 mg/kg/day in 2 divided doses. If clinically indicated, the dose may be increased by increments of up to 10 mg/kg/day at approximately weekly intervals to a maintenance dosage of no more than 46 mg/kg/day.\textsuperscript{[96]}

Children <8 years of age have an increased clearance (by about 30 to 40%) compared with older children and adults and, therefore, may need higher maintenance dosages to achieve effective seizure control.\textsuperscript{[35]}

Potential interactions between oxcarbazepine and other AEDs can result in changes in the concentration of the active metabolite of oxcarbazepine (MHD), reducing the therapeutic effect (section 3.4.1 and table IV). Strong inducers of CYP isozymes (i.e. carbamazepine, phenytoin and phenobarbital) decrease the plasma concentrations of MHD by 29 to 40%. Concomitant use of oxcarbazepine at dosages above 1200 mg/day and phenytoin elevates the plasma concentration of phenytoin by up to 40%. Therefore, during adjunctive therapy with phenytoin, a lower dose of phenytoin may be required.\textsuperscript{[35,95]}

Coadministration of oxcarbazepine with hormonal contraceptives may reduce the effectiveness of birth control as oxcarbazepine has been shown to reduce plasma concentrations of the hormonal

<table>
<thead>
<tr>
<th>Bodyweight (kg)</th>
<th>Target dosage (mg/day)</th>
</tr>
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<tbody>
<tr>
<td>25-29</td>
<td>900</td>
</tr>
<tr>
<td>29.1-39</td>
<td>1200</td>
</tr>
<tr>
<td>$&gt;$39</td>
<td>1800</td>
</tr>
</tbody>
</table>

Table VIII. Recommended daily dosage of oxcarbazepine, adjusted for bodyweight, in paediatric patients with epilepsy undergoing adjunctive therapy\textsuperscript{[90]}
components of oral contraceptives (section 3.4.2 and table IV). Other forms of nonhormonal contraceptives are recommended. \[35\]

The pharmacokinetics and metabolism of oxcarbazepine are not significantly affected by hepatic dysfunction (section 3.3) and dose adjustment is generally not needed in patients with mild to moderate hepatic dysfunction. \[35\] However, the pharmacokinetics of oxcarbazepine have not been evaluated in patients with severe hepatic impairment. In patients with impaired renal function (CLcr < 1.8 L/h), clearance is decreased (section 3.3) and oxcarbazepine therapy should be initiated at 300 mg/day and increased slowly to achieve the desired clinical response.

Serum sodium levels need to be monitored during treatment with oxcarbazepine, especially if the patient is receiving concomitant medication known to decrease serum sodium levels (for example, drugs that are associated with inappropriate antidiuretic hormone secretion) or if the symptoms of hyponatraemia (section 5.3) appear. \[35\]

Patients with a history of hypersensitivity to carbamazepine should be informed of a 25 to 30% chance that they will also experience hypersensitivity reactions to oxcarbazepine. If signs of hypersensitivity develop, oxcarbazepine treatment must be discontinued immediately. \[35\]

It is not known if oxcarbazepine is a human teratogen, but animal studies have shown an increase in fetal structural abnormalities at doses close to the maximum recommended human dose. Therefore, oxcarbazepine should be administered during pregnancy only if the potential benefit to the patient outweighs the potential risk to the fetus. Oxcarbazepine and its active metabolite are both excreted in human milk and, therefore, a decision to continue treatment in the nursing mother should consider the potential for serious adverse reactions to oxcarbazepine in the infant. \[35\] It is also recommended that folic acid supplementation be instituted at a dosage of 0.8 to 1 mg/day in women with epilepsy who are of childbearing age. Higher dosages (4 mg/day) are recommended for women with a history of child defects. \[98\]

Withdrawal of oxcarbazepine, and AEDs in general, is problematic in that the decision to discontinue treatment is often not based on well defined criteria. \[99-102\] The Quality Standards Subcommittee of the American Academy of Neurology, after analysing 53 studies, published a report with recommended guidelines on AED discontinuation in children and in adults. \[103\] It is recommended that adult and paediatric patients with a single type of partial or generalised seizure who have a normal neurological examination and IQ, a normalised EEG with treatment, and who have been seizure-free for 2 to 5 years on AEDs, be withdrawn from treatment with AEDs. Seizure recurrence should be <31.2% for children and <39% for adults if the above conditions are met. Discontinuation of AEDs may be appropriate in patients not meeting these criteria even though the risk of relapse may be higher. \[103\] To minimise the increased potential for seizure recurrence, AEDs, including oxcarbazepine, should be withdrawn gradually. \[35\]

7. Place of Oxcarbazepine in the Management of Epilepsy

The main objective in epilepsy management is the control of seizures. Individuals with epilepsy have a high incidence of depression, anxiety, interpersonal difficulty and lowered self-esteem often brought about by the social stigma attached to epilepsy and lifestyle limitations imposed by their condition. \[104,105\] A successful reduction in seizure frequency not only lowers the risk of harm to the patient but also improves the patient’s quality of life through improved self-image. People with epilepsy have a 2 to 3 times greater risk of death than those without, and standardised mortality ratios of ≤8 have been reported. \[106,107\] Causes of death attributed to epilepsy include trauma, suicide and pneumonia, \[106\] although the most common seizure-related death is sudden unexpected death in epilepsy. \[107\]

Estimates of the prevalence of epilepsy vary but are in the range of 0.4 to 1% of the world’s population. However, in some developing countries the prevalence is as high as 2%. \[108\] The incidence rate of
unprovoked seizures ranges from 20 to 70 per 100,000 persons in industrialised countries[106,109,110] and in developing countries may be >100 per 100,000.[106]

Partial epilepsy, which is often symptomatic of an underlying focal brain injury, accounts for about 60% of all epilepsy cases, whereas generalised seizures account for approximately 30%.[105,110]

Seizures are most common in the first 10 years of life and then decline until about age 50, whereupon the incidence increases again.[111] About 15 per 100,000 adults ≤50 years of age experience seizures, increasing to approximately 86 and 114 per 100,000 adults by ages 65 and 75 years, respectively.[112]

Identification of the cause of seizures is of paramount importance as treatment, by way of long term AED therapy, is often not needed. If therapeutic intervention of precipitating factors (for example, metabolic or systemic disorders) is achievable, specific treatment regimens could be implemented to correct the underlying cause. Alterations to daily activities (i.e. reducing stress and intake of alcohol and caffeine, increasing exercise and improving sleep) can help reduce seizure frequency,[105] as can a ketogenic diet.[113]

However, if the underlying cause cannot be determined and seizures recur, long term treatment with AEDs is warranted.[105] Although the older AEDs such as carbamazepine,phenytoin and valproic acid are the most common forms of medical treatment for partial and generalised tonic-clonic seizures, the use of newer drugs such as oxcarbazepine is becoming more frequent. New anticonvulsants such as oxcarbazepine have been developed because of the high incidence of adverse events associated with the established AEDs. Furthermore, complex drug interactions due to induction (carbamazepine and phenytoin) or inhibition (valproic acid) of hepatic microsomal isozymes or displacement from binding sites, are also a feature of these drugs. Oxcarbazepine does not interfere with the metabolism of most other AEDs to a great extent, although it does have clinically significant interactions with phenytoin, phenobarbital and lamotrigine (section 3.4.1) and also reduces the effectiveness of oral contraceptives (section 3.4.2).

Oxcarbazepine has proved effective in the management of partial seizures with or without secondary generalisation and generalised tonic-clonic seizures in adults and children as monotherapy and adjunctive therapy.

### 7.1 In Adults

Previous studies[64,65] showed oxcarbazepine monotherapy to be as effective as carbamazepine in the treatment of partial and generalised tonic-clonic seizures. Moreover, recent comparative data from monotherapy trials (section 4.1.1) have shown oxcarbazepine to reduce seizure frequency as effectively as phenytoin or valproic acid in newly diagnosed patients with partial and/or generalised tonic-clonic seizures. As many as 60% of patients with newly diagnosed epilepsy treated with dosages of oxcarbazepine up to 2400 mg/day as monotherapy can be expected to be free of seizures.

Data from 2 additional trials support the use of oxcarbazepine monotherapy (2400 mg/day) in the treatment of adult patients with seizures refractory to treatment with one or more AEDs (section 4.1.1). However, treatment response is lower than in patients with newly diagnosed epilepsy (25% of patients receiving oxcarbazepine 2400 mg/day were seizure-free compared with 2% patients receiving placebo in one trial).

The most common adverse events associated with oxcarbazepine therapy in adults are somnolence, dizziness, headache, nausea, vomiting, rash, diplopia and fatigue. However, in oxcarbazepine monotherapy trials, <8% of patients withdrew from treatment because of adverse events. Oxcarbazepine was tolerated better than phenytoin (particularly with respect to gum hyperplasia, tremor, diplopia and nystagmus; table VII), and valproic acid (particularly with respect to tremor, weight gain, alopecia and headache; section 5.1.1).

While monotherapy is the accepted choice for patients with newly diagnosed epilepsy, adjunctive therapy is important for patients with seizures...
intratable to medication with only one AED. Whereas switching medication from one AED to another is effective in about 40% of patients with partial seizures refractory to the first-line agent, adjunctive therapy with 2 or 3 drugs may be beneficial in a small minority of patients.

Data from 1 trial (section 4.1.2) showed oxcarbazepine, in conjunction with 1 to 3 AEDs, to be effective at controlling partial seizures in patients with seizures refractory to optimum dosages of the concomitant AEDs. However, the highest dosage of oxcarbazepine (2400 mg/day) was not tolerated well, with >65% of the patients discontinuing treatment because of adverse events (section 5.1.2). Lower dosages were also significantly more effective than placebo and were well tolerated.

Although usually asymptomatic, acute hyponatraemia (serum sodium level <125 mmol/L) occurs in about 2.7% of patients receiving oxcarbazepine treatment. The manufacturer recommends that the measurement of serum sodium levels be considered, especially if the patient is receiving concomitant medication known to decrease serum sodium levels or if the symptoms of hyponatraemia appear (section 6).

7.2 In Children

Between 0.5 and 1% of children have epilepsy and the onset of seizures usually occurs during infancy. The decision to initiate AED treatment in children (as well as adults) involves a risk-benefit analysis including the probability of seizure recurrence. However, the diagnosis of epilepsy in children is problematic and often requires seizure repetition. For this reason, around 75% of children with newly diagnosed epilepsy have previously had more than one seizure. AED therapy in children is difficult in that about 25% of paediatric patients treated with traditional AEDs remain refractory to treatment and experience troublesome adverse events. Therefore, newer AEDs such as oxcarbazepine are tried.

Oxcarbazepine is effective and well tolerated as adjunctive therapy in the treatment of children and adolescents with refractory partial seizures, as shown in a placebo-controlled trial (sections 4.2.2 and 5.2.2).

Although data are limited, oxcarbazepine monotherapy has been shown to be effective in the treatment of partial seizures and generalised tonic-clonic seizures in children and adolescents, achieving seizure control equivalent to that of phenytoin with significantly fewer adverse events (section 4.2.1). More extensive clinical experience is required to clearly establish efficacy.

7.3 Conclusions

Oxcarbazepine as monotherapy is a viable alternative to established AEDs in the treatment of partial and generalised tonic-clonic seizures in adults and children. However, additional data are required to solidify its role as a front-line choice for monotherapy in the treatment of children with epilepsy. Furthermore, oxcarbazepine is effective as adjunctive therapy in the treatment of refractory partial seizures in both adults and children. The drug is tolerated better than the older, established AEDs, and, while it does have clinically significant interactions with some drugs, it has a lower potential for drug interactions. These attributes make oxcarbazepine an effective component in the initial treatment of adults and children with newly diagnosed partial or generalised tonic-clonic seizures, and also an effective adjunct for medically intractable partial seizures in both adults and children.

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