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Tiagabine

A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in the Management of Epilepsy

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Synopsis

Tiagabine is a γ-aminobutyric acid (GABA) uptake inhibitor which is structurally related to nipecotic acid but has an improved ability to cross the blood-brain barrier. Clinical trials have shown that tiagabine is effective as add-on therapy in the management of patients with refractory partial epilepsy. In short term studies of this indication, tiagabine ≤64 mg/day for 7 to 12 weeks reduced the complex partial and simple partial seizure frequency by ≥50% in 8 to 31 and 28.2 to 37% of patients, respectively. Tiagabine appeared to produce a sustained reduction in seizure frequency in studies of up to 12 months' duration.

Data from preliminary studies are currently insufficient to confirm the usefulness of tiagabine when used as monotherapy or in the treatment of children with epilepsy. Further studies are, therefore, necessary to more fully elucidate the efficacy of the drug in these settings.

Adverse events associated with tiagabine are primarily CNS-related and include dizziness, asthenia, nonspecific nervousness and tremor. Skin rash or psychosis occurred with similar frequencies among tiagabine- and placebo-treated patients. With long term administration (≥1 year for many patients), the profile and incidence of adverse events was similar to that for short term therapy.

Tiagabine does not appear to affect the hepatic metabolism of other drugs such as carbamazepine and phenytoin. Possible disadvantages of tiagabine include its short plasma elimination half-life, necessitating 2 to 4 times daily administration, and its inducible hepatic metabolism.

Thus, tiagabine is a new antiepileptic agent with a novel mechanism of action, which has demonstrated efficacy in the adjunctive treatment of patients with refractory partial epilepsy. Further investigation of the efficacy of tiagabine is expected to provide a clearer definition of its place in the treatment of epilepsy and its relative merits in relation to other antiepileptic drugs.

Pharmacodynamic Properties

Tiagabine increases synaptosomal concentrations of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) via inhibition of the GABA transporter GAT-1. The increase in synaptic concentrations of GABA leads to potentiation of GABA-mediated inhibitory neurotransmission. Tiagabine lacks appreciable affinity for other receptor or uptake sites including benzodiazepine, histamine H_1, serotonin 5-HT_{1B} or dopamine D_1 or D_2 receptors or β_1- or β_2-adrenoceptors. It is not a substrate for the GABA uptake carrier and is therefore unlikely to act as a false transmitter.

Tiagabine is active in a number of animal seizure models, protecting against seizures induced by chemical [e.g. methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) and pentylenetetrazol (PTZ)] and nonchemical stimuli

(e.g. audiogenic and kindling). It is a more potent anticonvulsant than the conventional antiepileptics phenytoin, phenobarbital, carbamazepine and valproic acid against audiogenic and DMCM- and PTZ-induced tonic or clonic seizures in mice and rats. Tiagabine is also more potent than lamotrigine, gabapentin and vigabatrin in protecting against audiogenic and DMCM- and PTZ-induced tonic or clonic seizures in mice and was the only drug able to block PTZ-induced clonic seizures in mice. Tiagabine may be proconvulsant in animal models of non-convulsive epilepsy.

Results from short and long term studies in patients with epilepsy have revealed no clinically significant deterioration in cognitive performance or electroencephalographic changes during tiagabine therapy and suggest that the drug may even have a slight beneficial effect on cognition under certain circumstances.

Pharmacokinetic Properties

Tiagabine is well absorbed after oral administration and has an absolute oral bioavailability of 90%. Peak plasma concentrations occurred approximately 1 hour after administration and measured 43 to 552 μg/L in healthy volunteers after single-dose administration of tiagabine 2 to 24mg. Multiple-dose administration of tiagabine does not result in significant drug accumulation. The rate, but not the extent, of absorption of tiagabine is decreased by concomitant food intake. Tiagabine is widely distributed throughout the body (volume of distribution is approximately 1 L/kg) and approximately 96% of the drug in human plasma is bound to plasma proteins.

Tiagabine is extensively metabolised by the hepatic cytochrome P450 enzyme CYP3A. 63% of a radiolabelled orally administered dose was excreted in the faeces and 25% in the urine. The plasma clearance of tiagabine is 21.4 L/h in patients receiving concomitant enzyme-inducing antiepileptic drugs such as carbamazepine, phenytoin and primidone and 12.8 L/h in patients with epilepsy not receiving concomitant treatment with these agents. The elimination half-life of tiagabine ranges from 3.8 to 9 hours in patients with epilepsy; patients receiving concomitant treatment with enzyme-inducing antiepileptic drug therapy exhibit values at the lower end of this range. Conversely, the clearance of tiagabine is reduced in patients with hepatic impairment, which may necessitate dosage reduction. Renal impairment or old age do not appear to significantly reduce the clearance of tiagabine; however, clearance of the drug appears to be slightly increased in children.

Although there is some evidence to suggest a relationship between tiagabine plasma concentration and therapeutic effect, there are currently insufficient data to recommend routine monitoring of plasma tiagabine concentrations in patients receiving the drug.

Concomitant administration of tiagabine has been shown not to influence the pharmacokinetics of conventional antiepileptic drugs such as carbamazepine and phenytoin or other drugs including oral contraceptives, theophylline, warfarin and digoxin. A significant decrease (approximately 10 to 12%) in the peak plasma concentration and area under the plasma concentration-time curve for valproic acid has been reported in patients receiving concomitant tiagabine therapy; however, because valproic acid has a wide therapeutic range (50 to 100 mg/L), this decrease was considered to be of limited clinical significance.

Therapeutic Efficacy

The results of 5 double-blind placebo-controlled studies (2 crossover and 3 parallel-group studies) have shown tiagabine ≤64 mg/day to be effective as add-on therapy in patients with refractory partial epilepsy. According to a pooled analysis

of these studies, 23% of patients treated with tiagabine, compared with 9% of placebo-treated patients, experienced a reduction in total seizure frequency of at least 50% during 7 to 12 weeks of treatment. The reduction in 4-week overall seizure frequency (25 *vs* 0.1%) and increase in the number of seizure-free days (6 *vs* 0%) were significantly greater for tiagabine than for placebo recipients. Individual results from 3 of these studies showed a ≥50% decrease in seizure rate relative to baseline in 8 to 31% and 28.2 to 37% of patients with complex partial and simple partial seizures, respectively. A corresponding response rate of 63% was reported for patients who experienced secondarily generalised tonic-clonic seizures in 1 study.

The clinical benefits of adjunctive tiagabine therapy appear to be maintained during long term treatment. Approximately 30 to 40% of patients treated with tiagabine ≤80 mg/day for up to 12 months in nonblind extension studies continued to experience a ≥50% reduction in overall seizure frequency.

Initial studies have reported a beneficial effect with tiagabine monotherapy in some patients with epilepsy refractory to monotherapy with other antiepileptic drugs. Among 31 patients recruited to a dose-ranging study, 19 were converted to tiagabine monotherapy for ≥2 weeks and 12 of these patients completed the study at a mean dosage of 38.4 mg/day. In a second study, efficacy rates (≥50% reduction in complex partial seizure frequency from baseline) were 31 and 18%, respectively, after treatment with tiagabine 36 and 6 mg/day (intent-to-treat analysis). Notably, both studies reported a high rate of study withdrawal (>50%); this was not an unexpected finding, as the refractory nature of the disease in patients recruited to these studies made successful conversion to tiagabine monotherapy less likely.

The few data available from the only comparative study of tiagabine monotherapy (*vs* carbamazepine monotherapy) in patients with newly diagnosed partial epilepsy do not allow an accurate assessment of efficacy. Studies are therefore required to establish the efficacy of tiagabine in relation to conventional and newer antiepileptic agents.

In small noncomparative studies, tiagabine (0.25 to 1.5 mg/kg/day or 32 to 80 mg/day) also demonstrated efficacy as add-on therapy in children and adolescents (aged 2 to 16 years) with refractory partial epilepsy, producing a >50% reduction in partial seizure frequency in approximately 20 to 50% of patients.

Tolerability

The most frequent adverse events in 675 patients with refractory epilepsy treated with tiagabine as add-on therapy (typically ≤64 mg/day for up to 12 weeks) were dizziness (30%), asthenia (24%), nonspecific nervousness (12%) and tremor (9%) [pooled data from placebo-controlled studies]. This compared with a significantly lower incidence of 13, 12, 3 and 3%, respectively, among placebo recipients (n = 363). Diarrhoea, depressed mood and emotional lability were also significantly more frequent with tiagabine (4 to 7% *vs* 1 to 2%). Other adverse events, including psychosis and skin rash which are frequently associated with other antiepileptic drugs, occurred with a similar frequency among tiagabine- and placebo-treated patients. These and other symptoms were generally mild or moderate and occurred early in the course of therapy. Treatment discontinuation due to adverse effects has been reported in 15% of patients treated with adjunctive tiagabine therapy and 33% of patients treated with tiagabine monotherapy.

Longer term tolerability data (including results from 814 patients treated with tiagabine for ≥1 year), suggest that the profile and incidence of adverse effects

associated with long term tiagabine therapy are similar to those reported during short term therapy.

Clinically significant changes in haematological or liver function tests have not been observed during tiagabine therapy. Furthermore, the risk of status epilepticus appears to be minimal and similar to that reported for patients with epilepsy not treated with tiagabine.

Dosage and Administration

Dosage recommendations for the use of tiagabine as an adjunct to enzyme-inducing antiepileptic drug therapy in adult and adolescent patients with partial epilepsy differ between the US and Europe. In the US in adults, tiagabine should be initiated at a dosage of 4 mg once daily, which may be increased by 4 to 8 mg/day at weekly intervals until clinical response is achieved or a maximum dosage of 32 to 56 mg/day (administered in 2 to 4 divided doses) is reached. In adolescents (aged 12 to 18 years), the maximum recommended dosage is ≤32 mg/day.

In contrast, European guidelines recommend an initial dosage of 7.5 to 15 mg/day in adults and adolescents (aged >12 years), followed by weekly incremental increases of 5 to 15 mg/day; the usual maintenance dosage is 30 to 50 mg/day administered in 3 divided doses. If cessation of tiagabine therapy is necessary, the dosage should be reduced gradually over a period of 2 to 3 weeks.

Tiagabine should be administered with food, and dosage reduction may be necessary in patients with mild or moderate hepatic impairment. In Europe tiagabine is contraindicated in patients with severe hepatic impairment. There are currently insufficient data to recommend the use of tiagabine in pregnant or lactating women.

Tiagabine (fig. 1) is a novel uptake inhibitor of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. GABA uptake inhibitors represent a new class of antiepileptic drugs, of which tiagabine is the first to be introduced into clinical practice.

Tiagabine is a derivative of the GABA uptake inhibitor nipecotic acid. In contrast to the latter drug, tiagabine readily crosses the blood-brain barrier owing to the attachment of a lipophilic side chain to the nipecotic acid molecule.

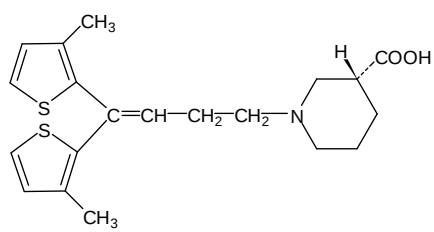

Fig. 1. Chemical structure of tiagabine.

This review evaluates the pharmacology and therapeutic potential of tiagabine in the management of epilepsy. All cited doses refer to the hydrochloride salt (the dose of tiagabine as free base can be calculated by multiplying by 0.91).

1. Pharmacodynamic Properties

1.1 Mechanism of Action

Tiagabine prevents GABA uptake by inhibiting GAT-1, which is 1 of at least 4 distinct GABA transporters responsible for the uptake of the neurotransmitter into neurons and glial cells after synaptic release.[1] The resultant increase in synaptic concentrations of GABA in turn leads to reduced neuronal excitability and, therefore, antiepileptic activity.

Consistent with this mechanism of action, tiagabine induces prolongation of GABAergic inhibitory impulses in rat hippocampus *in vitro*.[2-4] Furthermore, *in vivo* microdialysis techniques revealed that extracellular levels of GABA were in-

creased by up to 3-fold in the brains of non-anaesthetised rats after intraperitoneal administration of tiagabine 11.5 or 21.0 mg/kg,[5] and by 1.5-fold in the hippocampus of a patient with refractory partial epilepsy treated with a single oral dose of tiagabine 16mg.[6]

Tiagabine is a selective and reversible inhibitor of GABA uptake, its affinity for glial uptake being approximately 2.5-fold greater than that for neuronal uptake [IC_{50} (concentration of drug required to inhibit GABA uptake by 50%) was 0.18 μmol/L for glial and 0.45 μmol/L for neuronal uptake].[7] In contrast with nipecotic acid, tiagabine is not a substrate for the GABA uptake carrier and is therefore unlikely to act as a false transmitter at GABAergic neurons.[7] Moreover, tiagabine does not have significant affinity for other receptors or uptake sites. In rat brain, tiagabine binds to benzodiazepine, histamine H_1 and serotonin 5-HT_{1B} receptors at concentrations 20- to 400-fold greater than that required to inhibit synaptosomal GABA uptake (IC_{50} = 0.07 μmol/L), and it does not appreciably bind to other uptake sites or receptors such as dopamine D_1 or D_2 receptors, β_1- or β_2-adrenoceptors or muscarinic receptors.[7]

1.2 Effects in Animal Seizure Models

The anticonvulsant activity of single doses of tiagabine has been investigated in animal models of epilepsy induced by electrical, chemical and sensory stimuli and in genetic models of epilepsy.

Kindling, an experimental procedure whereby discrete regions of the brain are subjected to repeated electrical stimulation, is considered to be a model for human partial epilepsy with secondarily generalised seizures.[8] When administered intraperitoneally to amygdala-kindled rats, tiagabine attenuated the expression of secondarily generalised seizures [ED_{50} value (dose required to protect 50% of animals from seizures) of 2.5 mg/kg] and completely blocked the expression of partial seizures (ED_{50} value of 14.8 mg/kg).[9] Tiagabine also suppressed amygdala kindling-induced epileptogenesis in a dose-dependent manner in the rat.[10]

Intraperitoneal tiagabine was a more active anticonvulsant than the conventional antiepileptics phenytoin, phenobarbital, carbamazepine and valproic acid in protecting against audiogenic and methyl - 6,7 - dimethoxy - 4 - ethyl - β - carboline-3-carboxylate- (DMCM) and pentylenetetrazol-(PTZ) induced tonic or clonic seizures in mice and PTZ-induced tonic or clonic seizures in rats (table I).[13] However, tiagabine did not protect against maximal electroshock-induced tonic seizures in mice or rats.[9,13] Tiagabine also did not prevent tonic or clonic seizures induced by the potassium channel antagonists dendrotoxin and 4-aminopyridine in mice.[11,12]

When compared with the newer antiepileptic drugs lamotrigine, gabapentin and vigabatrin, tiagabine was the most potent antagonist of tonic or clonic seizures induced by DMCM, PTZ and sound in mice. Indeed, it was the only drug able to block PTZ-induced clonic seizures, although this was seen at low (0.29 to 3 mg/kg) but not at high doses (30 mg/kg) of tiagabine.[9] Intraperitoneal injection of tiagabine (30 mg/kg) also significantly inhibited inferior colliculus firing induced by acoustic stimulation in genetically epilepsy-prone rats.[14]

The anticonvulsant activity of tiagabine against light-induced myoclonus has been studied in the photosensitive baboon, a model of photomyoclonic seizures and myoclonic absence epilepsy in humans.[15] Intravenous tiagabine 0.25 to 1.0 mg/kg reduced the frequency of light-induced seizures. Protection was maximum with tiagabine 1.0 mg/kg but this dose was associated with impaired motor coordination, tremor and slow abnormal movements of the limbs. Lower intravenous doses of tiagabine (≤0.5 mg/kg) reduced light-induced seizure frequency and did not produce adverse behavioural effects.

In common with GABA agonists,[16] tiagabine may enhance the occurrence of spike-wave discharges in animal models of nonconvulsive epilepsy. In WAG/Rij rats, a genetic model of generalised nonconvulsive absence epilepsy, spike wave discharges were increased by tiagabine 3 and

Table I. Comparative anticonvulsant activity of tiagabine (TGB) and other antiepileptic drugs in animal models of epilepsy. All drugs were administered intraperitoneally

Stimulus	Type of seizure	Animal	ED_{50} (mg/kg)							
			TGB	LTG	GBP	VGB	PHE	PHB	CBZ	VLP
Chemically induced seizures										
4-aminopyridine[11]	Tonic	Mice	>74[a]			>1000[a]	34[a]	23[a]	19[a]	301[a]
Dendrotoxin[12]	Clonic	Mice	>60				9		37	278
DMCM[9,13]	Tonic	Mice	0.8	2	32	300				
	Clonic	Mice	0.8-1.0	>30	>300	483	≈1000	18	15	200
PTZ[9,13]	Tonic	Mice	0.8-1.2	11	77	>1000	6	32	5	100
		Rats	4.0				60	7	9	215
	Clonic	Mice	1.3-2.0	>30	>300	>1000	>500	32	400	285
		Rats	6				>64	20	>64	310
Electrically induced seizures										
MES[9,13]	Tonic	Mice	>30	9	>300	>1000				
		Rats	40				8		11	
Seizures in epilepsy-prone mice										
Audiogenic[9,13]	Tonic	Mice	0.4	2	11	502	11	4	7	38
	Clonic	Mice	0.4	2	25	543				

a Dose of drug which protected 50% of animals from 4-aminopyridine–induced lethality.

Abbreviations: CBZ = carbamazepine; DMCM = methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate; ED_{50} = dose which protects 50% of animals from seizures; GBP = gabapentin; LTG = lamotrigine; MES = maximal electroshock; PHB = phenobarbital; PHE = phenytoin; PTZ = pentylenetetrazol; VGB = vigabatrin; VLP = valproic acid.

10 mg/kg administered intraperitoneally but not by a 1 mg/kg dose.[17] In another study, intraperitoneal tiagabine ≥5 mg/kg controlled generalised tonic-clonic seizures in cobalt-lesioned rats with homocysteine thiolactone-induced status epilepticus but also produced spike wave discharges.[18] Absence seizure frequency and duration were also increased by intraperitoneal tiagabine ≥1 mg/kg in the lethargic (*lh/lh*) mouse model.[19]

Tiagabine reduced both seizure-induced damage to pyramidal cells in the hippocampus and impairment of spatial memory associated with hippocampal damage in the perforant pathway stimulation rat model of status epilepticus.[20] Neuronal cell death was also reduced by tiagabine in the hippocampus of gerbils subjected to cerebral ischaemia,[21] and in the rat cerebral ischaemia model of delayed pyramidal cell death.[22]

1.3 Effects on Psychomotor Function

Tolerance to the cognitive effects (rotarod activity, traction response and inhibition of exploratory locomotor activity) but not to the anticonvulsant effects of tiagabine has been reported in mice with DMCM-induced seizures given oral tiagabine 15 or 30 mg/kg twice daily for 21 days.[23]

Studies in patients with epilepsy suggest that tiagabine has a low propensity to cause impairment of cognitive and psychomotor function.[24-27] Compared with placebo (n = 57), administration of tiagabine 16 (n = 34), 32 (n = 45) or 56 mg/day (n = 26) for 12 weeks as add-on therapy to patients with partial epilepsy had no significant effect on mental ability or adjustment and mood.[24] Mental ability was assessed using the Lafayette Grooved Pegboard, Stroop, Controlled Oral Word Association, Symbol Digit Modalities, Rey Auditory Verbal Learning, Wonderlic Personnel and Digit Cancellation tests, and adjustment and mood were evaluated using the Profile of Mood States (POMS) test, the Washington Psychosocial Seizure Inventory (WPSI) and the Mood Rating Scale (MRS).

Similarly, long term follow-up revealed no significant deterioration in cognitive performance or

significant electroencephalographic changes from baseline after add-on treatment with tiagabine for 6 to 12 months (mean daily dose 65.7mg; n = 25) or 18 to 24 months (mean daily dose 67.6mg; n = 14).[26] Moreover, a significant improvement from baseline in the List Learning test and in auditory reaction times was reported after 18 to 24 months of tiagabine therapy.[26]

Changes from baseline in cognitive function have also been investigated in patients who were receiving tiagabine monotherapy for up to 12 weeks.[27] Significant improvements in psychosocial adjustment and mood (POMS, WPSI and MRS) were reported among patients who were successfully converted from other antiepileptic drugs to low dose tiagabine monotherapy (6 mg/day; n = 53), and some improvements in mental ability (including Lafayette Grooved Pegboard and Stroop test) were reported after conversion to high dose tiagabine monotherapy (36 mg/day; n = 39). Patients who were unable to receive monotherapy with tiagabine 36 mg/day (i.e. were on tiagabine and 1 other antiepileptic drug at the end of the study; n = 18) experienced some deterioration in psychosocial adjustment and mood (POMS and MRS).

2. Pharmacokinetic Properties

The pharmacokinetic profile of tiagabine has been investigated both in healthy volunteers and in patients with epilepsy, including children, the elderly, patients with renal and hepatic impairment and those receiving concomitant antiepileptic medication.

2.1 Absorption and Distribution

Tiagabine exhibits a linear pharmacokinetic profile. In a single-dose pharmacokinetic study conducted in fasting healthy volunteers, the absorption and elimination pharmacokinetics of tiagabine were linear over the dose range 2 to 24mg.[28] With an absolute oral bioavailability of 90%, tiagabine is almost completely absorbed after oral administration.[29]

Table II. Mean pharmacokinetic parameters of tiagabine after single- and multiple-dose administration to fasting healthy volunteers[28]

Dosage (mg/day) [no. of patients]	C_{max} (μg/L)	t_{max} (h)	$t_{½β}$ (h)	AUC (μg/L • h)
Single-dose administration				
2 [5]	43	0.8	6.9	228
8 [5]	150	1.0	5.4	727
12 [5]	241	1.3	8.0	1450
24 [4]	552	1.1	7.3	2190
Multiple-dose administration for 5 days[a]				
2 [6]	32	1.2	4.5	141
4 [6]	86	1.0	8.1	466
6 [6]	118	1.0	6.4	678
8 [6]	162	1.5	6.7	761
10 [6]	195	0.8	6.1	847
Multiple-dose administration for 14 days[a]				
6 [6]	131	1.0	7.6	704
12 [2]	226	1.5	5.0	1110

a Pharmacokinetic data obtained after the last dose.

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = peak plasma concentration; $t_{½β}$ = elimination half-life; t_{max} = time to C_{max}.

Single-dose administration of tiagabine 2 to 24mg to fasting healthy volunteers resulted in peak plasma concentrations (C_{max}) of 43 to 552 μg/L within approximately 1 hour (table II). Secondary peaks in the plasma concentration profile of tiagabine were also reported approximately 10 hours after administration of the drug, and were probably attributable to enterohepatic recycling.[28] Notably, multiple-dose administration of tiagabine (6 or 12 mg/day for 14 days) did not result in significant accumulation of the drug; C_{max} values on day 14 were 131 and 226 μg/L (table II).[28]

Administration of tiagabine with food decreases the rate but not the extent of drug absorption.[30,31] In a crossover study, the mean area under the plasma concentration-time curve (AUC) remained unchanged but the mean C_{max} value decreased (91.6 *vs* 164.2 μg/L; $p \leq 0.05$) and the mean time to C_{max} (t_{max}) increased (2.6 *vs* 0.9 hours; $p \leq 0.05$) in nonfasting compared with fasting healthy volunteers given a single oral dose of tiagabine 8mg.[31]

Tiagabine is widely distributed throughout the body (volume of distribution of approximately 1

L/kg) and approximately 96% of the drug in human plasma is bound to plasma proteins.[32]

2.2 Metabolism and Elimination

Tiagabine is extensively metabolised in the liver, predominantly by the cytochrome P450 enzyme CYP3A.[33] 5-oxo-isomers of tiagabine are the major metabolites found in both the plasma and urine; 2 additional metabolites found in the faeces have yet to be identified.[32,33]

Following oral administration of radiolabelled tiagabine 4mg to 4 healthy volunteers, approximately 63% of the dose was excreted in the faeces and 25% in the urine.[34] Less than 3% of an orally administered dose of tiagabine appears to be excreted unchanged in the urine.[28,34]

The plasma elimination half-life ($t_{½\beta}$) of tiagabine is 4.5 to 8.1 hours in healthy volunteers (table II).[28,35] In patients with epilepsy, $t_{½\beta}$ values ranged from 3.8 to 9 hours; $t_{½\beta}$ values at the lower end of the range (3.8 to 4.9 hours) were reported in patients receiving concomitant enzyme-inducing antiepileptic drugs (see section 2.5.2).[32,36] Plasma clearance of tiagabine is 12.8 L/h in patients with epilepsy not receiving concomitant therapy with enzyme-inducing antiepileptic drugs and this value is increased in patients receiving concomitant treatment with these agents (see section 2.5.2).[37,38]

2.3 Effect of Age and Disease on the Pharmacokinetics of Tiagabine

The pharmacokinetic profile of tiagabine was similar in healthy elderly volunteers (aged ≥65 years; n = 8) and healthy young volunteers (aged 18 to 33 years; n = 8) after single- (8mg) and multiple-dose administration (3mg 3 times daily for 5 days).[39] A statistically significant increase in the mean dose-adjusted AUC (103 *vs* 72 μg/L · h/mg; $p < 0.05$) on the final day of multiple-dose administration was reported in the elderly compared with the young group. However, the investigators attributed this difference to interindividual variation in the AUC of tiagabine as a result of variability in the cytochrome P450 enzyme CYP3A isoform.

Dose-adjusted C_{max} and AUC values of 18 μg/L/mg and 177 μg/L · h/mg, respectively, were reported after single-dose oral administration of tiagabine 0.1 mg/kg to children aged 3 to 10 years with complex partial epilepsy who were receiving concomitant non-enzyme-inducing antiepileptic drug therapy (valproic acid; n = 8).[40] Tiagabine t_{max} and $t_{½\beta}$ values were 2.4 and 5.7 hours, respectively. In children receiving concomitant enzyme-inducing antiepileptic drug therapy (carbamazepine or phenytoin; n = 17), the corresponding t_{max} and $t_{½\beta}$ values were 2.6 and 3.2 hours. A retrospective comparison with pharmacokinetic data from a single-dose (8mg) study in adult patients with epilepsy who were also taking valproic acid (n = 4), showed the clearance of tiagabine to be greater in children (also receiving valproic acid) when calculated according to bodyweight (0.25 *vs* 0.11 L/h/kg); when determined according to body surface area, clearance rates in children and adults were more similar (6.7 *vs* 4.6 L/h/m^2).[40]

Because tiagabine is extensively metabolised by the liver, elimination of the drug is reduced in patients with hepatic impairment. In patients with mild to moderate impairment (serum albumin level 2.8 to 3.7 g/dl; n = 7), the $t_{½\beta}$ of tiagabine was greater (11.7 or 15.9 *vs* 6.5 hours) and the C_{max} (172.4 *vs* 116.9 μg/L) and AUC (632.7 or 674.5 *vs* 395.8 μg/L · h) higher than in healthy volunteers (n = 6) after administration of tiagabine 4mg twice daily for 11 doses.[35] The area under the unbound plasma drug concentration-time curve, the unbound tiagabine concentration and the free-fraction of tiagabine were also increased in patients with hepatic impairment. Dose reduction and/or a decrease in the frequency of administration may therefore be necessary to maintain plasma concentrations of tiagabine within potential therapeutic levels in patients with hepatic impairment.

In contrast, dosage adjustment appears to be unnecessary for patients with impaired renal function receiving tiagabine therapy.[41]

2.4 Relationship Between Plasma Concentration and Therapeutic Effect

Few studies have investigated the relationship between tiagabine plasma concentration and therapeutic effect, and there are currently insufficient data to recommend routine monitoring of tiagabine plasma concentrations in patients receiving the drug. Rowan et al.[42,43] reported a greater reduction in complex partial seizure frequency with increasing tiagabine dosages and greater trough tiagabine plasma concentrations in a double-blind placebo-controlled trial. The median reduction in 4-week complex partial seizure frequency from baseline was 0.7, 0.8, 2.2 and 2.8 seizures after administration of placebo and tiagabine 16, 32 and 56 mg/day, respectively [correlation coefficient (r) = 0.2; p = 0.001]. At trough tiagabine concentrations of <20, 21 to 40 and >40 μg/L, the median reduction in 4-week complex partial seizure frequency was 1.7, 2.0 and 4.9 seizures, respectively, (r = 0.21; p = 0.001).

2.5 Pharmacokinetic Drug Interactions

2.5.1 Effect of Tiagabine on the Pharmacokinetics of Other Drugs

Administration of tiagabine 6 or 12 mg/day for 14 days did not significantly alter the clearance or $t_{½\beta}$ of phenazone (antipyrine) in 9 healthy volunteers.[28] These results suggest that tiagabine does not inhibit or induce hepatic microsomal enzyme systems. Accordingly, the plasma concentrations of other antiepileptic drugs, including carbamazepine and phenytoin, which are extensively metabolised by the liver, were not altered by the concomitant administration of tiagabine ≤52 mg/day for ≥18 days to patients with epilepsy.[44,45]

A decrease in C_{max} and AUC values for valproic acid (approximately 10 to 12%; $p \leq 0.05$) was reported in patients with epilepsy who received concomitant tiagabine ≤24 mg/day and valproic acid (dosage not specified) for 14 days.[46] However, because valproic acid has a wide therapeutic range (50 to 100 mg/L), this decrease was not considered to be clinically significant.

Results from studies involving healthy volunteers suggest that tiagabine does not significantly alter the pharmacokinetic profile of theophylline, warfarin or digoxin, which are all metabolised by hepatic enzymes.[47,48] Furthermore, coadministration of tiagabine had no clinically significant effect on sedative/cognitive impairment produced by ethanol or triazolam in healthy volunteers.[47]

Administration of tiagabine 2mg 4 times daily for 12 days to 10 healthy women who had been taking oral contraceptive therapy (ethinylestradiol 30μg plus levonorgestrel 150μg or desogestrel 150μg) for ≥6 months did not significantly alter the plasma concentrations of progesterone, ethinylestradiol, levonorgestrel, desogestrel, follicle-stimulating hormone or luteinising hormone.[49] Although breakthrough bleeding was reported in 2 patients during the study, plasma progesterone levels remained below threshold levels for ovulation in both women, suggesting that tiagabine does not interfere with oral contraceptive efficacy.

2.5.2 Effect of Other Drugs on the Pharmacokinetics of Tiagabine

The rate of elimination of tiagabine is markedly increased by coadministration with hepatic enzyme-inducing drugs such as carbamazepine, phenytoin and primidone. In a population pharmacokinetic analysis involving 511 patients with epilepsy, the clearance of tiagabine (2 to 80 mg/day) was approximately 67% greater in patients receiving concomitant antiepileptic enzyme-inducing therapy than in those who were not (21.4 *vs* 12.8 L/h).[37,38] As a consequence of enzyme induction, reductions of 40 to 70% in AUC and C_{max} values have been reported for tiagabine.[50,51] $t_{½\beta}$ values are also reduced in patients receiving tiagabine with enzyme-inducing antiepileptic drugs: 3.8 to 4.9 hours[36] versus 7 to 9 hours in patients receiving monotherapy.[32]) These findings suggest that patients receiving concomitant enzyme-inducing antiepileptic drug therapy will require higher dosages of tiagabine to achieve potential therapeutic plasma concentrations. In contrast, valproic acid, which does not induce hepatic microsomal enzyme

TABLE III GOES HERE LANDSCAPE

systems, does not appear to have a significant effect on tiagabine plasma concentrations.[50,51]

Drugs such as cimetidine and erythromycin, which inhibit cytochrome P450 enzyme systems, do not appear to significantly alter the pharmacokinetic profile of tiagabine.[47,52,53]

3. Therapeutic Efficacy

Because of ethical constraints which preclude the use of monotherapy of unproven efficacy in patients with epilepsy, the initial clinical assessment of new antiepileptic agents is confined to evaluation as add-on therapy in patients with epilepsy refractory to established antiepileptic drugs.[54,55] Only when a drug has demonstrated efficacy in this setting can it be evaluated as monotherapy.

Interpretation of results from add-on trials may be confounded by several factors, including complications associated with drug interactions, or pharmacodynamic synergism between the new and existing antiepileptic therapies. Furthermore, patients with refractory seizures are inherently difficult to treat, and drugs which may be effective in the treatment of less aggressive forms of epilepsy may not prove effective in standard add-on trials. Nevertheless, this approach continues to provide the main source of initial clinical efficacy data for new antiepileptic drugs.

Most clinical efficacy data on tiagabine are derived from add-on placebo-controlled studies; however, they have been augmented more recently by results from short term monotherapy trials. Available efficacy data are confined to patients with partial seizures with or without secondarily generalised seizures. Studies have included mainly adult patients with epilepsy, although some included patients as young as 10 years of age. Preliminary results are also available from a small number of studies which specifically evaluated the efficacy of tiagabine in children and adolescents. There are currently insufficient data to allow a proper assessment of the efficacy of tiagabine compared with other antiepileptic drugs.

Primary efficacy parameters used in clinical trials of tiagabine included the percentage reduction

Table III. Efficacy of tiagabine (TGB) as adjunctive therapy in patients with refractory partial epilepsy with or without secondarily generalised seizures: summary of 3 multicentre, double-blind, placebo (PL)–controlled studies evaluating treatment with TGB for 7-12wk

Reference	Patients receiving concomitant medication (%)	TGB dosage (mg) [no. of patients at entry]	Median 4wk baseline seizure frequency (no. of seizures)			Median decrease in 4wk seizure frequency *vs* baseline (no. of seizures)			Patients with ≥50% decrease in seizure frequency *vs* baseline (%)			Patients completing study (%)
			CP	SP	SGTC	CP	SP	SGTC	CP	SP	SGTC	
Richens et al.[44]a	CBZ (77), VGB (28), PHE (20), VLP (20)	TGB ≤52/day [94]	8.8	6.8	3.8	32.6[b]*	66.0[b]	61.0[b]*	26	NR	63	45
Sachdeo et al.[56]c	CBZ (69), VLP (38), PHE (36), PHB (8), PRI (8), CLO (7), ACE (5)	TGB 16 bid [106]	8.4	8.5	NR	1.6	1.4	0.8	31**	37*	NR	85
		TGB 8 qid [105]	7.9	9.2	NR	1.2*	2.1**	0.7	27**	29	NR	80
		PL [107]	8.0	8.0	NR	NR	+0.6[d]	0.3	10	16	NR	91
Uthman et al.[57]c	CBZ (69), PHE (32), VLP (27), PHB (26), PRI (13)	TGB 4 qid [61]	8.5	9.7	NR	0.8	2.3**	NR	8	28.2*	NR	92
		TGB 8 qid [88]	9.6	13.7	NR	2.2*	1.7*	NR	20**	34.7**	NR	81
		TGB 14 qid [57]	9.1	9.1	NR	2.8*	3.3**	NR	29**	36.4**	NR	70
		PL [91]	7.4	8.6	NR	0.7	+0.9[d]	NR	4	9.8	NR	88

a Crossover study; efficacy data provided for patients who completed the study (n = 42).
b Decrease in seizure frequency expressed as a percentage versus PL.
c Parallel-group study, intent-to-treat analysis.
d Absolute increase (+) in seizure rate.

Abbreviations and symbols: ACE = acetazolamide; bid = twice daily; CBZ = carbamazepine; CLO = clorazepate; CP = complex partial seizures; NR = value not reported; PHB = phenobarbital; PHE = phenytoin; PRI = primidone; qid = 4 times daily; SGTC = secondarily generalised tonic-clonic seizures; SP = simple partial seizures; VGB = vigabatrin; VLP = valproic acid; * $p < 0.05$, ** $p \leq 0.01$ *vs* PL.

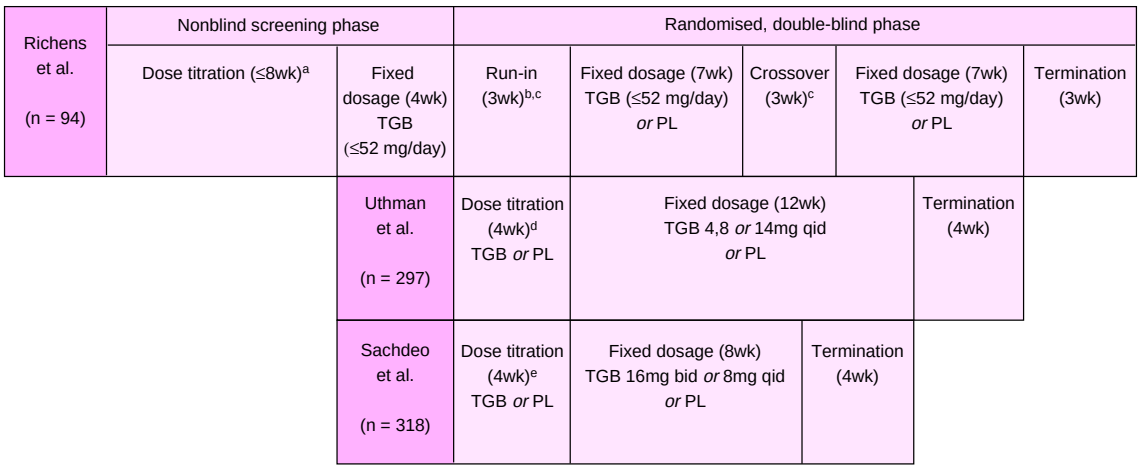

Fig. 2. Study design of 3 multicentre randomised double-blind placebo (PL)-controlled studies evaluating the efficacy of tiagabine (TGB) as add-on therapy in patients with refractory partial epilepsy. All studies were preceded by a baseline period of 8 to 12 weeks during which seizure frequency was established. TGB therapy was gradually reduced during the termination period. (Richens et al.[44]; Uthman et al.[57]; Sachdeo et al.[56]).

a Initial TGB dosage was 2mg qid; thereafter dosage was increased (not specified) at weekly intervals to a maximum of 52 mg/day or until seizure frequency was reduced by 25% or unacceptable adverse events developed.

b Patients were randomised to the double-blind study phase if they experienced a 25% reduction in seizure frequency, tolerated TGB well and did not require any change in the dosage of concomitant antiepileptic drug therapy.

c During the run-in and crossover periods patients were titrated off and on to TGB depending upon the sequence of treatment (PL then TGB or vice versa).

d Initial TGB dosage was 2mg qid; thereafter, the dosage was either increased by 8 mg/day after 2wk to 16 mg/day, by 8 mg/day on 3 successive weeks to 32 mg/day or by 16 mg/day on 3 successive weeks to 56 mg/day.

e TGB dosage titration schedule was either 4mg bid, 8mg bid, 12mg bid and 16mg bid, or 2mg qid, 4mg qid, 6mg qid and 8mg qid during weeks 1, 2, 3 and 4, respectively.

Abbreviations: bid = twice daily; qid = 4 times daily.

in seizure frequency and the proportion of responders (number of patients who experienced a ≥50% reduction from baseline in seizure frequency).

3.1 Add-on Therapy in the Management of Refractory Partial Epilepsy

3.1.1 Short Term Studies

The full published results of 3 short term, multicentre, randomised, double-blind, placebo-controlled studies indicate that tiagabine is effective as adjunctive therapy in the management of partial epilepsy.[44,56,57] All patients recruited to these studies were aged between 12 and 75 years, had a diagnosis of partial epilepsy (with or without secondarily generalised seizures) and had experienced ≥6 complex partial seizures while receiving conventional antiepileptic drug therapy (comprising 1 to 3 drugs) in the 8 weeks before study entry. Details of concomitant antiepileptic medication are provided in table III.

The design of these studies is detailed in figure 2. One study enrolled 94 patients and comprised 2 phases, a nonblind screening phase and a double-blind, placebo-controlled, crossover phase.[44] The screening phase included a period of ≤8-week during which the tiagabine dosage was titrated to a maximum of 52 mg/day, followed by a 4-week fixed dose phase. At the end of the fixed dose period, patients who experienced a ≥25% reduction in seizure frequency, tolerated tiagabine well and did not require a change in dosage of concomitant antiepileptic drugs were eligible to enter the double-blind crossover phase. This included a 3-week run-in period, a 7-week assessment period for the

first drug, a 3-week crossover period and a second 7-week assessment period for the second drug. 74 of 94 enrolled patients completed the screening phase and 46 of these patients were eligible to enter the double-blind phase.

The other 2 trials were of a parallel-group design and included a 4-week dose titration period, followed by 8 or 12 weeks of fixed dose therapy. One study randomised 297 patients to treatment with tiagabine 4, 8 or 14mg 4 times daily or placebo.[57] The other randomised 318 patients to tiagabine 16mg twice daily or 8mg 4 times daily or placebo.[56]

The study results are summarised in table III. 42 patients (45%) completed the crossover study and were evaluable for efficacy.[44] Tiagabine 12 to 52 mg/day (mean 33.4 mg/day) reduced the complex partial and secondarily generalised tonic-clonic seizure frequency by 32.6 and 61.0%, respectively, relative to placebo ($p < 0.05$). Simple partial seizure frequency was also reduced (66%) but the change was not statistically significant versus placebo. Among the patients who completed the study, 11 (26%) experienced a ≥50% reduction versus baseline in complex partial seizure frequency during tiagabine therapy. Secondarily generalised tonic-clonic seizure frequency was reduced by ≥50% in 17 of 27 patients (63%) who experienced these seizures.

In the dose comparison study, complex partial seizure frequency, and to a lesser extent simple partial seizure frequency, improved with increasing tiagabine dosage.[57] Compared with placebo, tiagabine 32 and 56 mg/day reduced the complex partial seizure frequency (relative to baseline) by ≥50% in more patients (20 and 29% *vs* 4%; $p < 0.01$) [fig. 3] and produced greater reductions (relative to baseline) in 4-week complex partial seizure frequency (2.2 and 2.8 *vs* 0.7 seizures; $p < 0.05$). Tiagabine 16 mg/day was less effective. The proportion of patients with simple partial seizures who responded to treatment was greater versus placebo for all 3 treatment groups (28.2 to 36.4 *vs* 9.8%; $p < 0.05$) [fig. 3]. However, tiagabine 16 mg/day produced a greater decrease in 4-week simple partial seizure frequency than tiagabine 32 mg/day (2.3 *vs* 1.7 seizures) [statistical significance not provided]. Reductions in secondarily generalised seizure frequency were also apparent in all 3 tiagabine dosage groups but were not statistically significant compared with placebo.

Broadly similar reductions in partial seizure rate were reported with twice-daily and 4-times-daily administration of tiagabine.[56] Complex partial seizure frequency was reduced by ≥50% relative to baseline in 31% of patients treated with tiagabine 16mg twice daily and 27% of patients treated with tiagabine 8mg 4 times daily. These reductions were statistically significant compared with placebo for both treatment groups ($p \leq 0.01$). Improvements in simple partial seizure frequency were more variable. Only the twice-daily regimen proved significantly more effective than placebo in reducing the simple partial seizure frequency by

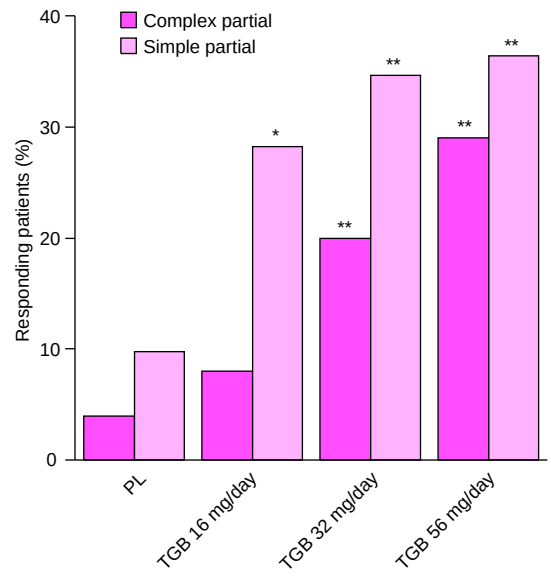

Fig. 3. Dose-response relationship for tiagabine (TGB) as add-on therapy for the management of refractory partial epilepsy. Relationship between TGB dosage (16, 32 and 56 mg/day) and response (≥50% reduction in seizure frequency from baseline) for simple partial and complex partial seizures among patients recruited to a randomised, double-blind, placebo-controlled, parallel-group study.[57] *$p < 0.05$, **$p < 0.01$ *vs* placebo.

Table IV. Overview of the results of a pooled analysis of 5 multicentre, randomised, double-blind, placebo-controlled studies of tiagabine 12-64 mg/day for 7-12wk as add-on therapy in a total of 951 enrolled patients with partial epilepsy[58]

Seizure type (no. of evaluable patients)	Patients with ≥50% reduction in seizure rate *vs* baseline (%)		Median reduction in 4wk seizure rate *vs* baseline (%)		Median increase in number of seizure-free days *vs* baseline (%)	
	tiagabine	placebo	tiagabine	placebo	tiagabine	placebo
All seizures (763)	23[a]	9[b]	25**	0.1	6**	0
Complex partial (750)	27	13	25**	3	5	0.8
Simple partial (424)	30	10	25[c]**	+2[cd]	NR*	NR
Secondarily generalised tonic-clonic (366)	40	30	35[c]*	0[c]	NR**	NR

a 95% CI 19-26%.
b 95% CI 6-13%.
c Values estimated from graph.
d Increase in seizure rate.
Abbreviations and symbols: CI = confidence interval; NR = value not reported; *p < 0.01; **p≤ 0.0001 *vs* placebo.

≥50% (37 *vs* 16%; p = 0.03); however, a significant reduction in 4-week seizure frequency compared with placebo was seen only with the 4-times-daily regimen (–2.1 *vs* +0.6 seizures; p ≤ 0.01). Reductions in secondarily generalised seizures were similar for both active treatment groups (table III).

Pooled data from the 3 add-on therapy trials described in table III and from 2 other studies (the full results of which have not been published) have been analysed.[58] The additional trials are a parallel-group study in 154 patients with partial epilepsy treated with tiagabine 30 mg/day or placebo and a crossover study in 88 patients with partial epilepsy treated with tiagabine 12 to 64 mg/day or placebo. Pooled analysis revealed that the proportion of patients experiencing a ≥50% reduction in overall seizure frequency during 7 to 12 weeks of therapy was greater in the tiagabine than the placebo treatment group [23 *vs* 9%; 95% confidence interval (CI) of 19 to 26% and 6 to 13%, respectively, p value not provided] (table IV).[58] In addition, tiagabine-treated patients experienced a greater median reduction from baseline in 4-week overall seizure frequency (25 *vs* 0.1%; p < 0.0001) and a greater median increase in the number of seizure-free days (6 *vs* 0%; p < 0.0001) than placebo recipients. When the results were analysed according to seizure type, tiagabine was judged to be effective in the treatment of both complex and simple partial seizures and secondarily generalised tonic-clonic seizures (table IV).

There are no direct comparisons of tiagabine and other antiepileptic drugs as add-on therapy in epilepsy. In a retrospective analysis of placebo-controlled randomised trials evaluating different antiepileptic drugs, no significant difference in efficacy was demonstrated between tiagabine, gabapentin, lamotrigine, topiramate, vigabatrin and zonisamide as add-on therapy in refractory partial epilepsy (based on odds ratio and 95% CIs relative to placebo for patients with ≥50% reduction in seizure frequency).[59]

An anecdotal report of a substantial improvement in seizure control after the addition of subtherapeutic doses of the GABA transaminase inhibitor vigabatrin (500mg at night) to tiagabine therapy (40 mg/day) in 2 patients with refractory epilepsy has led to the suggestion of possible synergy between GABAergic drugs. However, this hypothesis requires further investigation.[60]

3.1.2 Long Term Studies

The long term efficacy of tiagabine is being evaluated in 6 nonblind multicentre studies. Three of these trials are extensions of the placebo-controlled add-on studies described in the previous section. The other three were initiated as nonblind studies and enrolled a total of 1206 patients with epilepsy (any type) not adequately controlled with existing antiepileptic drug therapy.[32,58] The maximum permitted dosage of tiagabine was 80 mg/day in 4 of the studies and 64 mg/day in the remaining two, usually administered in 3 or 4 divided doses.

A pooled analysis of the 3 extension studies, which recruited a total of 772 patients treated with tiagabine ≤80 mg/day, revealed a ≥50% reduction in seizure frequency (all seizures and specific seizure types) in about 30 to 40% of patients treated for >3 to 6 months.[58] Except for secondarily generalised tonic-clonic seizures, this effect was generally maintained during 12 months of treatment (fig. 4). For secondarily generalised tonic-clonic seizures, the percentage of responders was decreased from 40.5% at >3 to 6 months to 28.4% at >12 months. According to a pooled analysis of all 6 long term studies, 15 to 30% of patients were seizure free for at least 2 months.[58]

In a briefly reported analysis of one of the long term extension studies, there was no loss of response during up to 24 months of tiagabine therapy (median dosage 56 mg/day after month 6).[61,62] In 171 patients, the median reduction from baseline in 4-week complex partial seizure frequency was 2.4, 3.1, 3.3 and 3.8 seizures at 0 to 6, 7 to 12, 13 to 18 and 19 to 24 months, respectively. All patients recruited to this study initially received tiagabine as add-on therapy.[63]

3.2 Monotherapy in the Management of Partial Epilepsy

Initial experience from 2 studies, a dose-ranging study[51,64] and a dose-comparison study,[51,65] suggests that tiagabine monotherapy has a beneficial effect in some patients with partial epilepsy refractory to monotherapy with other antiepileptic

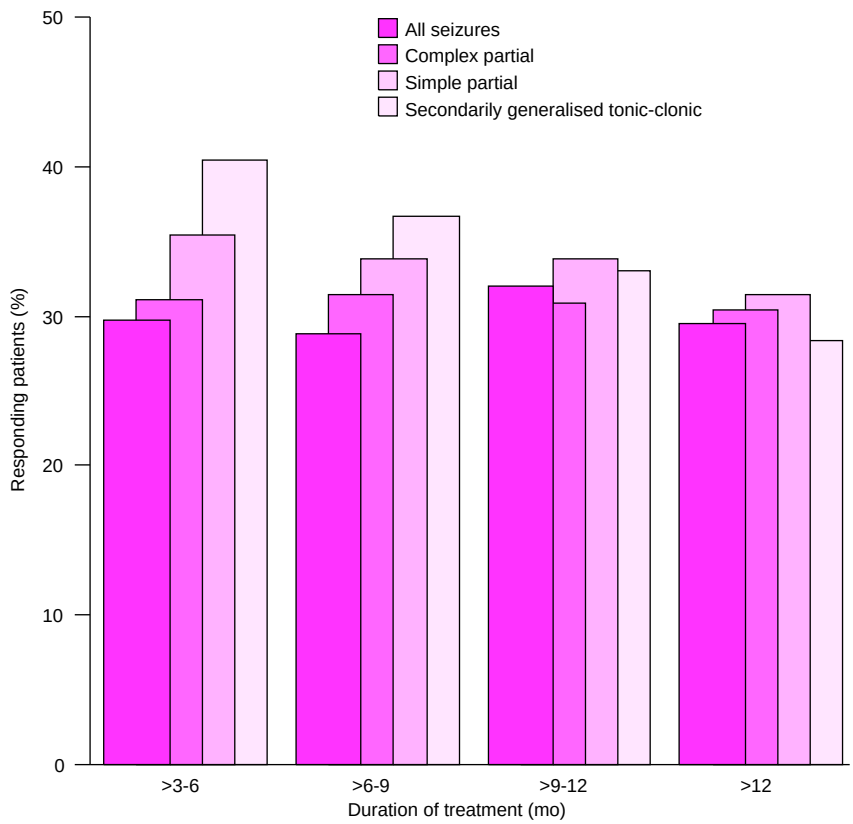

Fig. 4. Long term efficacy of tiagabine. Proportion of patients with partial epilepsy who responded to add-on tiagabine therapy (≤80 mg/day) [≥50% reduction from baseline in 4-week seizure frequency; intent-to-treat analysis] according to a pooled analysis of 3 nonblind studies (n = 772).[58]

drugs. In both studies, tiagabine therapy was gradually introduced before discontinuation of existing antiepileptic therapy (over a period of 3 to 4 weeks) to minimise the potential for withdrawal seizures. Notably, the optimal dosage for tiagabine was not identified in these 2 studies, a major factor being a high rate of study withdrawal (>50%). This was probably due to poor tolerance during the period of conversion to monotherapy, which involved simultaneous titration of tiagabine and tapering of baseline antiepileptic drugs. Moreover, the refractory nature of the disease in patients recruited to these studies made successful conversion to tiagabine monotherapy less likely.

In the nonblind dose-ranging study, 31 patients with complex partial epilepsy were initiated on tiagabine at a dosage of 0.25 mg/kg/day. This dosage was increased to 0.5 mg/kg/day within 7 days or to 0.35 mg/kg/day if the patient was not receiving concomitant enzyme-inducing antiepileptic drug therapy.[51,64] After a subsequent 2-week washout phase to allow time for reversal of enzyme induction in patients who had been receiving concomitant enzyme-inducing antiepileptic drug therapy, the dosage of tiagabine was adjusted to the maximum tolerated dosage during a 7-week dose evaluation period. More than half the patients (19 of 31; 61%) were converted to tiagabine monotherapy for ≥2 weeks, and 12 of these patients completed the study receiving a mean final dosage of tiagabine of 38.4 mg/day (range 24 to 54 mg/day).

In the double-blind, parallel-group, dose-comparison study, patients with complex partial epilepsy with or without secondarily generalised seizures were randomised to treatment with tiagabine 6 (n = 102) or 36 mg/day (n = 96).[51,65] This investigation comprised an 8-week baseline phase, a 6-week dose titration phase, a 12-week fixed dosage period and a 3-week termination period. Ongoing antiepileptic drug therapy was continued during the baseline period and discontinued over the last 4 weeks of the dose titration period. Patients treated with tiagabine 6 mg/day received this dosage throughout the dose titration and fixed dosage periods, whereas tiagabine was titrated to 36 mg/day during the first 2 weeks of the dose titration period in the high-dose therapy group.

141 of 198 patients (71%) discontinued this study prematurely. There was a trend towards increased discontinuation because of lack of efficacy in the low versus the high dosage group (41 *vs* 29%). The median 4-week complex partial seizure frequency for patients completing the fixed-dosage period (n = 57) was decreased from baseline after treatment with both low (4 *vs* 6.2 seizures; p = 0.002) and high dosage tiagabine therapy (4.8 *vs* 7 seizures; p = 0.025) [values estimated from a graph].[51] In an intent-to-treat analysis, seizure frequency was not significantly changed from baseline during the titration and fixed dosage period and was similar for both treatment groups. However, more patients in the high dosage group experienced a ≥50% reduction in complex partial seizure frequency than patients in the low dosage group (31 *vs* 18%; p = 0.038).

Tiagabine monotherapy (≤66 mg/day) demonstrated minimal efficacy in a small study involving 11 patients with complex partial epilepsy undergoing seizure assessment prior to surgery.[51,66]

Data on the comparative efficacy of tiagabine and existing antiepileptic medications are limited to the preliminary results of a double-blind, randomised, parallel-group study comparing tiagabine 10 to 20 mg/day (n = 147) and carbamazepine 400 to 800 mg/day (n = 144) as monotherapy in patients with newly diagnosed partial epilepsy.[67,68] Fewer tiagabine-treated patients completed the 44-week assessment period (primary efficacy end-point) than carbamazepine-treated patients (41 *vs* 54%; statistical significance not provided). This difference was mostly attributable to more patients in the tiagabine treatment group experiencing a second seizure during this period (20 *vs* 14% of patients). However, the utility of these results is limited because of the absence of standard efficacy measurements such as a reduction in seizure frequency and response rate. Moreover, a very narrow and possibly low tiagabine dosage range (10 to 20 mg/day) was selected for evaluation in this study.

3.3 Childhood Epilepsy

Although some of the add-on therapy and monotherapy studies already described (sections 3.1 and 3.2) recruited patients with epilepsy as young as 10 to 12 years of age, few studies have specifically evaluated the efficacy of tiagabine in children and adolescents. Preliminary data from 3 small noncomparative studies have indicated an improvement in seizure control in some children and adolescents with partial seizures treated with tiagabine.[69-71] This effect appears to be maintained over prolonged periods of time (up to 18 months or more).[71,72]

Partial seizure frequency was reduced by >50% in 20% of children (aged 2 to 15 years) with refractory partial seizures treated with add-on tiagabine 0.25 to 1.5 mg/kg daily (n = 24)[69] and in 6 of 11 adolescents (aged 12 to 16 years) with refractory partial epilepsy treated with add-on tiagabine 32 to 80 mg/day.[70] Tiagabine 32 to 80 mg/day also reduced the mean seizure frequency per month from baseline (73.6 *vs* 47.5 seizures per month; $p < 0.05$).[70] However, dosages of 0.25 to 1.5 mg/kg had only minimal efficacy in the treatment of primary generalised seizures in children.[69]

Among 25 children (aged 3 to 11 years) with partial epilepsy enrolled in a long term study, 18 (72%) were successfully converted to tiagabine monotherapy for ≥120 days (median duration 514 days). The median seizure-free period for these patients was 454 days.[71]

4. Tolerability

4.1 Add-on Therapy

Currently, the most detailed information on the tolerability profile of tiagabine is based on pooled analyses of 5 randomised double-blind placebo-controlled studies and 6 nonblind long term trials of tiagabine as add-on therapy in patients with refractory epilepsy.[73] In the placebo-controlled studies, a total of 675 patients (aged 12 to 77 years) treated with tiagabine (typically ≤64 mg/day for up to 12 weeks) and 363 patients treated with placebo for the same period were evaluable for tolerability. In the long term studies, which were either extensions of the short term studies or newly initiated trials, 1978 patients were treated with tiagabine (≤80 mg/day); of these, 814 received the drug for ≥1 year. 162 patients in the long term studies were aged 12 to 17 years and 24 were aged >65 years.

The majority of adverse events observed in adults treated with tiagabine in these studies were mild to moderate, associated with the CNS and appeared early on in therapy.[73] Serious adverse events (requiring hospitalisation or resulting in permanent disability or death) were usually unrelated to tiagabine therapy.[63] They occurred in 398 of 2600 patients (15.3%), with accidental injury (3%), confusion (1%), somnolence (0.8%) and depression (0.8%) the most frequently reported.[73]

In the short term studies, 91% of tiagabine-treated patients compared with 79% of placebo recipients experienced ≥1 treatment-emergent adverse event.[73] Dizziness (30 *vs* 13% of patients), asthenia (24 *vs* 12%), nonspecific nervousness (12 *vs* 3%), tremor (9 *vs* 3%), diarrhoea (7 *vs* 2%), depressed mood (5 *vs* 1%) and emotional lability (4 *vs* 1%) were the most common adverse events (all grades) associated with tiagabine therapy and were all significantly more frequent among tiagabine- than placebo-treated patients (fig. 5). Other adverse events including somnolence, headache, abnormal thinking (difficulty in concentrating or slowness of thought), abdominal pain, pharyngitis, ataxia, confusion, psychosis and skin rash, occurred with a similar frequency in the 2 treatment groups. Clinically significant effects on blood counts or liver function tests were not reported after tiagabine therapy. Treatment discontinuation due to adverse events was necessary in 15% of tiagabine- compared with 5% of placebo-treated patients and was mainly attributable to the development of dizziness, asthenia, somnolence or ataxia in the former group.

Long term tiagabine therapy was associated with a similar profile and incidence of adverse events to short term therapy.[73] The incidence of adverse events tended to peak during the first 1 to 6 months of tiagabine therapy and events generally

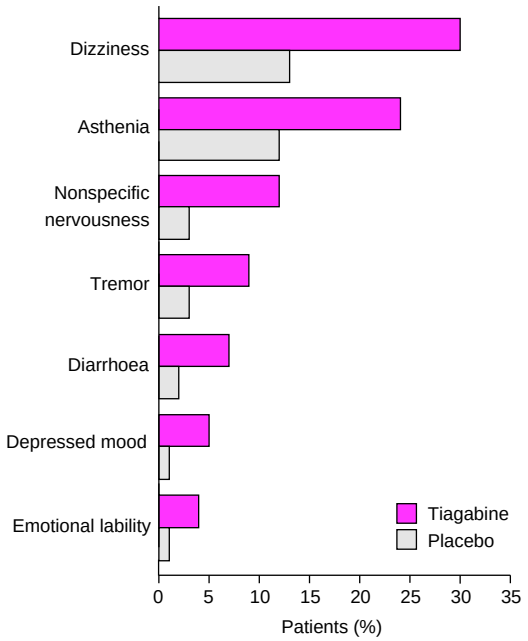

Fig. 5. Comparative tolerability of tiagabine and placebo. Incidence of treatment-emergent adverse events which were more frequent among tiagabine- than placebo-treated patients ($p < 0.05$). Data are derived from a pooled analysis of 5 randomised, double-blind, placebo-controlled studies (n = 1038) evaluating add-on tiagabine therapy in patients with refractory partial epilepsy.[73]

resolved within 1 month.[73,74] Excluding accidental injury (25% of patients), infection (23%) and flu syndrome (11%), the most frequently reported adverse events during long term therapy (up to 1 year or more) were dizziness (34%), somnolence (25%), asthenia (24%), headache (23%) and tremor (20%).[73] Other adverse events (nonspecific nervousness, confusion, abnormal thinking, nausea, ataxia and nystagmus) occurred with an incidence of 10 to 15%.[73]

Notably, data from this pooled analysis revealed no significant correlation between daily tiagabine dosage and the incidence of adverse events for the dosage ranges studied (≤24, >24 to 36, >36 to 48, >48 to 64, >64mg).[73] However, in another study, patients receiving tiagabine 16 mg/day were less likely to discontinue therapy because of adverse events than patients receiving tiagabine 32 or 56 mg/day (7 *vs* 15 or 16%); this difference was not statistically significant.[57] There was also a tendency for fewer patients receiving tiagabine 8mg 4 times daily to discontinue therapy because of adverse events than patients receiving 16mg twice daily (8 *vs* 12%) in a large clinical trial.[56]

4.2 Monotherapy

Although assessment of the tolerability profile of tiagabine may be confounded by its use in combination with other antiepileptic drugs, tolerability data from trials evaluating tiagabine as monotherapy support the findings of add-on therapy studies. The most frequently reported adverse events associated with tiagabine monotherapy were CNS-related and included dizziness, asthenia, difficulty concentrating and somnolence.[51] These adverse events were usually mild to moderate and necessitated treatment discontinuation in 78 of 236 patients (33%). Dosage comparison revealed a significantly ($p < 0.05$) greater incidence of dizziness (35 *vs* 15%), difficulty concentrating (23 *vs* 8%), paraesthesia (20 *vs* 7%) and nonspecific nervousness (16 *vs* 5%) and significantly more treatment withdrawals due to adverse events (43 *vs* 23%; $p < 0.05$) among patients treated with tiagabine 36 mg/day than with 6 mg/day.[51]

4.3 In Comparison with Other Agents

Data on the comparative tolerability of tiagabine and other antiepileptic drugs are limited. The preliminary results of a study comparing tiagabine 10 to 20 mg/day (n = 147) and carbamazepine 400 to 800 mg/day (n = 144) as monotherapy for up to 44 weeks indicated a similar incidence of adverse events in the 2 treatment groups.[67,68] 84% of tiagabine- and 90% of carbamazepine-treated patients experienced ≥1 adverse event; asthenia was the most common adverse event associated with carbamazepine therapy (33 *vs* 26% of patients) and dizziness was most frequent among the tiagabine-treated patients (29 *vs* 20%). The incidence of adverse events according to body system was similar for both treatment groups, except for those affecting the skin and appendages, which were more fre-

quent among carbamazepine-treated patients (22 *vs* 12%).

4.4 Other Adverse Events

Animal data[18] and anecdotal clinical reports relating to patients receiving tiagabine 48 to 60 mg/day[75] have led to concerns regarding a possible association between the development of status epilepticus and the use of tiagabine therapy. However, a recent evaluation of prospectively gathered data did not suggest such an association.[76,77] Combined data (reported as abstracts) from placebo-controlled add-on therapy studies indicated the development of status epilepticus in 4 of 494 (0.8%) tiagabine-treated patients compared with 2 of 275 patients (0.7%) receiving placebo. The corresponding figures for complex partial status epilepticus were 0.6 and 0.7%.[76,77] In a comparison of all tiagabine-treated patients (n = 2531) and 4 external cohorts of epilepsy patients not treated with tiagabine (n = 434), the incidence of status epilepticus (5 *vs* 6 to 9%) and of complex partial status epilepticus (3 *vs* 2 to 3%) was similar in all treatment groups.[76,77] However, the shorter duration of observation for the tiagabine–treated patients (median 1.7 *vs* 2.3 to 5 years) does warrant some caution when interpreting these results. It has been suggested, however, that a previous history of status epilepticus and not tiagabine therapy is a significant risk factor for recurrence of this condition.

Exacerbation of electroencephalogram (EEG) abnormalities in association with cognitive and neuropsychiatric adverse events has been reported in patients with a history of spike and wave discharges on EEG. In the documented cases in patients receiving tiagabine therapy, the individuals usually continued treatment with tiagabine but required a dosage adjustment.[78]

Spontaneous ecchymoses have been reported in patients treated with tiagabine and a full blood count including platelet count should be performed if ecchymoses develop.[79]

The absolute risk of congenital malformations in offspring born of mothers treated with antiepileptic drug therapy is approximately 7 to 10%, compared with 5% in the unexposed population.[80] There is no evidence to suggest an association between the use of tiagabine therapy during pregnancy and the development of teratogenic effects. In animal studies the drug showed no clinically significant teratogenic, carcinogenic or genetic effects.[32] However, human experience with tiagabine in this setting is limited and currently based on only 21 pregnancies, of which 8 proceeded normally.[81]

Overdosage with tiagabine (≤800mg) in approximately 20 patients was associated with a full recovery without any evidence of long term adverse effects.[82,83] The most common symptoms associated with tiagabine overdosage were confusion, somnolence, agitation, hostility, speech impairment, weakness, impaired consciousness and myoclonus. Supportive care with gastric lavage or activated charcoal aided recovery.

5. Dosage and Administration

Prescribing recommendations for tiagabine as adjunctive therapy to enzyme-inducing antiepileptic drugs in patients with partial epilepsy differ markedly between the US and Europe.

In adults receiving at least 1 concomitant enzyme-inducing antiepileptic drug, US recommendations state that tiagabine should be initiated at a dosage of 4mg once daily with food followed by weekly increments of 4 to 8mg until clinical response is achieved (table V).[78] In adolescents (aged 12 to 18 years), the initial dosage (4mg) may be increased by 4mg after 2 weeks and thereafter by 4 to 8mg at weekly intervals. The recommended oral maintenance dosage is 32 to 56 mg/day in adults and ≤32 mg/day in adolescents, administered in 2 to 4 divided doses.

In Europe, treatment of adults and adolescents (aged >12 years) with tiagabine should be initiated at a dosage of 7.5 to 15 mg/day followed by weekly increments of 5 to 15 mg/day. The recommended oral maintenance dosage for tiagabine as add-on therapy is 30 to 50 mg/day in 3 divided doses with food (table V).[79] In patients with a history of serious behavioural problems including generalised

Table V. US and European dosage recommendations for tiagabine as adjunctive therapy in adolescents and adults with epilepsy taking at least 1 enzyme-inducing antiepileptic drug

	US[78]		Europe[79]
	adults (aged >18y)	adolescents (aged 12-18y)	adults and adolescents (aged >12y)
Initiation dosage	4 mg/day	4 mg/day	7.5-15 mg/day
Titration schedule	↑ by 4-8mg at weekly intervals	↑ by 4mg at beginning of week 2; thereafter ↑ by 4-8mg at weekly intervals	↑ by 5-15 mg/day at weekly intervals
Usual maintenance dosage	32-56 mg/day in 2-4 divided doses	≤32 mg/day in 2-4 divided doses	30-50 mg/day in 3 divided doses

anxiety and depression, treatment should be initiated at a low initial dosage under close clinical supervision. In common with other antiepileptic drugs, abrupt discontinuation of tiagabine therapy may cause seizure recurrence. If cessation of tiagabine therapy is necessary, the dose should be reduced gradually over a period of 2 to 3 weeks.[79]

Mild or moderate hepatic impairment may necessitate dosage reduction. In Europe, tiagabine is contraindicated in patients with severe hepatic impairment.[79] Tiagabine may cause dizziness or other CNS-related symptoms, therefore, patients should be advised neither to drive or operate other complex machinery until they have gained sufficient experience on tiagabine to gauge whether or not it adversely affects their mental and/or motor performance.[79]

Experience is limited in patients receiving tiagabine who are not receiving concomitant enzyme-inducing antiepileptic drugs, and specific US dosage recommendations for the use of tiagabine in this setting are not yet available. European prescribing guidelines state that the maintenance dosage of tiagabine should initially be reduced to 15 to 30 mg/day in patients not taking enzyme-inducing drugs.[79] Dosage recommendations for the use of tiagabine in children are not yet available, and there are currently insufficient data to recommend the use of tiagabine in pregnant or lactating women (see section 4.4).

6. Potential Place of Tiagabine in the Management of Epilepsy

Epilepsy is characterised by intermittent and excessive synchronous discharge of groups of cortical neurons. It is the most common serious neurological condition, with an estimated prevalence of approximately 0.4 to 0.8% in the general population.[84] According to the International League Against Epilepsy classification, seizures can be subdivided into generalised, partial and unclassifiable.[85] A seizure is considered generalised when there is no evidence of an anatomic localisation or focal onset; partial seizures originate from a defined focal region of the brain. Consciousness is maintained during simple partial seizures, but is impaired or lost during complex partial seizures. Partial seizures may sometimes become bilateral, involving both sides of the cortex, and are then referred to as secondarily generalised.

There is clearly a need for more effective, better tolerated antiepileptic drugs. Established antiepileptic agents such as phenytoin, carbamazepine and valproic acid provide adequate seizure control for many patients;[86] however, seizure control remains suboptimal for many individuals. According to a prospective analysis of 1102 patients with partial epilepsy, only 23 to 26% of patients with complex partial seizures alone were seizure free after 1 year of treatment with standard antiepileptic drug therapy; the corresponding figures for patients with secondarily generalised tonic-clonic seizures alone or partial seizures with secondarily generalised tonic-clonic seizures were 48 to 55% and 25 to 32%.[87] Moreover, treatment with established antiepileptic agents is frequently complicated by poor drug tolerability and drug interactions.[88,89]

During the last 10 years there has been substantial progress in understanding of the cellular and neurochemical mechanisms underlying epilepsy. This has enabled the rational development of drugs

which interfere with mechanisms known to be involved in neuronal excitability, as opposed to the chance discovery of antiepileptic drugs through empirical drug screening programmes. Tiagabine is the product of such a rational drug development programme and is the first selective and specific GABA uptake inhibitor to be introduced into clinical practice.

Tiagabine has demonstrated efficacy in the treatment of simple and complex partial seizures (with and without secondarily generalised seizures) when used as add-on therapy in patients receiving other antiepileptic drugs. The reduction in seizure frequency appears to be maintained during long term therapy (up to 12 months or more). In preliminary studies, tiagabine monotherapy had a beneficial effect in some patients with partial epilepsy refractory to other antiepileptic drugs, and when used in children with refractory partial epilepsy. Direct comparisons with conventional and newer antiepileptic agents such as vigabatrin and lamotrigine are lacking and are necessary to establish the place of tiagabine in the management of epilepsy. Such studies should encompass relative comparisons of efficacy both as monotherapy and as add-on therapy and include an assessment of cost effectiveness and quality of life.

Although there is some evidence to suggest a relationship between tiagabine plasma concentrations and therapeutic effect, there are currently insufficient data to recommend routine monitoring of tiagabine plasma concentrations.

Possible disadvantages of tiagabine are its short plasma elimination half-life, necessitating frequent administration of the existing formulation, and inducible hepatic metabolism. Because the metabolism of tiagabine is enhanced by enzyme-inducing drugs such as phenytoin and carbamazepine, an increase in tiagabine dosage is frequently necessary when the drug is used as add-on therapy. However, in its favour, tiagabine does not appear to significantly alter the pharmacokinetics of other antiepileptic drugs such as carbamazepine and phenytoin. Nor does it produce clinically significant drug interactions with frequently prescribed drugs such as warfarin, theophylline, cimetidine, digoxin or oral contraceptives. This contrasts with drugs such as phenytoin and carbamazepine which accelerate the metabolism of warfarin and theophylline. Clinical experience to date has shown that tiagabine is generally well tolerated. Neurological adverse events, including dizziness, asthenia and nonspecific nervousness, account for the majority of adverse events associated with tiagabine therapy but appear to be generally mild to moderate. Notably, skin rash, gingival hyperplasia, hirsutism and psychosis, frequently associated with conventional antiepileptic drug therapy, do not appear to be a problem with tiagabine.

In conclusion, tiagabine is a new antiepileptic drug with a novel mechanism of action. It has shown efficacy as an adjunct to existing drug regimens in the treatment of partial epilepsy with or without secondarily generalised seizures. Areas which require further investigation include the use of tiagabine as monotherapy, its use in children with epilepsy and its efficacy against other epileptic seizure types. In addition, direct comparative studies will be required to definitively position tiagabine in the treatment of epilepsy. Meanwhile, tiagabine may be a useful alternative therapeutic option for the adjunctive treatment of partial epilepsy.

References

1. Borden LA, Dhar TGM, Smith KE, et al. Tiagabine, SK&F 89976-A, CI-966, and NNC-711 are selective for the cloned GABA transporter GAT-1. Eur J Pharmacol Mol Pharmacol 1994 Oct 14; 269: 219-24
2. Rekling JC, Jahnsen H, Laursen AM. The effect of two lipophilic τ-aminobutyric acid uptake blockers in CA1 of the rat hippocampal slice. Br J Pharmacol 1990 Jan; 99: 103-6
3. Roepstorff A, Lambert JDC. Comparison of the effect of the GABA uptake blockers, tiagabine and nipecotic acid, on inhibitory synaptic efficacy in hippocampal CA1 neurones. Neurosci Lett 1992 Nov 9; 146: 131-4
4. Thompson SM, Gähwiler BH. Effects of the GABA uptake inhibitor tiagabine on inhibitory synaptic potentials in rat hippocampal slice cultures. J Neurophysiol 1992 Jun; 67: 1698-701
5. Fink-Jensen A, Suzdak PD, Swedberg MDB, et al. The τ-aminobutyric acid (GABA) uptake inhibitor, tiagabine, increases extracellular brain levels of GABA in awake rats. Eur J Pharmacol 1992 Sep 22; 220: 197-201

6. During M, Mattson R, Scheyer R, et al. The effect of tiagabine HCl on extracellular GABA levels in the human hippocampus [abstract]. Epilepsia 1992; 33 Suppl. 3: 83
7. Braestrup C, Nielsen EB, Sonnewald U, et al. (R)-N-[4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl]nipecotic acid binds with high affinity to the brain τ-aminobutyric acid uptake carrier. J Neurochem 1990 Feb; 54: 639-47
8. Upton N. Mechanisms of action of new antiepileptic drugs: rational design and serendipitous findings. Trends Pharmacol Sci 1994; 15 (12): 456-63
9. Dalby NO, Nielsen EB. Comparison of the preclinical anticonvulsant profiles of tiagabine, lamotrigine, gabapentin and vigabatrin. Epilepsy Res 1997; 28: 63-72
10. Dalby NO, Nielsen EB. Tiagabine exerts an anti-epileptogenic effect in amygdala kindling epileptogenesis in the rat. Neurosci Lett 1997; 229: 135-7
11. Yamaguchi S, Rogawski MA. Effects of anticonvulsant drugs on 4-aminopyridine-induced seizures in mice. Epilepsy Res 1992 Mar; 11: 9-16
12. Coleman MH, Yamaguchi S, Rogawski MA. Protection against dendrotoxin-induced clonic seizures in mice by anticonvulsant drugs. Brain Res 1992 Mar 13; 575: 138-42
13. Nielsen EB, Suzdak PD, Andersen KE, et al. Characterization of tiagabine (NO-328), a new potent and selective GABA uptake inhibitor. Eur J Pharmacol 1991 Apr 24; 196: 257-66
14. Faingold CL, Randall ME, Anderson CA. Blockade of GABA uptake with tiagabine inhibits audiogenic seizures and reduces neuronal firing in the inferior colliculus of the genetically epilepsy-prone rat. Exp Neurol 1994 Apr; 126: 225-32
15. Smith SE, Parvez NS, Chapman AG, et al. The τ-aminobutyric acid uptake inhibitor, tiagabine, is anticonvulsant in two animal models of reflex epilepsy. Eur J Pharmacol 1995 Feb 6; 273: 259-65
16. Coenen AML, Drinkenburg WHIM, Inoue M, et al. Genetic models of absence epilepsy, with emphasis on the WAG/Rij strain of rats. Epilepsy Res 1992; 12: 75-86
17. Coenen AML, Blezer EHM, van Luijtelaar ELJM. Effects of the GABA-uptake inhibitor tiagabine on electroencephalogram, spike-wave discharges and behaviour of rats. Epilepsy Res 1995 Jun; 21: 89-94
18. Walton NY, Gunawan S, Treiman DM. Treatment of experimental status epilepticus with the GABA uptake inhibitor, tiagabine. Epilepsy Res 1994 Dec; 19: 237-44
19. Hosford DA, Wang Y. Utility of the lethargic (lh/lh) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. Epilepsia 1997 Apr; 38: 408-14
20. Halonen T, Nissinen J, Jansen JA, et al. Tiagabine prevents seizures, neuronal damage and memory impairment in experimental status epilepticus. Eur J Pharmacol 1996 Mar 28; 299: 69-81
21. Inglefield JR, Perry JM, Schwartz RD. Postischemic inhibition of GABA reuptake by tiagabine slows neuronal death in the gerbil hippocampus. Hippocampus 1995; 5 (5): 460-8
22. Johansen FF, Diemer NH. Enhancement of GABA neurotransmission after cerebral ischemia in the rat reduces loss of hippocampal CA1 pyramidal cells. Acta Neurol Scand 1991 Jul; 84: 1-6
23. Suzdak PD. Lack of tolerance to the anticonvulsant effects of tiagabine following chronic (21 day) treatment. Epilepsy Res 1994 Dec; 19: 205-13
24. Dodrill CB, Arnett JL, Sommerville KW. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. Neurology 1997 Apr; 48: 1025-31
25. Sveinbjornsdottir S, Sander JW, Patsalos PN, et al. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. Seizure 1994 Mar; 3: 29-35
26. Kälviäinen R, Äikiä M, Mervaala E, et al. Long-term cognitive and EEG effects of tiagabine in drug-resistant partial epilepsy. Epilepsy Res 1996; 25: 291-7
27. Dodrill CB, Arnett JL, Shu V, et al. The effects of tiagabine monotherapy on abilities, adjustment and mood. Epilepsia. In press
28. Gustavson LE, Mengel HB. Pharmacokinetics of tiagabine, a τ-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiple doses. Epilepsia 1995 Jun; 36: 605-11
29. Jansen JA, Oliver S, Dirach J, et al. Absolute bioavailability of tiagabine [abstract]. Epilepsia 1995; 36 Suppl. 3: S159
30. Inami M, Watanabe H, Takahashi A, et al. Tiagabine in healthy Japanese subjects: single- and multiple-dose study [abstract]. Epilepsia 1995; 36 Suppl. 3: S158-159
31. Mengel H, Gustavson LE, Soerensen HJ, et al. Effect of food on the bioavailability of tiagabine HCl [abstract]. Epilepsia 1991; 32 Suppl. 3: 6
32. Novo Nordisk. Tiagabine. Product monograph
33. Bopp BA, Nequist GE, Rodrigues AD. Role of the cytochrome P450 3A subfamily in the metabolism of [^{14}C]tiagabine by human hepatic microsomes [abstract]. Epilepsia 1995; 36 Suppl. 3: S159
34. Bopp BA, Gustavson LE, Johnson MK, et al. Disposition and metabolism of orally administered ^{14}C-tiagabine in humans [abstract]. Epilepsia 1992; 33 Suppl. 3: 83
35. Lau AH, Gustavson LE, Sperelakis R, et al. Pharmacokinetics and safety of tiagabine in subjects with various degrees of hepatic function. Epilepsia 1997 Apr; 38: 445-51
36. So EL, Wolff D, Graves NM, et al. Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. Epilepsy Res 1995 Nov; 22: 221-6
37. Samara E, Gustavson L, El Shourbàgy T, et al. Population analysis of the pharmacokinetics of tiagabine. Tiagabine. 22nd International Epilepsy Congress; 1997 Jun 29-Jul 4; Dublin
38. Samara E, Gustavson L, El Shourbagy T, et al. Population analysis of the pharmacokinetics of tiagabine (Gabitril™) [abstract]. Epilepsia 1997; 38 Suppl. 3: 145
39. Snel S, Jansen JA, Mengel HB, et al. The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. J Clin Pharmacol 1997; 37: 1015-20
40. Gustavson LE, Boellner SW, Granneman GR, et al. A single-dose study to define tiagabine pharmacokinetics in pediatric patients with complex partial seizures. Neurology 1997 Apr; 48: 1032-7
41. Cato A, Qian JX, Gustavson LE, et al. Pharmacokinetics and safety of tiagabine in subjects with various degrees of renal function [abstract]. Epilepsia 1995; 36 Suppl. 3: S159
42. Rowan AJ, Gustavson L, Shu V, et al. Dose concentration relationship in a multicentre tiagabine (Gabitril™) trial [abstract]. Epilepsia 1997; 38 Suppl. 3: 40
43. Rowan AJ, Sommerville KW, Gustavson L, et al. Dose-concentration relationships in a multicentre tiagabine trial. Tiagabine. 22nd International Congress; 1997 Jun 29-Jul 4; Dublin
44. Richens A, Chadwick DW, Duncan JS, et al. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. Epilepsy Res 1995 May; 21: 37-42

45. Gustavson LE, Cato A, Guenther HJ, et al. Lack of clinically important drug interactions between tiagabine and carbamazepine, phenytoin, or valproate [abstract]. Epilepsia 1995; 36 Suppl. 3: S159-160
46. Gustavson LE, Sommerville KW, Boellner SW, et al. Lack of a clinically significant pharmacokinetic drug interaction between tiagabine and valproate. Online J Curr Clin Trials [serial online] 1997 Feb. Available from: URL: http://www.ojcct.com.default.html
47. Mengel H, Jansen JA, Sommerville K, et al. Tiagabine: evaluation of the risk of interaction with theophylline, warfarin, digoxin, cimetidine, oral contraceptives, triazolam, or ethanol [abstract]. Epilepsia 1995; 36 Suppl. 3: S160
48. Snel S, Jansen JA, Pedersen PC, et al. Tiagabine, a novel antiepileptic agent: lack of pharmacokinetic interaction with digoxin. Data on file
49. Mengel HB, Houston A, Back DJ. An evaluation of the interaction between tiagabine and oral contraceptives in female volunteers. J Pharm Med 1994 Jul; 4: 141-50
50. Richens A, Gustavson LE, McKelvy JF, et al. Pharmacokinetics and safety of single-dose tiagabine HCl in epileptic patients chronically treated with four other antiepileptic drug regimens [abstract]. Epilepsia 1991; 32 Suppl. 3: 12
51. Schachter SC. Tiagabine monotherapy in the treatment of partial epilepsy. Epilepsia 1995; 36 Suppl. 6: S2-6
52. Thompson MS, Groes L, Schwietert HR, et al. An open label sequence listed two period crossover pharmacokinetic trial evaluating the possible interaction between tiagabine and erythromycin during multiple administration to healthy volunteers [abstract]. Epilepsia 1997; 38 Suppl. 3: 64
53. Thomsen MS, Groes L, Schwietert HR, et al. Tiagabine: investigation of possible interaction with erythromycin during multiple dosing in healthy subjects. Tiagabine. 22nd International Epilepsy Congress; 1997 Jun 29-Jul 4; Dublin
54. Eadie MJ. Problems in the assessment of potential antiepileptic drugs. CNS Drugs 1994 Mar; 1: 167-71
55. Pledger GW, Schmidt D. Evaluation of antiepileptic drug efficacy: a review of clinical trial design. Drugs 1994 Oct; 48: 498-509
56. Sachdeo RC, Leroy RF, Krauss GL, et al. Tiagabine therapy for complex partial seizures: a dose-frequency study. Arch Neurol 1997 May; 54: 595-601
57. Uthman BM, Rowan AJ, Ahmann PA, et al. Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. Arch Neurol. In press
58. Ben-Menachem E. International experience with tiagabine add-on therapy. Epilepsia 1995; 36 Suppl. 6: S14-21
59. Marson AG, Kadir ZA, Hutton JL, et al. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. Epilepsia 1997; 38 Suppl. 8: 859-80
60. Leach JP, Brodie MJ. Synergism with GABAergic drugs in refractory epilepsy [letter]. Lancet 1994 Jun 25; 343: 1650
61. Schachter S, Carlson H, Deaton R, et al. Maintenance of tiagabine therapy for complex partial seizures [abstract]. Epilepsia 1997; 38 Suppl. 3: 145
62. Schachter S, Sommerville KW, Carlson H, et al. Maintenance of tiagabine efficacy for complex partial seizures. Tiagabine. 22nd International Epilepsy Congress; 1997 June 29-Jul 4; Dublin
63. Novo Nordisk. Data on file. Denmark
64. Ramsay RE, Slater JD, Aranguiz C, et al. Open treatment with tiagabine and conversion to monotherapy of patients with uncontrolled partial and generalized seizures [abstract]. Epilepsia 1993; 34 Suppl. 6: 103
65. Schachter S, Biton V, Boellner S, et al. Safety and efficacy of tiagabine HCl monotherapy in the treatment of partial seizures: high dose versus low dose [abstract]. Epilepsia 1995; 36 Suppl. 3: S148
66. Alarcon G, Binnie CD, Elwes RDC, et al. Monotherapy antiepileptic drug trials in patients undergoing presurgical assessment: methodological problems and possibilities. Seizure 1995; 4: 293-301
67. Brodie MJ, Bomhof MAM, Kälviäinen R, et al. Double-blind comparison of tiagabine and carbamazepine monotherapy in newly diagnosed epilepsy [abstract]. Epilepsia 1997; 38 Suppl. 3: 66
68. Brodie MJ, Bomhof MAM, Riekkinen P, et al. Double-blind comparison of tiagabine and carbamazepine monotherapy in newly diagnosed epilepsy: preliminary results. Tiagabine. 22nd International Epilepsy Congress; 1997 Jun 29-Jul 4; Dublin
69. Uldall P, Bulteau C, Pedersen SA, et al. Single-blind study of safety, tolerability, and preliminary efficacy of tiagabine as adjunctive treatment of children with epilepsy [abstract]. Epilepsia 1995; 36 Suppl. 3: S147-148
70. Stauffer A, Mikati M, Holmes G, et al. Efficacy of tiagabine in older pediatric patients with refractory partial seizures [abstract]. Neurology 1995 Apr; 45 Suppl. 4: 249
71. Boellner SW, Deaton R, Sommerville W. Long-term treatment of partial seizures with tiagabine in children [abstract]. Epilepsia 1997 Dec; 38 Suppl. 8: 208
72. Pellock JM, Deaton R, Sommerville KW. Use of tiagabine as long-term therapy for complex partial seizures in adolescents [abstract]. Epilepsia 1997 Dec; 38 Suppl. 8: 105
73. Leppik IE. Tiagabine: the safety landscape. Epilepsia 1995; 36 Suppl. 6: S10-13
74. Sommerville KW, Hearell M, Deaton R, et al. Adverse events with long-term tiagabine therapy [abstract]. Epilepsia 1997 Dec; 38 Suppl. 8: 106
75. Schapel G, Chadwick D. Tiagabine and non-convulsive status epilepticus. Seizure 1996 Jun; 5: 153-6
76. Shinnar S, Berg A, Hauser WA, et al. Evaluation of the incidence of status epilepticus in association with tiagabine therapy [abstract]. Epilepsia 1997; 38 Suppl. 3: 65
77. Shinnar S, Berg AT, Hauser WA, et al. Evaluation of the incidence of status epilepticus in association with tiagabine therapy. Tiagabine. 22nd International Epilepsy Congress; 1997 June 29-Jul 4; Dublin
78. Abbott Laboratories. Tiagabine prescribing information. Chicago (IL), 1997 Oct
79. Novo Nordisk. Tiagabine prescribing information. Bagsvaerd, Denmark, 1996 Nov
80. Lindhout D, Omtzigt JGC. Teratogenic effects of antiepileptic drugs: implications for the management of epilepsy in women of childbearing age. Epilepsia 1994; 35 Suppl. 4: S19-28
81. Collins S, Donnelly J, Krupa D, et al. Pregnancy and tiagabine exposure. In: 49th Annual Meeting, American Academy of Neurology (abstracts on diskette). Boston: Am Acad Neurol, 1997
82. Parks BR, Dostrow VG, Sommerville KW. Experience with clinical overdoses of tiagabine [abstract]. 8th International Bethel-Cleveland Clinic Epilepsy Symposium. Antiepileptic Drug Treatment State of the Art and Further Perspectives; 1997 Apr 24-27; Bielefeld, 144

83. Leach JP, Stolarek I, Brodie MJ. Deliberate overdose with the novel anticonvulsant tiagabine. Seizure 1995 Jun; 4: 155-7
84. Langtry HD, Wagstaff AJ. Management of epilepsy. Defining the role of lamotrigine. Dis Manage Health Outcomes 1997 May; 1 (5): 254-70
85. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34 (4): 592-6
86. Brodie MJ, Dichter MA. Antiepileptic drugs. N Engl J Med 1996 Jan; 334 (3): 168-75
87. Mattson RH, Cramer JA, Collins JF, et al. Prognosis for total control of complex partial and secondarily generalised tonic-clonic seizures. Neurology 1996; 47: 68-76
88. Dichter MA, Brodie MJ. New antiepileptic drugs. N Engl J Med 1996 Jun 13; 334: 1583-90
89. Patsalos PN, Sander JW. Newer antiepileptic drugs: towards an improved risk-benefit ratio. Drug Saf 1994 Jul; 11: 37-67

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