Therapeutic Class Overview
Anticonvulsants-Benzodiazepines

Therapeutic Class

- **Overview/Summary:** Of the various benzodiazepines available, the four agents currently approved by the Food and Drug Administration (FDA) for the treatment of seizure disorders are clobazam (ONFI®), clonazepam (Klonopin®), clorazepate (Tranxene-T®) and diazepam (Valium®, Diastat®).[1-5] The precise mechanism by which the benzodiazepines exert their antiepileptic and anxiolytic effects is unknown, although it is believed to be related to their ability to enhance the activity of gamma aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Specifically, benzodiazepines bind to the $GABA_A$ receptor subtype and enhance the chloride channel's conductance by increasing the frequency of gated channel opening.[6-8] Clobazam may be associated with less sedation compared to the other benzodiazepines.[9] Clonazepam is used to treat myoclonic, atonic and absence seizures that are resistant to treatment with other antiepileptic drugs. It is generally less effective for absence seizures than ethosuximide or valproate.[10] Clonazepam is unique in that is approved for use when acute or chronic administration of an anticonvulsant is required. The use of clorazepate is generally limited to refractory partial seizures, and is only indicated as an adjunctive therapy.[10] Diazepam is the standard initial therapy for status epilepticus and is available in oral and rectal formulations. The use of benzodiazepines in the management of epilepsy may be limited by the potential for development of tolerance and decreased sedative or anticonvulsant effects.[10] Clonazepam, clorazepate and diazepam are available generically. Clobazam is currently a branded product.[11] With regard to the pharmacokinetic properties of these agents, clonazepam has an intermediate duration of action (10 to 24 hours), while clobazam, clorazepate and diazepam are considered to be long-acting (>24 hours) benzodiazepines. Clorazepate and diazepam are both metabolized to desmethyldiazepam, an active metabolite primarily responsible for the anticonvulsant effects of both agents. Clobazam undergoes metabolism to N-desmethylclobazam, an active metabolite, while clonazepam does not have any active metabolites despite hepatic metabolism. In cases where chronic maintenance therapy is required (e.g., epilepsy or anxiety), the long-acting agents are preferred, and as a result of their increased duration of action, effective therapeutic drug concentrations can be maintained.[12]

Table 1. Current Medications Available in the Class[1-5,11]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Clobazam (ONFI®)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥2 years of age	Tablet: 5 mg 10 mg 20 mg	-
Clonazepam (Klonopin®, Klonopin® Wafers)	Alone or as an adjunct in the treatment of Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures or in patients with absence seizures (petit mal) who have failed to respond to succinimides	Tablet: 0.5 mg 1 mg 2 mg Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg	✔
Clorazepate (Tranxene-T®)	Adjunctive therapy in the management of partial seizures	Tablet: 3.75 mg 7.5 mg	✔

		15 mg	
Diazepam (Diastat AcuDial®, Diastat Pediatric®, Valium®)	Adjunctive use in convulsive disorders, management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity	Ampule, disposable syringe, vial:* 5 mg/mL Oral concentrate: 5 mg/mL Oral solution: 5 mg/5 mL Rectal gel:* 2.5 mg 10 mg 20 mg Tablet: 2 mg 5 mg 10 mg	✔

* This medication is administered by a medical professional or caregiver.

Evidence-based Medicine

- In a double-blind, randomized controlled study (N=238), clobazam was compared to placebo in patients two to 60 years of age with Lennox-Gastaut syndrome. Following 12 weeks of treatment with clobazam, all three doses (0.25, 0.5 and 1.0 mg/kg) significantly decreased the weekly drop seizure rates compared to placebo (-41.2 to -68.3 vs -12.0%; *P*<0.0001 for all). In addition, weekly total (drop and non-drop) and non-drop seizure rates decreased with clobazam. Patients receiving clobazam also experienced higher responder rates (≥50% decrease in average weekly seizure rate) compared to patients receiving placebo (58.6 to 77.6 vs 31.6%; *P*<0.0001).[13]
- In an open-label study by Booker et al (N=59), 21 patients were considered to have had an "excellent" response to therapy. Specifically, clorazepate was effective for generalized minor motor seizures, including absence, akinetic seizure and myoclonic seizure although generalized tonic-clonic seizures were less responsive.[14] In a small crossover study, there was a trend towards improved control of partial elementary seizures for patients receiving clorazepate compared to phenobarbital (difference, -8; 95% CI, -23.9 to 3.5) as well as those with partial complex seizures (difference, -6; 95% CI, -3.9 to 0.4). Significantly more patients preferred treatment with clorazepate over phenobarbital (*P*<0.01). Overall, patients reported significantly less subjective (*P*<0.01) and objective toxicity (*P*<0.05) with clorazepate compared to phenobarbital.[15]
- In an open-label study of patients diagnosed with progressive myoclonic epilepsy (N=26), clonazepam plus valproate sodium significantly improved median scores for myoclonus, general performance, and locomotor ability compared to baseline values (*P*<0.001 for all). Speech was also significantly improved.[16] Bensch et al reported 14 of 20 children with treatment-resistant epilepsy who received clonazepam experienced a lower mean number of seizures compared to placebo in short-term crossover study (*P*<0.05). In patients with absence seizures who continued to experience frequent seizures despite anticonvulsant therapy, the addition of clonazepam significantly reduced seizure frequency compared to the addition of placebo (*P*<0.05).[17] In patients recently diagnosed with psychomotor epilepsy, both clonazepam and carbamazepine significantly reduced seizure frequency compared to baseline over three years (*P*<0.05 for both). There was no significant difference in seizure frequency between the treatments (difference, 0.2; 95% CI, -0.3 to 0.4).[18] In patients with Lennox-Gastaut syndrome or infantile spasms, clonazepam was effective at improving or controlling

seizure activity in eight of 37 patients in one study. Moreover, after six months, six of the eight patients remained seizure-free and two others experienced significantly fewer seizures compared to baseline.[19]

- Pavlidou et al reported significantly lower rates of status epilepticus recurrence for high-risk children who received rectal diazepam compared to those who did not receive treatment (38 vs 83%; *P*=0.005).[20] A higher proportion of patients treated with diazepam were seizure-free 12 hours following administration compared to placebo (55 vs 34%; *P*=0.031) in one study in addition to a prolonged time to the next seizure (*P*=0.007).[21] Significantly more out-of-hospital status epilepticus seizures were terminated by arrival at the emergency department following treatment with lorazepam or diazepam compared to placebo (59.1 and 42.6 vs 21.1%, respectively; *P*=0.001). There was no difference in likelihood of seizure termination at arrival between lorazepam and diazepam treatments (OR, 1.9; 95%, 0.9 to 4.3).[22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The treatment of epilepsy calls for highly individualized care, with a variety of different antiepileptic drugs recommended or considered potential treatment options in each seizure type.[23-30]
  - According recent clinical guidelines for the management of epilepsy by the National Institute for Clinical Excellence, clonazepam may be considered for absence, myoclonic and idiopathic generalized seizures if a patient has failed first-line treatment options (sodium valproate) and subsequent adjunctive or second-line therapies are ineffective or not tolerated.[23]
  - The International League Against Epilepsy states clonazepam, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide may have some efficacy for initial monotherapy of newly diagnosed or untreated juvenile myoclonic epilepsy in children.[28]
  - The role of clorazepate in the management of epilepsy is not described within the current consensus guidelines.[23-30]
  - Clobazam is recognized as an effective treatment in various types of seizures, usually for use in refractory disease when first-line treatments are ineffective or not tolerated. For the treatment of Lennox-Gastaut specifically, sodium valproate should be offered first-line, with lamotrigine offered as adjunctive therapy if sodium valproate is ineffective or not tolerated.[23]
  - For patients with convulsive or non-convulsive status epilepticus diazepam is recommended if lorazepam or intravenous access is unavailable.[29-30]
- Other Key Facts:
  - Clobazam, while being approved in Europe for many years, was only recently approved by the FDA in October, 2011.[31]
  - Clonazepam, clorazepate and diazepam are available generically. Clobazam is currently a branded product.[11]
  - The metabolism of these agents is complex with extensive cytochrome P450 isoenzyme involvement, and the importance of the interaction is dependent on whether the offending drugs are inducers or inhibitors of this enzyme system.[1-5]

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Therapeutic Class Review
Anticonvulsants-Benzodiazepines

Overview/Summary

The benzodiazepines have been a mainstay in the pharmacologic management of epilepsy since their development in the 1960's. Of the various benzodiazepines available, the four agents currently Food and Drug Administration (FDA)-approved for the treatment of seizure disorders are clobazam (ONFI®), clonazepam (Klonopin®), clorazepate (Tranxene-T®) and diazepam (Valium®, Diastat®).[1-5] The primary advantages of benzodiazepines as anticonvulsants are their high efficacy rates, quick onset of action and minimal toxicity relative to other available anticonvulsants. The precise mechanism by which the benzodiazepines exert their antiepileptic and anxiolytic effects is unknown, although it is believed to be related to their ability to enhance the activity of gamma aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Specifically, benzodiazepines bind to the $GABA_A$ receptor subtype, but are not a substitute for GABA. They allosterically bind to the receptor at a different location than GABA and enhance the chloride channel's conductance by increasing the frequency of gated channel opening.[6-8] Although the benzodiazepines are FDA-approved for various other indications including symptomatic management of acute alcohol withdrawal, anxiety disorders and muscle spasms, the focus of this review will be on their use in the management of epilepsy.[9]

Seizure disorders may be classified by electroencephalogram recordings and clinical symptoms into two main categories–generalized seizures and partial seizures. Generalized seizures involve both hemispheres of the brain, and result in a loss of consciousness. Generalized seizures are further subdivided into absence (petit mal), atonic, clonic, myoclonic, tonic, and tonic-clonic (grand mal) seizures and infantile spasms. Partial (focal) seizures originate in one hemisphere and result in an asymmetric motor manifestation (unless they proceed to secondarily generalized). Partial seizures without a loss of consciousness are classified as simple partial, while an alteration of consciousness is classified as complex partial. Complex partial seizures can progress to generalized tonic-clonic seizures. In addition to classification by seizure type, epilepsies can be classified by syndromes that may encompass one or many different seizure types (e.g., Lennox-Gastaut syndrome).[10]

These agents and their respective FDA-approved are listed in Table 2. Clobazam, while being approved in Europe for many years, was only recently approved by the FDA in October, 2011.[11] Clobazam may be associated with less sedation compared to the other benzodiazepines.[12] Clonazepam is used to treat myoclonic, atonic and absence seizures that are resistant to treatment with other antiepileptic drugs. It is generally less effective for absence seizures than ethosuximide or valproate.[13] Clonazepam is unique in that it is approved for use when acute or chronic administration of an anticonvulsant is required. The use of clorazepate is generally limited to refractory partial seizures, and is only indicated as an adjunctive therapy.[13] Diazepam is the standard initial therapy for status epilepticus and is available in oral and rectal formulations. The use of benzodiazepines in the management of epilepsy may be limited by the potential for development of tolerance and decreased sedative or anticonvulsant effects.[13] Clonazepam, clorazepate and diazepam are available generically. Clobazam is currently a branded product. All of the agents are dosed multiple times per day.

The benzodiazepines as a class can be characterized by their pharmacokinetic profiles and duration of action. Clonazepam has an intermediate duration of action (10 to 24 hours), while clobazam, clorazepate and diazepam are considered to be long-acting (>24 hours). Both clorazepate and diazepam are metabolized to the active metabolite desmethyldiazepam, which is primarily responsible for the anticonvulsant effects of both agents. Clobazam undergoes metabolism to N-desmethylclobazam, an active metabolite, while clonazepam does not have any active metabolites despite hepatic metabolism. In cases, where chronic maintenance therapy is required (e.g., epilepsy or anxiety), the long-acting agents are preferred, and as a result of their increased duration of action, effective therapeutic drug concentrations can be maintained. It is important to note that the metabolism of these agents is complex

with extensive cytochrome P450 isoenzyme involvement, and the importance of the interaction is dependent on whether the offending drugs are inducers or inhibitors of this enzyme system.[14]

According recent clinical guidelines for the management of epilepsy by the National Institute for Clinical Excellence, clonazepam may be considered for absence and myoclonic seizures if a patient has failed first-line treatment options and subsequent adjunctive therapy is ineffective or not tolerated. Although clobazam is recommended for various types of seizures within the guidelines, its use in the United Stated is limited to adjunctive therapy in patients with Lennox–Gastaut syndrome. The role of clorazepate is not defined within the currently available guidelines. For patients with convulsive or non-convulsive status epilepticus diazepam is recommended if intravenous access or lorazepam is unavailable.[15-22]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Products		
Clobazam (ONFI®)	Benzodiazepine	-
Clonazepam (Klonopin®, Klonopin® Wafers)	Benzodiazepine	✔
Clorazepate (Tranxene-T®)	Benzodiazepine	✔
Diazepam (Diastat AcuDial®, Diastat Pediatric®, Valium®)	Benzodiazepine	✔

Indications

Table 2. Food and Drug Administration Approved Indications[1-5,23,24]

Generic Name	Clobazam	Clonazepam	Clorazepate	Diazepam
Single-Entity Product				
Absence seizures (petit mal)		✔ ‡		
Adjunctive use in convulsive disorders				✔ §
Akinetic seizures		✔ †		
Myoclonic seizures		✔ †		
Partial seizures			✔ ‖	
Relief of skeletal muscle spasms				✔ ¶
Seizures associated with Lennox-Gastaut syndrome	✔ *	✔ †		
Short-term management of anxiety disorders			✔	✔
Symptomatic relief of acute alcohol withdrawal			✔	✔
Treatment of panic disorder with or without agoraphobia		✔		

*As adjunctive therapy in patients two years of age and older
†Alone or as an adjunct therapy
‡ Clonazepam may be useful for patients with petit mal (absence) seizures who have failed to respond to succinimide anticonvulsants.
§ Diazepam rectal gel is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity.
‖ As adjunctive therapy
¶ Due to reflex spasm to local pathology (such as inflammation of the muscles or joints or secondary to trauma), spasticity causes by upper motor neuron disorders (such as cerebral palsy and paraplegia), athetosis and stiff-man syndrome

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,23,24]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Clobazam	89	82	N-desmethylclobazam	36 to 42
Clonazepam	90	<2	None	30 to 40
Clorazepate	91	62 to 67	Nordiazepam	2.29 to 48†
Diazepam	98 (oral)*	75	N-desmethyldiazepam, N-methyloxazepam, oxazepam	20 to 54

*The absolute bioavailability of diazepam rectal gel to diazepam injectable is 90%. The absolute bioavailability of diazepam injectable emulsion compared to intravenous injection of diazepam is 93%.
† The elimination half-life of clorazepate is approximately 2.29 hours; however, nordiazepam, an active metabolite primarily responsible for the anticonvulsant properties of clorazepate has a half-life of approximately 48 hours.

Clinical Trials

The clinical studies demonstrating the safety and efficacy of the benzodiazepines in the management of epilepsy are outlined in Table 4.[25-49]

In a double-blind, randomized controlled study (N=238), clobazam was compared to placebo in patients two to 60 years of age with Lennox-Gastaut syndrome. Following 12 weeks of treatment with clobazam, all three doses (0.25, 0.5 and 1.0 mg/kg) significantly decreased the weekly drop seizure rates compared to placebo (-41.2 to -68.3 vs -12.0%; *P*<0.0001 for all). In addition, weekly total (drop and non-drop) and non-drop seizure rates decreased with clobazam. Patients receiving clobazam also experienced higher responder rates (≥50% decrease in average weekly seizure rate) compared to patients receiving placebo (58.6 to 77.6 vs 31.6%; *P*<0.0001). The proportions of patients who were at least minimally improved ranged from 71.2 to 80.7% (physicians' assessment) and 79.2 to 81.6% (caregivers' assessment) with clobazam compared to 47.3 and 45.5% with placebo. Adverse events that were noted to have occurred with ≥10% difference between placebo and clobazam were somnolence, pyrexia, lethargy, drooling, and constipation.[25]

In a second study by Conry et al (N=68), the number of drop seizures per week was significantly reduced from baseline for patients receiving low-dose and high-dose clobazam (*P*=0.0162 and *P*<0.0001, respectively). The mean drop seizure rate was reduced from baseline in both clobazam treatment groups. The reduction in drop seizure rates was significantly greater in the high-dose group compared to the low-dose group (*P*=0.0001). A significantly greater proportion of patients treated with high-dose clobazam compared to the low-dose group experienced a reduction from baseline in weekly drop seizure rates of ≥25% (89 vs 56%; *P*=0.0025), ≥50% (83 vs 38%; *P*=0.0001) and ≥75% (67 vs 25%; *P*=0.0006). There was no difference between groups with regard to the proportion of seizure-free patients (*P*=0.0629).[26]

The available literature suggests that clorazepate may be effective for various types of epileptic seizures. In one study, Booker and colleagues reported that generalized minor motor seizures, including absence, akinetic seizure, and myoclonic seizure, were responsive to clorazepate although generalized tonic-clonic seizures were less responsive. Of eight patients with generalized seizures, six were controlled following clorazepate therapy. For patients with a response to clorazepate (N=20), 12 of these patients experienced symptomatic improvements in alertness and attention spans following clorazepate treatment.[29] In a small crossover study by Troupin et al (N=8) four patients with major generalized seizures experienced improvements in seizure frequency while receiving clorazepate treatment compared to phenobarbital over four months. In addition, all patients subjectively reported increased alertness following a switch from phenobarbital to clorazepate.[30] In a similar study, there was a trend towards improved control of partial elementary seizures for patients receiving clorazepate compared to phenobarbital (difference, -8; 95% CI, -23.9 to 3.5) as well as those with partial complex seizures (difference, -6; 95% CI, -3.9 to 0.4). Significantly more patients preferred treatment with clorazepate over

phenobarbital (*P*<0.01). Overall, patients reported significantly less subjective (*P*<0.01) and objective toxicity (*P*<0.05) with clorazepate compared to phenobarbital.[31]

In patients with Lennox-Gastaut syndrome or infantile spasms, clonazepam was effective at improving or controlling seizure activity in eight of 37 patients in one study. Moreover, after six months, six of the eight patients remained seizure-free and two others experienced significantly fewer seizures compared to baseline. Temporary remission in seizure activity occurred in six patients, while seven other patients achieved lasting improvements in seizure activity with the addition of adrenocorticotropic hormone due to a suboptimal response to clonazepam.[34] In an open-label study of patients diagnosed with progressive myoclonic epilepsy (N=26), clonazepam plus valproate sodium significantly improved median scores for myoclonus, general performance, and locomotor ability compared to baseline values (*P*<0.001 for all). In addition, speech was significantly improved in these patients after four months of treatment. Combination treatment, however, did not improve scores for grand mal seizures, or alertness.[35] Bensch et al reported 14 of 20 children with treatment-resistant epilepsy who received clonazepam experienced a lower mean number of seizures compared to placebo in short-term crossover study (*P*<0.05). In patients with absence seizures who continued to experience frequent seizures despite anticonvulsant therapy, the addition of clonazepam significantly reduced seizure frequency compared to the addition of placebo (*P*<0.05). Of the patients in the study (N=20), eight became seizure-free with clonazepam therapy, while one other patient experienced a 75% reduction in seizure frequency compared to baseline.[36] Clonazepam was compared to carbamazepine in patients who were recently diagnosed with psychomotor epilepsy. Over three years of treatment, both clonazepam and carbamazepine significantly reduced seizure frequency compared to baseline (*P*<0.05 for both). Furthermore, for patients receiving treatment for at least one month, there was no significant difference in seizure frequency between the treatments (difference, 0.2; 95% CI, -0.3 to 0.4).[39]

Diazepam is a well established treatment for the emergency management of status epilepticus. Pavlidou et al reported significantly lower rates of status epilepticus recurrence for patients who received rectal diazepam compared to those who did not receive treatment (38 vs 83%; *P*=0.005).[40] In patients with acute repetitive seizures classified as primary generalized or complex partial, the administration of rectal diazepam was associated with significantly fewer seizures following administration (0 vs 2; *P*=0.029). Moreover a higher proportion of patients treated with diazepam were seizure-free 12 hours following administration compared to placebo (55 vs 34%; *P*=0.031), and also experienced a significantly prolonged time to the next seizure (*P*=0.007).[41] Dreifuss et al reported that for patients with complex partial or generalized seizures, despite being on a stable anticonvulsant regimen for at least four weeks, the administration of rectal diazepam significantly reduced post-administration seizure frequency and improved the caregiver's assessment of the treatment outcome compared to placebo (*P*<0.001 for both).[42] In a subanalysis, children experienced significantly fewer seizures (0.00 vs 0.25; *P*=0.001) and were more likely to be seizure-free 12 hours following administration with diazepam compared to placebo (59 vs 31%; *P*=0.001).[43] Cereghino reported similar results in a subanalysis of adults, with significantly lower seizure frequency (0.00 vs 0.13; *P*=0.001) more seizure-free patients in the diazepam treatment group (71 vs 28%; *P*<0.001).[44]

In a study of adult patients with out-of-hospital status epilepticus lasting longer than five minutes, significantly more seizures were terminated by arrival at the emergency department following treatment with lorazepam or diazepam compared to placebo (59.1 and 42.6 vs 21.1%, respectively; *P*=0.001). There was no difference in likelihood of seizure termination at arrival between lorazepam and diazepam treatments (OR, 1.9; 95%, 0.9 to 4.3).[47] In a study by Treiman et al (N=518), adults with overt or subtle generalized convulsive status epilepticus, treatment was significantly more effective with lorazepam (64.9%) phenobarbital (58.2%), diazepam/phenytoin (55.8%) compared to phenytoin alone (43.6%; *P*<0.02). For subtle status epilepticus, no significant differences were demonstrated between treatment groups (*P*<0.18).[49]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Seizure disorders				
Ng et al[25] CONTAIN Clobazam 0.25 mg/kg/day vs clobazam 0.5 mg/kg/day vs clobazam 1 mg/kg/day vs placebo	DB, MC, PC, PG, RCT Patients 2 to 60 years of age, weighing ≥12.5 kg, and an onset of LGS before 11 years of age	N=238 12 weeks	Primary: Change in baseline weekly drop seizure rate Secondary: Change in baseline weekly non-drop and total seizure rates, responder rate, physicians' and caregivers' global assessments and safety	Primary: All doses of clobazam significantly decreased the weekly drop seizure rate compared to placebo (-41.2%; *P*=0.0120, -49.4%; *P*=0.0015, and -68.3%; *P*<0.0001 vs -12.1%). There was a linear trend (*P*<0.0001) of increasing efficacy with increasing clobazam dosage. Secondary: Weekly rates of non-drop seizures increased by 76.3, 53.3 and 3.3% with placebo, clobazam 0.25 mg/kg/day and clobazam 0.5 mg/kg/day, but decreased by -40.0% with clobazam 1 mg/kg/day (differences were not significant; *P* values not reported). All doses of clobazam significantly decreased the weekly total (drop and non-drop) seizure rate compared to placebo (-34.8%; *P*=0.0414, -45.3%; *P*=0.0044, and -65.3%; *P*<0.0001 vs 9.3%). Responder rates increased with increasing clobazam dosages. Patients with ≥50% decrease in weekly seizure rate were 31.6% with placebo compared to 43.4 (*P*=0.3383), 58.6 (*P*=0.0159), and 77.6% (*P*<0.0001) with clobazam 0.25, 0.5 and 1 mg/kg/day. The likelihood of achieving ≥50% decrease was significantly greater with clobazam 0.5 mg/kg/day (medium-dose) compared to placebo (OR, 2.8; 95% CI, 3.0 to 18.5; *P*<0.0001). Physician and caregiver assessments indicated that clobazam significantly improved symptoms at all doses. The proportions of patients who were at least minimally improved ranged from 71.2 to 80.7% (physicians' assessment) and 79.2 to 81.6% (caregivers' assessment) with clobazam compared to 47.3 and 45.5% with placebo. The proportions of patients experiencing at least one adverse event were 67.8, 72.4, 88.7 and 76.3% with placebo, clobazam 0.25 mg/kg/day, clobazam 0.5 mg/kg/day, and clobazam 1 mg/kg/day.

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				Adverse events that were noted to have occurred with ≥10% difference between placebo and any clobazam dose were somnolence, pyrexia, lethargy, drooling, and constipation.
Conry et al[26] clobazam 0.25 mg/kg/day vs clobazam 0.5 mg/kg/day	Phase II, DB, DR, MC, RCT Patients with LGS who weighed >12.5 kg and were diagnosed before the age of 11; currently experiencing greater than one type of generalized seizure (including drop seizures [atonic, tonic, or myoclonic])] for ≥6 months, despite stable antiepileptic drug regimen	N=68 14 weeks	Primary: Reduction in drop seizure rates from baseline Secondary: Proportion of patients considered treatment responders (≥25%, ≥50%, ≥75% and 100% reduction in drop seizures), number of patients with decreases in the number of non-drop seizures, responses on the investigator and parent/caregiver global evaluation and safety	Primary: The number of drop seizures per week was reduced from baseline in both the low- and high-dose clobazam treatment groups (from 5 to 661 to 0 to 470 drop seizures in the low dose group and from 8 to 924 to 0 to 198 drop seizures per week in the high-dose group). The mean drop seizure rate was reduced from in the low-dose (from 141 ± 188 to 91 ± 122 drop seizures per week) and high-dose clobazam treatment groups (from 207 ±229 to 32 ± 57 drop seizures per week). The percent reduction in drop seizures from baseline was statistically significant in both the low-dose (P=0.0162) and high-dose clobazam groups (P<0.0001). The reduction in drop seizure rates was significantly greater in the high-dose clobazam group compared to the low-dose group (P=0.0001). Secondary: There was a significantly greater number of patients in the high-dose clobazam group compared to the low-dose group that experienced a reduction in weekly drop seizure rates of ≥25% (89 vs 56%; P=0.0025), ≥50% (83 vs 38%; P=0.0001) and ≥75% (67 vs 25%; P=0.0006) from baseline. More patients in the high-dose clobazam group remained seizure-free compared to the low-dose group; however, the between-group difference was not significant (22 vs 6%; P=0.0629). There was a statistically significant reduction in non-drop seizures in the high-dose clobazam treatment group (P<0.0001); however, the difference in the low-dose group was not significantly different from baseline (P=0.1466). Moreover, the reduction in non-drop seizure rates was significantly greater in the high-dose group compared to the low-dose group (P =0.0222). Results from the parent/caregiver global evaluations demonstrated that

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				patients in the high-dose clobazam group were more likely to show significant improvements in overall symptoms compared to the low-dose group. In total, 94% of patients in the high-dose group and 55% of patients in the low-dose group were "much improved" or "very much improved" by week three compared to baseline. At week seven these percentages increased in the high-dose group and decreased in the low-dose group. The results of the investigator global evaluation were similar to the caregiver evaluations. The high-dose group had a greater proportion of patients considered to be "much improved" or "very much" improved at week three (*P*=0.0001) and week seven (*P*<0.0001) compared to the low-dose clobazam group. Adverse events experienced by ≥5% of patients included somnolence, lethargy, sedation, salivary hypersecretion, constipation, aggression, hypomania and insomnia. The incidence of treatment-emergent adverse events was similar between the low-dose group (84%) and the high-dose group (86%). The low- and high-dose groups experienced a similar in incidence of mild (47 vs 44%), moderate (34 vs 36%) and severe (3 vs 6%) adverse events.
Naidu et al[27] Clorazepate 3.75 mg BID All patients also received valproate or carbamazepine except in cases where a parent refused treatment.	OL, PRO Children with intractable seizures that were not responsive to conventional antiepileptic drugs	N=11 1 year	Primary: Frequency of seizures, EEG activity, serum levels and adverse events Secondary: Not reported	Primary: The frequency of seizures was decreased in all patients following the addition of clorazepate to valproate or carbamazepine (*P* value not reported). Follow-up EEGs documented decreases in interictal and ictal epileptiform activity in all patients following the addition of clorazepate therapy. One patient showed no epileptiform activity on follow up. "Excellent" seizure control was achieved in children who received clorazepate as monotherapy due to parental refusal to administer valproate or carbamazepine. "Good" seizure control was achieved with serum levels considered to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				be at or near the lower limit of the therapeutic range (0.5 to 1.5 µg/ml). The beneficial effect of subtherapeutic levels of clorazepate could not be attributed to changes in valproate levels prior to or during clorazepate therapy. Few adverse events occurred in patients receiving clorazepate, with the exception of unsteadiness. No significant toxicity was reported. Secondary: Not reported
Fujii et al[28] Clorazepate 0.31 mg/kg/day divided QD to TID and titrated to seizure control	OL, PRO Patients with partial seizures, secondary generalized seizures or unclassified seizures occurring more than once weekly that were refractory to conventional antiepileptic drugs	N=31 2 years	Primary: Response to therapy and adverse events Secondary: Not reported	Nine patients with partial epilepsy (50% of enrolled patients with partial seizures) responded to clorazepate therapy, and of these, four patients (22.2%) showed an “excellent” response. Only two patients with Lennox syndrome (22.2% of enrolled patients with Lennox syndrome) and none with West syndrome showed improvement. Despite experiencing a response, the patients with Lennox syndrome did not experience an “excellent” response. One patient with undetermined generalized epilepsy had daily seizures prior to clorazepate therapy, but seizures ceased following the addition of clorazepate. After a period of one month, the seizures reappeared and could not be controlled by increasing the dose of clorazepate. Three patients with partial epilepsy who were non-responders to clorazepate also experienced an initial transient decrease in seizure frequency, which lasted from five weeks to three months. Once seizure frequency increased again, seizures could not be controlled by increasing clorazepate doses. Generalized tonic-clonic seizure was the most responsive to clorazepate therapy, followed by simple partial seizure, tonic seizure, complex partial seizure, atonic seizure and atypical absence. No severe adverse effects were reported. Fourteen patients (45%) complained of drowsiness; however, the drowsiness spontaneously

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				resolved in eight of these patients. Five patients complained of drowsiness before anticonvulsive effects were achieved, and the clorazepate dose could not be increased to an effective level. Secondary: Not reported
Booker et al[29] Clorazepate 0.4 to 2.0 mg/kg/day divided QD to QID Clorazepate was added to the patient's current antiepileptic treatment regimen.	OL, PRO Patients with persistent, frequent seizures (major generalized, absence, akinetic, myoclonic, infantile spasms focal motor and psychomotor) that occurred despite treatment with standard epileptic drugs	N=59 3 months	Primary: Response to treatment and adverse events Secondary: Not reported	Primary: Twenty one patients were considered to have an "excellent" response to treatment. In patients with an "excellent" response, the mean serum concentration of the active metabolite N-desmethyldiazepam was 1.21 µg/mL. A total of eight subjects in this group had major generalized seizure attacks. Three were completely controlled prior to the study. Three of the remaining five subjects experienced control in response to clorazepate. An "excellent" response occurred in seven patients with absence seizures, four patients with myoclonic seizures, three each in patients with major generalized and akinetic seizures and two each in patients with infantile spasms and focal motor seizures. Twelve of the 20 patients experienced significant improvement in alertness and attention span. Improvement generally occurred within the first two to three weeks of treatment and was associated with a significant decrease in seizures. Three patients reported improvements in educational performance. Two other patients returned to school after previously being limited to home-bound education. Two patients suffering from akinetic attacks responded to treatment enough that that they could walk unsupported. Four subjects experienced a "partial" response. One experienced a 50% reduction in myoclonic attacks, but this did not result in any improvement in social or vocational performance. One patient experienced a 50% reduction in akinetic attacks, but the required dose caused sedation and ataxia.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Thirty five patients were considered non-responders. Three patients had an increase in the number of major generalized seizures while taking clorazepate and four complained of excessive sedation. The remaining 28 patients experienced no decrease in seizure frequency. Secondary: Not reported
Troupin et al[30] Clorazepate 0.3 mg/kg divided BID and titrated to seizure control or intolerance vs phenobarbital 1.9 to 2.1 mg/kg daily All patients received phenytoin throughout the study period, and all patients received phenobarbital for the first two months prior to randomization.	OL, PRO, XO Patient 18 years of age or older with more than four major generalized seizures of focal origin or more than four major generalized seizures per month	N=8 14 months (2 month lead-in with phenobarbital; 4 month XO for each treatment followed by 4 months phenytoin monotherapy)	Primary: Seizure frequency, adverse events and drug levels Secondary: Not reported	Primary: Four of eight patients had fewer seizures while taking clorazepate, with an average reduction in seizure frequency of 30% (*P* value not reported). Three of the four patients who experienced fewer seizures with phenobarbital treatment had a higher phenobarbital level during the study block compared to their baseline level. Two of the patients who had their lowest monthly seizure frequency while taking clorazepate had higher phenytoin levels during the clorazepate block compared to their baseline phenytoin levels. During the final block with phenytoin monotherapy, three patients had as few or fewer seizures compared to the seizure frequency with the addition of clorazepate or phenobarbital. The remaining three had a modest increase in seizures during this time period. Five patients did not experience any adverse events for the entire 10 months of active treatment with clorazepate and phenobarbital. During the clorazepate treatment period, three patients had objective adverse events consistent with increased phenytoin levels (ataxia and mental dulling). Two patients during the phenobarbital study block, experienced prominent sleepiness related to the phenobarbital, and one experienced ataxia related to high phenytoin levels with low phenobarbital levels. All patients subjectively reported an increase in alertness following a switch to clorazepate from phenobarbital. Most also complained spontaneously of a decrease in alertness but without actual sleepiness following return to phenobarbital. The increase in alertness during the clorazepate block was confirmed by reports from relatives and caregivers.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in the mean serum levels for patients whose seizure frequency was lower during the clorazepate block and those with fewer seizures during the phenobarbital block. Secondary: Not reported
Wilensky et al[31] Clorazepate up to 90 mg daily plus phenytoin daily (frequency not specified) vs phenobarbital up to 300 mg daily plus phenytoin daily (frequency not specified) All patients received phenytoin throughout the study period. All patients received phenobarbital for the first two months before randomization.	DB, PRO, XO Patients 18 years of age or older experiencing four or more partial seizures per month (simple or complex, with or without secondary generalization); subjects must have been on a stable antiepileptic drug regimen as shown by therapeutic drug levels	N=55 10 months (2 month lead-in with phenobarbital; 4 month XO for each treatment)	Primary: Patient drug preference, seizure frequency, toxicity and neuropsycho-logic results Secondary: Not reported	Primary: A significantly higher number of patients preferred treatment with clorazepate over phenobarbital (31 vs 12; *P*<0.01). Of patients with complex partial or secondary generalized seizures, 20 of 26 patients preferred to receive clorazepate treatment (*P*<0.01). Nine of 11 patients with partial seizures preferred clorazepate, while four of six patients with elementary partial seizures preferred phenobarbital (*P* values not reported). There was a trend towards a lower total number of seizures with clorazepate compared to phenobarbital (median difference, -6.5; 95% CI, -4.0 to 0.4). Similarly, there was a trend towards a lower number of seizures per month with clorazepate compared to placebo with regard to partial elementary seizures (median difference, -8; 95% CI, -23.9 to 3.5), partial complex seizures (median difference, -6; 95% CI, -3.9 to 0.4) but not for secondary generalized seizures (median difference, 0.4; 95% CI, -0.1 to 0.6). The objective signs of toxicity included nystagmus with or without diplopia, gait disturbance, coordination problems, speech difficulties and mental status changes. Subjective toxicity symptoms included mental status changes (memory problems, nervousness, depression, irritability and concentration difficulties), drowsiness, unsteadiness, visual problems, dizziness/drunk, sexual dysfunction and bloating. Overall, clorazepate was associated with significantly less toxicity on subjective (*P*<0.01) and objective symptoms (*P*<0.05) compared to phenobarbital. The results of the Wechsler Memory Scale (logical memory) test

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				favored treatment with phenobarbital, while the Stroop I and the Marching Test (bilateral) was better performed with clorazepate treatment. A fourth test, the Auditory Vigilance Test (errors), also showed a statistically significant difference favoring clorazepate (*P*<0.05 for all). Secondary: Not reported
Dasheiff et al[32] Clorazepate 15 to 120 mg daily (frequency not specified) vs methsuximide 600 to 2,700 mg daily (frequency not specified)* vs valproate 500 to 4,000 mg daily (frequency not specified) Patients usually remained on at least one of the first-line antiepileptic drugs	OL, PRO Patients with complex partial epilepsy with or without secondary generalization, with or without simple partial seizures ("auras"), and who had failed phenytoin, carbamazepine and phenobarbital	N=66 3 years	Primary: Change in seizure frequency, number of patients who were seizure-free and safety Secondary: Not reported	Primary: The seizure frequency was determined to be decreased in six eight and fifteen patients treated with clorazepate, methsuximide and valproate, respectively. None of the anticonvulsant treatments were shown to reduce seizure frequency during treatment compared to baseline values (*P*>0.05 for all). Seven patients tolerated the medications and became seizure-free for up to six months with treatment (three patients each in the clorazepate and valproate groups and one patient receiving methsuximide). Only the patient receiving clorazepate was seizure-free at one year. The most frequently reported adverse events were gastrointestinal in nature, followed by mental status changes and problems with coordination. Valproate produced various adverse events including nausea, dysphagia, weight gain, or weight loss but significant elevation of liver function tests occurred only once and were reversible. Secondary: Not reported
Nanda et al[33] Clonazepam up to 3 mg	2 OL, PRO Patients aged 11	N=30 and N=36	Primary: Improvements in seizure	Primary: In the initial double-blind study, 12 of 15 patients with frequent myoclonic jerks (12 of whom also had tonic-clonic seizures),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily divided BID	to 40 with epilepsy were included in a one-year open label extension study following nine weeks of double-blind treatment with clonazepam or placebo In the second open-label study patients were aged 11 to 44 with a diagnosis epilepsy who were taking a combination of phenytoin, phenobarbitone and primidone	12 and 16 months	frequency and adverse events Secondary: Not reported	experienced a reduction in seizure frequency and myoclonic jerks by 100%. Three patients had reductions of 80%. Tonic-clonic seizures were ceased in eight patients and four other patients experienced a reduction of seizures of 50%. The effectiveness of clonazepam therapy in the patients who improved was maintained for the following year. In the present open-label study, the clonazepam dose was increased to maintain effectiveness in four patients. Four patients were able to reduce the doses of their other anticonvulsants or stop therapy altogether while taking clonazepam. In the double-blind trial four patients had atypical absences with tonic-clonic seizures, of which, clonazepam reduced seizure frequency by 100% in three of these patients. In the other patient, clonazepam had no effect on seizure frequency. Two of the three patients with absence seizures were still benefiting from clonazepam throughout the one-year open-label study. Eleven patients in the double-blind trial experienced focal attacks and tonic-clonic seizures. Only four patients experienced a 50% reduction in tonic-clonic seizures during double-blind treatment with clonazepam, and only two patients continued to experience a 50% improvement one year later. In the second (16 month) open-label study, seven patients with myoclonic epilepsy and tonic-clonic seizures experienced a 100% reduction in seizure activity and were seizure-free at one year. Of seven patients with photosensitive epilepsy, six experienced a cessation of seizures and the seventh patient experienced a reduction in seizures of 80%. In patients with only tonic-clonic seizures, clonazepam was less effective, as only two of six patients experienced an improvement of 50%, while one patient had improvements of less than 50% and one other patient experienced worsening of seizures on clonazepam. Sixteen patients with frontotemporal epilepsy received clonazepam

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				although only nine patients experienced a reduction in attacks of 50% and continued to remain on the drug. Drowsiness was reported in 66% of patients within the first week of clonazepam treatment, but generally improved after the first week. After week one, only six patients (all in the open-label trial) continued to experience drowsiness. These patients were also ataxic, with hypotonicity of trunk and lower limb muscles. One patient in the open-label trial became depressed while on clonazepam. A change of personality, with irritability and violent behavior was reported in one patient. After one year, no patients on treatment (45 patients) complained of any side effects. Secondary: Not reported
Vasella et al[34] Clonazepam 0.1 mg/kg divided TID or QID and titrated weekly until seizures were controlled on until a dose of 0.3 mg/kg was reached	PRO Infants and children with infantile spasms or Lennox-Gastaut syndrome.	N=37 Up to 16 months	Primary: Response to treatment and adverse events Secondary: Not reported	Primary: Seizures were considerably improved or completely controlled in eight patients treated with clonazepam (five patients with infantile spasms and three with Lennox-Gastaut). Spasms ceased within one to two weeks in three patients by the third week of treatment in one patient. After six months of treatment, six patients remained seizure-free and two patients had significantly fewer seizures. Improvement in the EEG was observed in four of these patients, while four patients had transient or no improvements in EEG. Temporary remission of seizures occurred in six patients (three with infantile spasms and three with Lennox-Gastaut) treated with clonazepam. Seizures disappeared within two to four weeks in five patients but reoccurred within three weeks to seven months. In the other patient the number of seizures was reduced for one year. Seven patients received ACTH in addition to clonazepam and achieved lasting improvements. Five patients received ACTH because seizures recurred despite a good initial response to clonazepam therapy. Two of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				these patients received ACTH because clonazepam did not sufficiently improve seizures. Five patients receiving ACTH in addition to clonazepam remained seizure-free for 1 to 17 months following therapy. Six of the seven patients who received ACTH had marked improvements in their EEGs. Five patients received ACTH one to four weeks after clonazepam was started and achieved a temporary response to treatment. In four patients, seizures disappeared initially but recurred in less than eight months despite continued clonazepam therapy. Improvement in the EEG was less marked than in the group with lasting improvement after ACTH. Eight patients experienced minimal or no change in seizure activity, despite clonazepam treatment. One or more adverse events were reported in 19 patients treated with clonazepam, with the most common being mucous obstruction of nasopharynx, increased salivation and difficulty swallowing (eight patients). Other adverse events included drowsiness (five patients), constipation (three patients), ataxia (three patients), muscular weakness and hypotonia (two patients) and hyperexcitability (one patient). Secondary: Not reported
Iivanainen et al[35] Clonazepam 1 mg daily plus valproate sodium 300 mg daily both divided BID Clonazepam was titrated to a maximum of 6 to 10 mg daily and valproate	OL, PRO Patients with 18 years of age or older with progressive myoclonic epilepsy who did not benefit from	N=26 Up to 72 months	Primary: Change from baseline scores for grand mal seizures, myoclonus, locomotion, general performance,	Primary: After four months of treatment with clonazepam and valproate sodium, mean clinical variable scores were significantly improved for myoclonus (P<0.001), general performance (P<0.001), locomotor ability (P<0.01) and speech (P<0.05). Scores for alertness and grand mal seizures improved; however, the difference was not statistically significant (P=NS). The most dramatic improvement occurred in locomotor ability. Five patients "learned" to walk again during the new therapy after being bedridden for three to five years.

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was titrate to a maximum dose of 1500 to 1800 mg daily.	treatment with combinations of phenytoin, carbamazepine, phenobarbital, primidone and diazepam		speech, alertness and adverse events Secondary: Not reported	At the 72 month evaluation (N=19), median clinical scores remained significantly improved compared to baseline values for myoclonus (*P*<0.01), locomotion (*P*<0.05), and general performance (*P*<0.05). Although improved compared to baseline values, scores for grand mal seizures and speech were not significantly different after 72 months (*P*=NS). Fourteen patients reported mild fatigue and slight vertigo following the initiation of clonazepam. All adverse events were temporary and there were no abnormalities in the results of blood and urine tests during the study that were attributed to the medication. Secondary: Not reported
Bensch et al[36] Clonazepam up to 0.25 mg/kg divided BID or TID vs placebo The maximum dose was 10 mg daily. Clonazepam was administered in addition to the patient's background anticonvulsant therapy that remained unchanged through the evaluation period.	DB, MC, PRO, XO Children of all ages with all types of seizures who had tried all available antiepileptic drugs and continued to experience at least one fit per week	N=20 2 months	Primary: Improvements in seizure frequency, patient preference, percentage reduction in seizure frequency and adverse events Secondary: Not reported	Primary: Clonazepam was determined to be significantly more effective than placebo in reducing seizure frequency in 14 patients compared to four patients who experienced greater seizure improvements with placebo (*P*<0.05). In the remaining two cases there was no difference in seizure frequency between clonazepam and placebo. There was no difference in patient/caregiver treatment preference between clonazepam and placebo with 12 cases preferring clonazepam over placebo, while eight patients preferred placebo over clonazepam (*P*=NS). Compared to baseline, significantly more patients experienced a decrease in seizure frequency when treated with clonazepam compared to placebo (9 vs 3 and 7 vs 4 in both crossover periods, respectively; *P*<0.05 for both). Five patients were seizure-free following clonazepam treatment, while five others experienced at least a 75% reduction in seizure frequency and three had reductions of more than 50%. Two patients were

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				seizure-free when receiving placebo, while one patient had a reduction of more than 75% and two had a reduction of more than 50%. Adverse events were reported during the clonazepam period by 18 of 20 parents of patients completing the trial. Only sleep disorder was reported during the placebo period. The most common adverse events were tiredness, vertigo and psychiatric disturbances, mainly aggressiveness. Five patients withdrew from the study due to adverse events. Secondary: Not reported
Dahlin et al[37] Clonazepam 0.02 mg/kg intramuscular injection* vs placebo A single-blind pilot study (N=6) was conducted over three consecutive 24-hour periods. Following the pilot study, the current study was initiated.	DB, PC, RCT, XO Patients 18 years of age or younger with a diagnosis of epilepsy and frequent epileptiform discharges on routine or sleep EEGs; no changes in antiepileptic drug regimen during the study period	N=10 Duration not reported	Primary: Change in epileptiform activity on EEG Secondary: Not reported	Primary: In the pilot study, epileptiform activity consisted of focal or multifocal spike-and-slow waves in two children and sharp and- slow-wave complexes in two other children, whereas one child had generalized spike-and-slow waves. Compared to placebo, the change from baseline in epileptiform activity was greater with clonazepam treatment (-62 vs 2%; *P* value not reported). In the double-blind study, the epileptiform activity consisted of focal or multifocal spike-and-slow waves in two children and sharp-and-slow wave complexes in six, while two children had generalized spike-and-slow waves. The epileptiform activity appeared as single or a few repetitive discharges in six children and as episodes of repetitive discharges in four. Compared to baseline, treatment with clonazepam was associated with a 69% reduction in EEG epileptiform activity (*P*=0.003). In addition, clonazepam showed a significantly greater reduction in epileptiform activity compared to patients receiving placebo (*P*=0.0015). The pooled results from the pilot study and the double-blind study demonstrated that clonazepam treatment was associated with significantly fewer discharges of epileptiform activity on EEG compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to treatment with placebo (*P*=0.0032). Secondary: Not reported
Mikkelsen et al[38] Clonazepam up to 6 mg daily based on age (frequency not reported) vs placebo Patients less than six years of age received a 0.25% clonazepam solution or placebo.	SB, XO Patients who experienced at least six seizures every four weeks in spite of adequate traditional treatment with antiepileptic drugs	N=20 8 weeks	Primary: Change in seizure frequency, proportion of seizure-free patients and adverse events Secondary: Not reported	Primary: In patients with simple absence seizures (N=10), clonazepam was significantly more effective at reducing seizure frequency compared to placebo (*P*<0.05). Clonazepam was more effective in seven cases, while clonazepam and placebo were equally effective in three cases. During clonazepam treatment, eight patients became seizure-free and one had more than a 75% reduction in the daily number of seizures. The maximal efficacy of treatment was obtained within the first two weeks. No patients developed grand mal seizures during the trial. Nine of ten patients with absence seizures experienced adverse events during treatment with clonazepam, mostly varying degrees of sedation. In four patients, the adverse events of clonazepam subsided within one week. Five patients had lasting side-effects. Of patients with myoclonic atonic epilepsy (N=10), clonazepam was more effective than placebo in seven cases, and treatments were equal in three cases (*P*<0.05). Seven patients became free or nearly free from seizures while receiving clonazepam. The maximum efficacy of clonazepam was obtained within the first three weeks. One patient with concomitant grand mal epilepsy had no change in seizure frequency with clonazepam. Five patients reported no side-effects with clonazepam, while two had transient and three had lasting adverse events. Most consisted of varying degrees of sedation. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Mikkelsen et al[39] Clonazepam 6 mg divided TID vs carbamazepine 900 mg divided TID In patients <18 years of age and with a body weight of less <60 kg, carbamazepine was administered at a dose corresponding to 15 mg/kg.	DB, RCT Previously untreated patients with recently diagnosed psychomotor epilepsy	N=36 6 months	Primary: Changes in seizure frequency, proportion of seizure-free patients at six months, adverse events and serum levels Secondary: Not reported	Primary: Both clonazepam and carbamazepine were associated with significant reductions from baseline in seizure activity (*P*<0.01); however, no difference were reported between the two treatments (*P*>0.10). For patients receiving treatment for at least one month, the number monthly seizures was 0.2 for carbamazepine and zero for clonazepam (difference, 0.2; 95% CI, -0.3 to 0.4). The proportion of seizure-free patients during the six months of treatment was 49% of those treated with carbamazepine and 46% on clonazepam (*P* value not reported). Only one patient did not experience adverse events during treatment. Overall, adverse events were brief and no differences were observed between the two groups with regard to sedation, headache, dizziness, impaired memory, marital relations, irritability or complaints (*P*>0.05). Carbamazepine plasma levels were within the range of 16 to 40 µmoles/L. The plasma clonazepam levels were higher and had greater variations between patients (20 to 685 nmoles/L). Secondary: Not reported
Pavlidou et al[40] Intermittent rectal diazepam 0.33 mg/kg every eight hours (first day) followed by every 12 hours on the next day (maximum 7.5 mg/dose) vs	PRO, R Children aged 6 months to 3 years who experienced a first febrile seizure	N=139 3 years	Primary: Recurrence rates Secondary: Not reported	Primary: The 36-month seizure recurrence rates were significantly higher in high-risk patients who received no treatment compared to patients who received diazepam (83 vs 38%; *P*=0.005). No significant difference in seizure recurrence rate was reported between diazepam and no treatment for children considered intermediate risk (55 vs 35%; *P*=0.341) or low risk (46 vs 33%; *P*=0.412). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
no treatment				
Cereghino et al[41] Diazepam 5 to 20 mg rectally vs placebo	DB, MC, PC, PG, RCT Outpatients or institutionalized patients ≥2 years of age with a history of acute repetitive seizures (primary generalized, complex partial with or without becoming secondarily generalized, or simple partial with a motor component) with at least two seizure episodes within the previous year and at least one seizure in previous six months	N=158 Duration not reported	Primary: Seizure count following drug administration Secondary: Time to next seizure, time elapsed between administration plus 15 minutes to the occurrence of the next seizure within the 12-hour observation period, caregiver and investigator global assessments and safety	Primary: Patients receiving treatment with diazepam experienced fewer post-treatment seizures compared to patients receiving placebo (0 vs 2; *P*=0.029). Secondary: The time to next seizure was significantly prolonged with diazepam administration compared to placebo (*P*=0.007). More patients who received diazepam were seizure-free in the 12-hour post-treatment observation period compared to placebo (55 vs 34%; *P*=0.031). The mean caregiver global assessment score was higher in the diazepam treatment group compared to the placebo group (6.73 vs 5.60; *P*=0.018). Similarly, the mean investigator global assessment score was higher with diazepam compared to the placebo-treated group (7.55 vs 5.57*; P*=0.001). There was a trend toward a higher incidence of adverse events in the diazepam group compared to the placebo group (46 vs 28%); however, the difference was not statistically significant. The most frequently reported adverse events were somnolence, headache and diarrhea. There were no episodes of respiratory depression reported. No changes in laboratory parameters were observed.
Dreifuss et al[42] NINDS Diazepam 0.2 to 0.5 mg/kg rectally	DB, MC, PC, PG, RCT Patient 2 to 60 years of age who	N=125 Duration not reported	Primary: Seizure frequency and global assessment of	Primary: Diazepam was significantly more effective compared to placebo both for reducing seizure frequency and for improving the care giver's global assessment of the treatment outcome (*P*<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. Adults received three doses, one dose at onset, and two more doses four and 12 hours after onset.	weighted ≤100 kg with at least four episodes of acute repetitive seizures during the preceding year and at least one in the preceding three months; despite a stable antiepileptic drug regimen		treatment outcome by the caregiver Secondary: Time to first recurrence of seizures after the initial treatment and safety	The frequency of seizures was significantly lower in children receiving diazepam compared to placebo (*P*<0.001) and for adults receiving diazepam compared to placebo (*P*=0.02). The caregiver's global assessment of treatment outcome was significantly improved for children receiving diazepam compared to placebo (*P*<0.001). No significant difference was reported for global assessment among adults treated with diazepam or placebo (*P*=0.09). Secondary: The time to the first seizure recurrence was significantly prolonged in the diazepam group compared to placebo (*P*<0.001). There were no reports of respiratory difficulty in patients receiving diazepam. Thirty-five patients reported at least one adverse effect, but the difference between the diazepam and placebo groups was not significant (46.7 vs 30.4%, respectively; *P*=0.13).
Kriel et al[43] Diazepam 2.5 to 20 mg rectally (Study 1) or diazepam 5 to 20 mg rectally (Study 2) vs placebo In Study 1, children received a second dose four hours after the initial treatment.	2 DB, PC, PRO, RCT Children 2 to 17 years of age previously enrolled in either the NINDS (Study 1) or Athena Neuroscience study (Study 2) with multiple seizures (complex partial or generalized type [tonic, clonic, tonic-	N=185 Duration not reported	Primary: Seizure frequency, time to next seizure, and caregiver's global evaluation of outcome and safety Secondary: Not reported	Primary: There was a significant reduction in seizure frequency among children administered diazepam compared to placebo (0.00 vs 0.25; *P*=0.001). In addition, significantly more diazepam-treated children remained seizure-free during the 12-hour observation period compared to placebo (59 vs 31%; *P*=0.001). The time to the next seizure was significantly longer in diazepam-treated children compared to children who received placebo (*P*=0.0002). Compared to placebo, children receiving diazepam had greater improvements in the caretaker's global evaluation in Study 1 (*P*<0.001), but not in Study 2 (*P*=0.053). Somnolence was the only adverse event that occurred significantly more frequently in the diazepam group (*P*=0.0095). The most frequently reported adverse events were somnolence, headache,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	clonic, atypical absence, or myoclonic]) despite a stable antiepileptic drug regimen			diarrhea, ataxia, incoordination, skin reactions and rectal pain. There were no reports of respiratory depression in either treatment group. Secondary: Not reported
Cereghino et al[44] Diazepam 2.5 to 20 mg rectally (Study 1) or diazepam 5 to 20 mg rectally (Study 2) vs placebo In Study 1, adults received three doses: at onset, four hours later and 12 hours following initial treatment.	2 DB, PC, PRO, RCT Patients 18 years of age or older previously enrolled in either the NINDS (Study 1) or Athena Neuroscience study (Study 2) with multiple seizures (complex partial or generalized type [tonic, clonic, tonic-clonic, atypical absence, or myoclonic]) despite a stable antiepileptic drug regimen	N=96	Primary: Seizure frequency, time to next seizure, and caregiver's global evaluation of outcome and safety Secondary: Not reported	Primary: The median number of seizures per hour was significantly lower with diazepam administration compared to placebo (0 vs 0.13; *P*=0.001). In addition, a higher proportion of patients in the diazepam group were seizure-free 12 hours following administration compared to the placebo group (71 vs 28%; *P*<0.001). Following rectal administration of diazepam, the time to next seizure was significantly prolonged compared to patients receiving placebo (*P*<0.001). Global assessment as provided by the patient's caregiver was significantly improved in Study 1 (*P*=0.02), but not in Study 2 (*P*=0.17). The proportion of patients experience at least one adverse event was 32% of the diazepam group and 23% of the placebo group. The most frequently adverse events were somnolence (13%) and dizziness (6%). The median respiratory rates did not differ between the two treatment groups. Secondary: Not reported
Mitchell et al[45] Diazepam 0.2 to 0.5 mg/kg rectally once	OL, PRO Patients ≥2 years of age with seizure clusters	N=149 24 months	Primary: Seizure frequency and adverse events and respiratory	Primary: In the 12 hours following diazepam administration, the median seizure frequency was zero for all 149 patients. Seventy seven percent of diazepam administrations prevented seizures in the 12 hours after treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients previously enrolled in the NINDS study were allowed two doses four hours apart. The remaining patients were administered once dose no more frequent than every five days and no more than five times per month.	or prolonged seizures who were enrolled in one of two previous double-blind, placebo-controlled trials or a single-dose safety trial		rates following administration, caregiver and physician global ratings at 24 months, hospitalizations, emergency room visits and paramedic calls for treatment Secondary: Not reported	In patients receiving at least two doses of diazepam (N=125), the median number of seizures was zero for both first and last administrations, with 63% of subjects having no subsequent seizures after the first administration, and 69% having none after the last administration. (*P* value not reported). There was no difference in the number of seizures that occurred in the 12 hour post-administration period among high utilizers of diazepam (two to seven administrations) and the high utilizers (8 to 78 administrations). After first administration of diazepam, three of 149 subjects received additional medical treatment, and six were treated in emergency room. After the second administration (N=125), one patient received medical treatment at home, and four were treated in the emergency room. Following a third administration (N=110) two patients received medical treatment in the home and six were treated in the emergency room. Somnolence was the most frequently reported adverse event, occurring in 17% of subjects. Somnolence due to diazepam was difficult to differentiate from that due to postictal sleep, but was considered to be related to medication in 9% of reports. Hypoventilation was transient in two subjects, neither of which required treatment. No serious adverse events, as defined by the FDA, were attributed to diazepam treatment Caregivers and investigators rated diazepam treatment positively at both 12 and 24 months. Secondary: Not reported
Leppik et al[46] Diazepam 10 mg IV	AC, DB, MC, RCT Adult patients	N=78 Duration not reported	Primary: Seizure control following administration,	Primary: Seizure control was achieved following a single administration of diazepam or lorazepam in 58 and 78% of epileptic episodes, respectively (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs lorazepam 4 mg IV A second dose was administered if seizures continued or recurred after ten minutes. Because the known duration of action of diazepam is 20 to 30 minutes, patients were given a loading dose of phenytoin even if seizures had not recurred 30 minutes following administration of study drug.	with convulsive (generalized tonic-clonic), absence, partial elementary or partial complex status epilepticus		onset of action and adverse events Secondary: Not reported	A second dose of diazepam was given to 13/14 patients not responding to a single dose and seizures became controlled in six of these cases. A second dose of lorazepam was given to eight patients; seizures were controlled in four. Overall, a similar proportion of epileptic episodes were terminated with one or two doses of diazepam and lorazepam (76 vs 89%; *P*=NS). The time from injection to control of seizure activity for patients treated with diazepam ranged from an immediate effect to ten minutes (median time, two minutes). With lorazepam administration, the range was immediate to 15 minutes (median, three minutes), and the difference was not statistically significant (*P*=NS). Adverse events occurred on ten occasions. These included five of 41 treatments with diazepam and five of 40 with lorazepam. No deaths attributable to study medication occurred. No reactions at the site of injection occurred. Pulse rate, BP, and respiratory rate after treatment did not differ between the two drug groups. No abnormal laboratory findings attributable to the study drugs were reported. Secondary: Not reported
Alldredge et al[47] Diazepam 5 mg IV once vs lorazepam 2 mg IV once vs placebo	DB, MC, RCT Adults ≥18 years of age with an out-of-hospital diagnosis of status epilepticus experiencing prolonged (five minutes or more) or repetitive	N=205 Duration not reported	Primary: Proportion of status epilepticus cases that were terminated by the time of arrival at the emergency department Secondary:	Primary: Status epilepticus was terminated at arrival at the emergency department in 59.1 percent of patients treated with lorazepam, 42.6 percent of patients receiving diazepam and 21.1 percent of patients given placebo (*P*=0.001). The termination of status epilepticus was more likely with lorazepam (OR, 5.4; 95% CI, 2.3 to 13.2) and diazepam (OR, 2.8; 95% CI, 1.2 to 6.7) compared to placebo. There was no difference in the likelihood of seizure termination rates between lorazepam and diazepam (OR, 1.9; 95%, 0.9 to 4.3). Secondary: An out-of-hospital complication (hypotension, cardiac dysrhythmia or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
If seizures recurred or continued four minutes or more after the first injection, then an identical second injection was administered.	generalized convulsive seizures		Out of hospital complications, complications upon transfer, duration of status epilepticus before hospital arrival, neurologic outcome at discharge, disposition of patient from emergency room	respiratory intervention) occurred in seven patients treated with lorazepam, seven patients receiving diazepam and 16 patients treated with placebo (10.6 and 10.3 vs 22.5%, respectively; *P*=0.08). The most common complication was a change in respiratory status requiring ventilation assistance. Cardiorespiratory complications at the time when patients were transferred to emergency-department personnel (complications at transfer) occurred in 13 patients (7%), with no significant differences between treatment groups (*P*=0.39). For patients remaining in status epilepticus, the time from arrival at the emergency department to the termination of status epilepticus did not differ significantly among the three treatment groups (*P* value not reported). The transfer location discharge, or death of patients following treatment in the emergency department was not significantly different among the three treatment groups (*P*=0.26). There was no difference between diazepam, lorazepam and placebo with regard to neurologic outcomes of patients at the time of hospital discharge (*P*=0.25).
Appleton et al[48] Lorazepam IV or rectally (dose not specified) vs diazepam IV or rectally (dose not specified)	MA Children between ages 1 month and 16 years presenting to an Accident and Emergency department or to a hospital ward in an acute tonic-clonic convulsion	N=102 1 year	Primary: Efficacy (cessation of the presenting convulsion, seizure recurrence within 24 hours of initial termination, need for additional drugs) and safety	Primary: One to two intravenous doses stopped the convulsion in 70% of lorazepam-treated patients compared to 65% of patients receiving IV diazepam (RR, 1.09; 95% CI, 0.77 to 1.54). A single dose of rectal lorazepam stopped the convulsion in all children (6/6), compared to 6/19 children treated with rectal diazepam (RR, 3.17; 95% CI, 1.63 to 6.14). Approximately 22% of children treated with IV lorazepam and 35% children receiving IV diazepam experienced another convulsion within 24 hours after presentation (RR, 0.63; 95% CI, 0.27 to 1.46).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	Approximately 4% of children receiving IV lorazepam required additional antiepileptic drugs to terminate the presenting seizure compared to 15% of children who received diazepam (RR, 0.25; 95% CI, 0.03 to 2.03). The incidence of respiratory depression occurring in the lorazepam-treated group was 4% compared to 21% in the diazepam treatment group (RR, 0.18; 95% CI, 0.02 to 1.37). Secondary: Not reported
Treiman et al[49] Diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenobarbital 15 mg/kg vs phenytoin 18 mg/kg	DB, MC, R Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (when all motor and electrical seizure activity stopped within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes) and adverse events Secondary: Not reported	Primary: For treatment success in overt status epilepticus, a significant difference in success rates was reported: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02). For subtle status epilepticus, there were no significant differences between the treatment groups (P<0.18). Lorazepam showed significantly higher treatment success compared to phenytoin in pair wise comparison of overt status epilepticus (P<0.002). There were no significant differences among any of the treatment groups with respect to adverse effects or 30 day outcomes. Secondary: Not reported

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: ACTH= adrenocorticotropic hormone, EEG= electroencephalogram, IV= intravenously, LGS= Lennox–Gastaut syndrome

Special Populations

Table 5. Special Populations[1-5,23,24]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Products					
Clobazam	Dose adjustment is required; the initial dose should be 5 mg daily for elderly patients and a maximum dose of 20 mg twice-daily is recommended, depending on weight. FDA-approved for use in children ≥2 years of age.	No dosage adjustment required in patients with mild to moderate renal impairment.	Hepatic dose adjustment is required; the initial dose should be 5 mg daily for patients with mild to moderate hepatic impairment and a maximum dose of 20 mg twice-daily is recommended.	C	Yes
Clonazepam	The dose selection for an elderly patient should start at the low end of the dosing range, due to a greater frequency of decreased hepatic and/or renal function. Dose adjustment is required in children <10 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; however, clonazepam undergoes hepatic metabolism and therefore, caution should be used when administering clonazepam to these patients.	D	Yes*
Clorazepate	The dose selection for an elderly patient should start at the low end of the dosing range, due to a greater frequency of decreased hepatic and/or,	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	D	Yes*

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	renal function. FDA-approved for use in children ages ≥9 years of age.				
Diazepam	Dose adjustment is recommended; the initial dose should be 2 to 2.5 mg once- or twice-daily for all elderly patients and increase as needed and tolerated. FDA-approved for use in children ages ≥6 months of age.	Use caution in patients with renal impairment.	Use caution in patients with hepatic impairment.	D	Yes*

*The manufacturer recommends that mothers receiving this agent should not breast-feed.

Adverse Drug Events

Table 6. Adverse Drug Events[1-5,23,24]

Adverse Event	Clobazam	Clonazepam	Clorazepate	Diazepam
Cardiovascular				
Chest pain	-	✔	-	-
Decreased systolic blood pressure	-	-	✔	-
Edema		✔	-	-
Flushing	-	✔	-	-
Hypotension	-	✔	-	✔
Palpitations	-	✔	-	-
Shortness of breath	-	✔	-	-
Central Nervous System				
Abnormal coordination	-	6	-	-
Aggression	8	✔	-	-
Agitation	✔	✔	-	-
Amnesia	-	✔	-	-
Anxiety	✔	✔	-	-
Apathy	✔	✔	-	✔
Aphonia	-	✔	-	-
Ataxia	5	5 to 30	✔	✔
Blurred vision	-	1	✔	✔

Change in libido	-	-	-	✔
Confusion	-	1	✔	✔
Coma	-	✔	-	-
Decreased libido	-	1	-	-
Delusions	✔	-	-	-
Depersonalization	-	✔	-	-
Depression	✔	7	✔	✔
Diplopia	✔	✔	✔	✔
Disinhibition	-	✔	-	-
Dizziness	-	8	✔	-
Dreaming, excessive	-	✔	-	-
Drooling	9	-		
Drowsiness	-	50	✔	✔
Drunkenness	-	✔	-	-
Dry mouth	-	✔	✔	-
Dysarthria	3	2	-	✔
Excitement	-	✔	-	✔
Glass-eyed appearance	-	✔	-	-
Hallucinations	✔	✔	-	✔
Head fullness	-	✔	-	-
Headache	-	✔	✔	✔
Hemiparesis	-	✔	-	-
Hoarseness	-	✔	-	-
Hostility	-	✔	-	-
Hypoesthesia	-	✔	-	-
Hypotonia	-	✔	-	-
Hysteria	-	✔	-	-
Illusion	-	✔	-	-
Impotence	-	1	-	-
Inattention	-	✔	-	-
Increased libido	-	✔	-	-
Insomnia	5	✔	✔	✔
Intellectual ability reduced	-	2	-	-
Irritability	7	✔	✔	-
Lethargy	10	-	-	-
Memory impairment	-	4	-	-
Migraine	-	✔	-	-
Nervousness	-	3	✔	-
Nightmares	-	✔	-	-
Nystagmus	-	✔	-	-
Paresis	-	✔	-	-
Paresthesia	-	✔	-	-
Psychosis	-	✔	-	-
Psychomotor hyperactivity	4	-	-	-
Rage	-	-	-	✔
Sedation	5	-	-	-
Sleep disturbances	-	✔	-	✔
Slurred speech	-	✔	✔	✔
Somnolence	22	37	-	-
Tremor	-	✔	✔	✔
Vertigo	-	✔	-	✔

Visual disturbances	✔	✔	-	-
Vivid dreams	-	✔	-	-
Dermatological				
Acne flare	-	✔	-	-
Burning skin	-	✔	-	-
Contact dermatitis	-	✔	-	-
Pruritus	-	✔	-	-
Pustular reaction	-	✔	-	-
Rash	-	✔	✔	✔
Skin disorder	-	✔	-	-
Xeroderma	-	✔	-	-
Gastrointestinal				
Abdominal distress	-	1	-	-
Abdominal pain	-	-	-	-
Abdominal distention	✔	-	-	-
Anorexia	-	✔	-	-
Bowel movements, frequent	-	✔	-	-
Change in appetite	-	✔	-	-
Constipation	5	2	-	✔
Decreased appetite	3	1	-	-
Diarrhea	-	✔	-	-
Dyspepsia	-	✔	-	-
Dysphagia	-	-	-	-
Emesis	-	-	-	-
Flatulence	-	✔	-	-
Gastritis	-	✔	-	-
Gastrointestinal complaints	-	✔	✔	-
Gastrointestinal inflammation	-	✔	-	-
Gastrointestinal pain	-	-	-	-
Heartburn	-	-	-	-
Hemorrhoids	-	✔	-	-
Hepatic dysfunction	-	-	-	-
Hepatomegaly	-	✔	-	-
Increased appetite	-	✔	-	-
Jaundice	-	-	-	✔
Kidney function test abnormalities	-	-	✔	-
Liver function test abnormalities	-	-	✔	-
Nausea/vomiting	7	✔	-	✔
Pyrosis	-	✔	-	-
Upset stomach	-	✔	-	-
Genitourinary				
Bladder dysfunction	-	✔	-	-
Cystitis	-	✔	-	-
Dysmenorrhea	-	3	-	-
Dysuria	-	✔	-	-
Enuresis	-	✔	-	-
Genitourinary complaints	-	-	✔	-

Incontinence	-	✔	-	✔
Menstrual disorders/ irregularities	-	✔	-	-
Micturition frequency	-	1	-	-
Nocturia	-	✔	-	-
Pelvic pain	-	✔	-	-
Polyuria	-	✔	-	-
Urine discoloration	-	✔	-	-
Urinary retention	-	✔	-	✔
Urinary tract bleeding	-	✔	-	-
Urinary tract infection	4	1	-	-
Vaginal discharge/itching	-	-	-	✔
Hematologic				
Anemia	✔	✔	-	-
Decreased hematocrit	-	-	✔	-
Dermal bleeding	-	✔	-	-
Eosinophilia	-	✔	-	-
Leukopenia	✔	✔	-	-
Neutropenia	-	-	-	✔
Thrombocytopenia	✔	✔	-	-
Laboratory Test Abnormalities				
Elevated alkaline phosphatase	-	✔	-	-
Elevated liver transaminases	-	✔	-	-
Hepatic enzymes increased	✔	-	-	-
Musculoskeletal				
Ankle pain	-	✔	-	-
Arthralgia	-	✔	-	-
Back pain	-	✔	-	-
Feet pain	-	✔	-	-
Fracture, traumatic	-	✔	-	-
Hypertonia	-	✔	-	-
Jaw pain	-	✔	-	-
Knee pain	-	✔	-	-
Knee swelling	-	✔	-	-
Leg cramps	-	✔	-	-
Leg pain	-	✔	-	-
Lumbago	-	✔	-	-
Muscle cramps	-	✔	-	-
Muscle pain	-	✔	-	-
Muscle spasm	✔	-	-	✔
Muscle weakness	-	✔	-	-
Myalgia	-	1	-	-
Shoulder pain	-	✔	-	-
Tendinitis	-	✔	-	-
Respiratory				
Aspiration	✔	-	-	-
Asthmatic attack	-	✔	-	-
Bronchitis	2	1	-	-
Chest congestion	-	✔	-	-

Cough	5	2	-	-
Dyspnea	-	✔	-	-
Pharyngitis	-	2	-	-
Pleurisy	-	✔	-	-
Pneumonia	4	✔	-	-
Respiratory depression	✔	-	-	-
Rhinitis	-	2	-	-
Sinusitis	-	4	-	-
Sneezing, excessive	-	✔	-	-
Upper respiratory infection	12	8	-	-
Other				
Abnormal vision	-	-	✔	-
Abrasions	-	✔	-	-
Allergic reaction	-	2	-	-
Alopecia	-	✔	-	-
Breast pain	-	✔	-	-
Colpitis	-	1	-	-
Dehydration	-	✔	-	-
Deterioration, general	-	✔	-	-
Earache	-	✔	-	-
Eye irritation	-	✔	-	-
Eye twitching	-	✔	-	-
Falling	-	✔	-	-
Fatigue	5	7	✔	✔
Fever	13	-	-	-
Eye irritation	-	25	-	-
Inappropriate behavior	-	✔	-	-
Infection	-	4	-	-
Lower extremity pain	-	✔	-	-
Lymphadenopathy	-	✔	-	-
Melena	-	✔	-	-
Nasal congestion	-	✔	-	-
Nosebleed	-	✔	-	-
Purpura	-	-	-	✔
Salivation, decreased	-	✔	-	-
Scotomata	-	✔	-	-
Shivering	-	✔	-	-
Stevens-Johnson syndrome	-	-	-	✔
Stridor	-	✔	-	-
Swollen lymph nodes	-	✔	-	-
Tinnitus	-	✔	-	-
Taste alteration	-	✔	-	-
Thyroid nodule	-	✔	-	-
Urticaria	-	✔	-	-
Visual field defect	-	✔	-	-
Weight gain	-	✔	-	-

Contraindications/Precautions

The benzodiazepines are contraindicated in patients with a known hypersensitivity to the specific drug being prescribed and in those with acute narrow-angle glaucoma. In addition, clonazepam is contraindicated in patients with evidence of significant liver disease. [1-5,23,24]

Clorazepate and diazepam are not recommended for use in depressive neuroses or in psychotic reactions.[3-5]

The benzodiazepines are associated with somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were dose-related. Somnolence and sedation generally appear within the first month of treatment and may subside with continued treatment. Patients should be monitored for somnolence and sedation, especially if the patient is using other agents that are central nervous system depressants. Patients should not engage in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effects of these agents are known. [1-5,23,24]

Clonazepam may cause increased salivation. Considered should be give prior to administering the drug to patients who may have difficulty handling secretions. Because of this and the possibility of respiratory depression, clonazepam should be used with caution in patients with chronic respiratory diseases. [2,23,24]

The benzodiazepines should not be discontinued abruptly, and the dose should be tapered weekly prior to discontinuation. Benzodiazepines should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation or status epilepticus. Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported with abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms are usually limited to patients who received excessive doses over an extended period of time, followed by an abrupt discontinuation. Generally milder withdrawal symptoms (e.g., dysphoria, anxiety, and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic doses for several months. [1-5,23,24]

Patients with a history of substance abuse should be under careful surveillance when receiving benzodiazepines or other psychotropic agents because of the predisposition of such patients to habituation and dependence. [1-5,23,24]

Antiepileptic drugs (AEDs), including the benzodiazepines, increase the risk of suicidal thoughts or behavior in patients taking these drugs regardless of indication. Patients receiving treatment with any AED regardless of indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo (adjusted relative risk 1.8, 95% confidence interval [CI]:1.2 to 2.7). In these trials, which had median treatment durations of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. Four suicides occurred in patients treated with AEDs and none occurred in placebo-treated patients. The number is too small to allow any conclusion about drug effect on suicide. [1-5,23,24]

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week following the start of drug treatment with AEDs and persisted for the duration of treatment assessed. Since most trials included in the analysis were less than 24 weeks in duration, the risk of suicidal thoughts or behavior beyond 24 weeks cannot be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior arise during treatment, consideration should be give to whether the emergence of these symptoms may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm.[1-5,23,24]

When used in patients in whom several different types of seizure disorders coexist, clonazepam and diazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam may produce absence status. [2,4,5,23,24]

An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies. There may also be nonteratogenic risks associated with the use of benzodiazepines during pregnancy. Neonatal flaccidity, respiratory and feeding difficulties, and hypothermia have been reported in children born to women receiving benzodiazepines late in pregnancy. Moreover, children born to women receiving benzodiazepines late in pregnancy may be at increased risk of experiencing withdrawal symptoms during the postnatal period. [1-5,23,24]

In general, the use of benzodiazepines in women of childbearing potential, and during a known pregnancy, should only be considered when the clinical situation outweighs the risk to the fetus. Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs. A majority of mothers taking anticonvulsant medication during their pregnancy deliver healthy infants. Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with fetus hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus. [1-5,23,24]

Drug Interactions

Table 7. Drug Interactions[1-5,23,24]

Generic Name	Interacting Medication or Disease	Potential Result
Benzodiazepines (all)	Ethanol	Increased central nervous system (CNS) effects and impaired psychomotor function have been observed. Patients should be cautioned to avoid the use of alcohol and benzodiazepines concurrently. With acute ethanol ingestion, increased benzodiazepine absorption and decreased hepatic metabolism may occur.
Benzodiazepines (all)	Opioid analgesics (buprenorphine, methadone)	Increased sedation and strength of opioid effects have been observed with the concomitant use of benzodiazepines and opioid analgesics. Patients should be advised against driving or operating

Generic Name	Interacting Medication or Disease	Potential Result
		machinery while taking these agents simultaneously.
Benzodiazepines (all)	Barbiturates	Concurrent use of benzodiazepines and barbiturates may result in additive respiratory depression. Patients should be monitored for respiratory depression when these drugs are used in combination and a dose reduction of one or both agents may be necessary.
Benzodiazepines (all)	Centrally-acting muscle relaxants	Concurrent use of benzodiazepines and centrally-acting muscle relaxants may result in additive respiratory depression. Patients should be monitored for respiratory depression when these drugs are used in combination and a dose reduction of one or both agents may be necessary.
Benzodiazepines (all)	Chloral hydrate	Concurrent use of benzodiazepines and chloral hydrate may result in additive respiratory depression. Patients should be monitored for respiratory depression when these drugs are used in combination and a dose reduction of one or both agents may be necessary.
Benzodiazepines (clonazepam, clorazepate, diazepam,)	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir-ritonavir, nelfinavir, ritonavir, saquinavir)	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism resulting in large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism. Coadministration of these protease inhibitors with benzodiazepines metabolized by CYP3A4 is contraindicated.
Benzodiazepines (clobazam, clonazepam, clorazepate, diazepam)	Azole antifungals	Increased and prolonged serum levels, CNS depression, and psychomotor impairment has been noted with certain benzodiazepines undergoing oxidative metabolism and may possibly continue for several days after stopping the azole antifungal agent. Consider giving a lower benzodiazepine dose or a benzodiazepine that undergoes glucuronidation (e.g., lorazepam, oxazepam and temazepam) when giving fluconazole.
Benzodiazepines (clonazepam, clorazepate, diazepam)	Rifamycins	When used with rifamycins, the pharmacologic effects of certain benzodiazepines may be decreased due to an increase in the oxidative metabolism of the benzodiazepine (CYP450). Clinical response to the benzodiazepine should be monitored when starting or stopping rifamycins and the dose may be adjusted as needed.
Benzodiazepines (clobazam)	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines. Hydantoin levels and effects should be monitored when the benzodiazepine dose is started or stopped.
Benzodiazepines (clonazepam)	Nonnucleoside reverse transcriptase (NNRT) inhibitors	Nonnucleoside reverse transcriptase (NNRT) inhibitors may inhibit the hepatic metabolism (CYP3A4) of the benzodiazepine. The pharmacologic effects of certain benzodiazepines may be increased

Generic Name	Interacting Medication or Disease	Potential Result
	(delavirdine, efavirenz)	and the duration prolonged, leading to protracted sedation and respiratory depression. NNRT inhibitors should not used simultaneously with certain benzodiazepines.
Benzodiazepines (clobazam)	Thioridazine	Concurrent use of clobazam and thioridazine may result in increased thioridazine plasma concentrations.
Benzodiazepines (clobazam)	Hormonal contraceptives	The administration of clobazam with hormonal contraceptives may reduce the concentration decrease the effectiveness of the hormonal contraceptive. Effective use of additional non-hormonal contraceptives is recommended during concurrent use and for 28 days after discontinuing clobazam.
Benzodiazepines (clobazam)	CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine)	Moderate and strong inhibitors of CYP2C19 may increase exposure to N-desmethylclobazam, an active metabolite. A dose reduction may be necessary if clobazam is being coadministered with a moderate or strong inhibitor of CYP2C19.
Benzodiazepines (diazepam)	Diltiazem	Increased CNS depression and prolonged effects have been observed with the use of diltiazem and certain benzodiazepines.
Benzodiazepines (diazepam)	Macrolides and related antibiotics (clarithromycin, erythromycin, telithromycin)	Increased CNS depression and prolonged sedation have been noted with concomitant use of certain benzodiazepines and macrolide related agents. Consider benzodiazepines undergoing conjugative metabolism that are unlikely to interact (e.g., lorazepam, oxazepam and temazepam).

Dosage and Administration

Table 8. Dosing and Administration[1-5,23,24]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Products			
Clobazam	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥2 years: Tablet: initial, 5 (≤30 kg) or 10 mg/day (>30 kg); maintenance, titrate as tolerated over 13 days to 20 (≤30 kg) or 40 mg/day (>30 kg); doses >5 mg/day should be administered in two divided doses	Safety and efficacy in children <2 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg
Clonazepam	Alone or as an adjunct in the treatment of Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic	Alone or as an adjunct in the treatment of Lennox-Gastaut syndrome	Tablet: 0.5 mg 1 mg 2 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	seizures or in patients with absence seizures (petit mal) who have failed to respond to succinimides: Orally disintegrating tablet, tablet: initial, 0.5 mg PO TID; maintenance, may increase daily dose by 0.5 to 1 mg PO every three days; maximum: up to 20 mg (divided TID)	(petit mal variant), akinetic and myoclonic seizures or in patients with absence seizures (petit mal) who have failed to respond to succinimides in children ≤10 years of age or up to 30 kg: Orally disintegrating tablet, tablet: initial, 0.01 to 0.03 mg/kg/day PO divided BID or TID; maintenance, may increase daily dose by 0.25 to 0.5 mg PO every three days; maximum: total daily dose of 0.1 to 0.2 mg/kg/day (divided TID)	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg
Clorazepate	Adjunctive therapy in the management of partial seizures: Tablet: initial, 7.5 mg PO TID; maintenance, increase dose by 7.5 mg/week; maximum: 90 mg/day PO (divided TID)	Adjunctive therapy in the management of partial seizures in children 9 to 12 years: Tablet: initial, 7.5 mg PO BID; maintenance, may increase dose by 7.5 mg/week; maximum: 60 mg/day PO (divided BID)	Tablet: 3.75 mg 7.5 mg 15 mg
Diazepam	Adjunctive use in convulsive disorders: Oral concentrate, oral solution, tablet: initial, 2 to 10 mg PO BID to QID Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity in patients 12 years of age and older: Ampule, disposable syringe, vial: initial, 5 to 10 mg IV every ten to fifteen minutes to a total dose of 30 mg; may	Adjunctive use in convulsive disorders in children 6 months or older: Oral concentrate, oral solution, tablet: initial, 1 to 2.5 mg PO TID or QID Adjunct in status epilepticus and severe recurrent convulsive seizures children 30 days to 5 years of age: Ampule, disposable syringe, vial: initial, 0.2 to 0.5 mg IV slowly (preferred) or IM	Ampule, disposable syringe, vial: 5 mg/mL This medication is administered by a medical professional or caregiver. Oral concentrate: 5 mg/mL Oral solution: 5 mg/5 mL Rectal gel: 2.5 mg 10 mg 20 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	repeat in two to four hours if needed, rectal gel: 0.2 mg/kg rectally; may repeat in 4 to 12 hours if needed	every two to five minutes up to a maximum of 5 mg Adjunct in status epilepticus and severe recurrent convulsive seizures children ≥5 years of age: Ampule, disposable syringe, vial: initial, 1 mg IV slowly (preferred) or IM every two to five minutes up to a maximum of 10 mg and repeat in two to four hours if necessary Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity in children 2 to 5 years of age: Rectal gel: initial, 0.5 mg/kg rectally once; when required, a second dose may be administered 4 to 12 hours following the first dose Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity in children 6 to 11 years of age: Rectal gel: initial, 0.3 mg/kg	This medication is administered by a medical professional or caregiver. Tablet: 2 mg 5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
		rectally once; when required, a second dose may be administered 4 to 12 hours following the first dose	

IM=intramuscularly, IV=intravenously

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Clinical Excellence: **The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care (2012)**[15]	Treatment of atonic or tonic seizures • First-line treatment in children, young people, and adults with tonic or atonic seizure: sodium valproate. • Offer lamotrigine as adjunctive treatment if sodium valproate is ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. Treatment of generalized tonic-clonic seizures • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable. • Consider carbamazepine and oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin. Treatment of infantile spasms • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when an infant presents with infantile spasms. • Offer a steroid or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. • Offer vigabatrin as first-line treatment to infant with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid. Treatment of Lennox-Gastaut syndrome • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Lennox-Gastaut syndrome. • Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. • Offer lamotrigine as adjunctive treatment if first-line treatments are ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by

Clinical Guideline	Recommendations
	the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. • Only offer felbamate in centers providing tertiary epilepsy specialist care and when treatment with all of the antiepileptics listed above have proved ineffective or not tolerated. Treatment of myoclonic seizures • First-line treatment in children, young people, and adults with myoclonic seizures: valproate, unless unsuitable. • Consider levetiracetam or topiramate if sodium valproate is unsuitable or not tolerated. • Offer levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist or consider clobazam, clonazepam, piracetam*, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of absence seizures • First-line treatment in children, young people, and adults with absence seizures: ethosuximide or sodium valproate. If there is a high risk of generalized tonic-clonic seizures, offer sodium valproate first, unless it is unsuitable. • Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptics are ineffective, consider a combination of two of these three antiepileptics as adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of focal seizures • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: carbamazepine or lamotrigine. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic is ineffective. • For refractory focal seizures, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment to all patients with focal seizures if first-line treatments are ineffective or not tolerated. • For refractory focal seizures, if adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptics that may be considered by a specialist are eslicarbazepine

Clinical Guideline	Recommendations
	acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Treatment of Dravet syndrome • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Dravet syndrome. • Consider sodium valproate or topiramate as first-line treatment in children with Dravet syndrome. • Discuss with a tertiary epilepsy specialist if first-line treatments are ineffective or not tolerated, and consider clobazam or stiripentol as adjunctive treatment. • Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, or late-onset childhood occipital epilepsy (Gastaut type) • Discuss with the child or young person, and their family and/or caretakers, whether antiepileptic drug treatment is indicated. • Offer carbamazepine or lamotrigine as first-line treatment to children and young people. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic drug tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic drug is ineffective. • Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptic drugs that may be considered are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Treatment of idiopathic generalized epilepsy • First-line treatment in children, young people, and adults with idiopathic generalized epilepsy: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable or not tolerated. • Consider topiramate. • Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective for not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of juvenile myoclonic epilepsy • First-line treatment in children, young people, and adults with juvenile myoclonic epilepsy: sodium valproate. • Consider lamotrigine, levetiracetam, or topiramate if sodium valproate is unsuitable or not tolerated.

Clinical Guideline	Recommendations
	• Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of epilepsy with generalized tonic-clonic seizures only • First-line treatment in children, young people, and adults with epilepsy with generalized tonic-clonic seizures only: lamotrigine, sodium valproate. • Consider carbamazepine or oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. Treatment of childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes • First-line treatment in children, young people, and adults: ethosuximide, sodium valproate. • Offer lamotrigine if first-line treatments are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptic drugs are ineffective, consider a combination of two of these three antiepileptic drugs adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.
European Federation of Neurological Societies: **European Federation of Neurological Societies Guideline on the Management of Status Epilepticus (2010)**[16]	Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus • The preferred treatment is intravenous (IV) administration of lorazepam 0.1 mg/kg. Depending on the patient's general medical condition, initiation with a lower dose of 4 mg and a repeated dose if status epilepticus is not terminated within 10 minutes may be considered. • If IV lorazepam is not available, diazepam 10 mg directly followed by phenytoin 18 mg/kg or equivalent fosphenytoin may be given instead. • If possible, pre-hospital treatment is recommended, and in generalized convulsive status epilepticus, IV lorazepam 2 mg is as effective as diazepam 5 mg. • Out-of-hospital, IV administration of benzodiazepines in generalized convulsive status epilepticus is as safe as placebo treatment. • Complex partial status epilepticus should be treated initially in the same way as generalized convulsive status epilepticus. • In the rare patients with previously untreated subtle status epilepticus, the initial anticonvulsant treatment should be identical to that of overt generalized convulsive status epilepticus. General management of refractory status epileptics • Generalized convulsive status epilepticus that does not respond to initial anticonvulsant substances needs to be treated on an intensive care unit.

Clinical Guideline	Recommendations
	Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus • Immediate infusion of anesthetic doses of midazolam, propofol, or barbiturates. Because of a lack of evidence, there is no one recommended agent over another. • Simultaneously, initiate the chronic medication the patient will be treated with in the future. • In cases of elderly patients in whom intubation and artificial ventilation would not be justified, further non-anaesthetizing anticonvulsants may be tried. Pharmacological treatment for refractory complex partial status epilepticus • General anesthesia should be postponed and further non-anaesthetizing anticonvulsants may be tried (phenobarbital, valproic acid and levetiracetam). • Because of a lack of evidence, there is no recommendation as to the non-anesthetizing anticonvulsant of choice. • If the treatment regimen includes the administration of anesthetics, the same protocol applies as described for generalized convulsive status epilepticus.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2004)**[17]	• At this time, there are no studies that assessed the efficacy and tolerability of the new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) in adults with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Lamotrigine can be included in the treatment options for children with newly diagnosed absence seizures. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide in children with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Patients with newly diagnosed partial or mixed seizure disorders who require treatment can be initiated on carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproic acid. The choice of drug will depend on individual patient characteristics. At this time, there is insufficient evidence to determine effectiveness in newly diagnosed patients for levetiracetam, tiagabine and zonisamide.
American Academy of Neurology/American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2004)**[18]	• Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children. At this time, there is insufficient evidence to recommend use of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, or zonisamide for refractory generalized tonic-clonic seizures in adults and children. • Lamotrigine and topiramate may be used to treat drop attacks associated with Lennox-Gastaut syndrome in adults and children. • Lamotrigine, oxcarbazepine, and topiramate can be used as monotherapy in adults with refractory partial epilepsy. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine, or zonisamide in monotherapy for refractory partial epilepsy. • Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are appropriate treatment options as

Clinical Guideline	Recommendations
	adjunctive therapy for refractory partial epilepsy in adults. • Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of refractory partial seizures in children. At this time, there is insufficient evidence to recommend levetiracetam, tiagabine, or zonisamide as adjunctive treatment of refractory partial seizures in children.
United States Expert Opinion: **Treatment of Epilepsy in Adults (2005)**[19]	Initial monotherapy for generalized seizures • Valproate is the treatment of choice for initial monotherapy of generalized tonic-clonic seizures. Lamotrigine and topiramate are alternatives. • Ethosuximide and valproate are the treatments of choice for initial monotherapy of absence seizures. Lamotrigine is an alternative. • Valproate is the treatment of choice for initial monotherapy of myoclonic seizures. Initial monotherapy for partial seizures • Carbamazepine and oxcarbazepine are treatments of choice for initial monotherapy of simple partial seizures. Lamotrigine and levetiracetam are alternatives. • Carbamazepine, lamotrigine, and oxcarbazepine are treatments of choice for complex partial seizures. Levetiracetam is an alternative. • Carbamazepine and oxcarbazepine are treatments of choice for secondarily generalized seizures. Lamotrigine and levetiracetam are alternatives. • Lamotrigine is the treatment of choice for (stable and ill) elderly patients with symptomatic localization-related epilepsy. Gabapentin is an alternative in ill elderly patients, and levetiracetam is an alternative in stable and ill elderly patients.
International League Against Epilepsy: **Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2006)**[20]	Initial monotherapy for generalized seizures • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproic acid may be considered as candidates for initial monotherapy of newly diagnosed or untreated generalized tonic-clonic seizures in adults. • Carbamazepine, phenobarbital, phenytoin, topiramate, and valproic acid may be considered as candidates for initial monotherapy of newly diagnosed or untreated generalized tonic-clonic seizures in children. • Ethosuximide, lamotrigine, and valproic acid may be considered as candidates for initial monotherapy of newly diagnosed or untreated absence seizures in children. • Clonazepam, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide may have some efficacy for initial monotherapy of newly diagnosed or untreated juvenile myoclonic epilepsy in children. Initial monotherapy for partial seizures • Carbamazepine, phenytoin, and valproic acid should be considered as first-line options for initial monotherapy of newly diagnosed or untreated partial-onset seizures in adults. Gabapentin and lamotrigine should be considered as first-line options for initial monotherapy of newly diagnosed partial-onset seizures in elderly adults. • Oxcarbazepine should be considered as a first-line option for initial monotherapy of newly diagnosed or untreated partial-onset seizures in children.
The Status Epilepticus	• Give high flow oxygen, measure blood glucose, and confirm epileptic

Clinical Guideline	Recommendations
Working Party: **The Treatment of Convulsive Status Epilepticus in Children (2000)**[21]	seizure. Immediate IV access • If IV access is available give lorazepam 0.1 mg/kg IV. • Repeat lorazepam once if seizing at 10 minutes. • If seizing continues after an additional 10 minutes, administer phenytoin 18 mg/kg IV or phenobarbital (if already on phenytoin) 20 mg/kg IV and paraldehyde 0.4 mL/kg rectally mixed with an equal volume of olive oil. • Rapid sequence induction of anesthesia using thiopental 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes. No immediate IV access • Give diazepam 0.5 mg/kg rectally. • Add lorazepam 0.1 mg/kg IV if still seizing at 10 minutes or paraldehyde 0.4 mL/kg rectally if no IV access. • If seizure activity continues for another 10 minutes, give phenytoin 18 mg/kg IV or phenobarbital 20 mg/kg IV (or intraosseous if no IV access) in addition to paraldehyde 0.4 mL/kg mixed with same volume of olive oil, rectally if not already given and contact anesthetist or intensive care medic. • Rapid sequence induction of anesthesia using thiopental 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes after the initiation of paraldehyde.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[22]	• Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or cluster of seizures. • IV phenobarbital is the treatment of choice and IV lorazepam or fosphenytoin are also first-line options for the initial therapy of neonatal status epilepticus. • Lorazepam is the treatment of choice and IV diazepam is also a first-line option for the initial therapy of all types of pediatric status epilepticus. • Rectal diazepam or IV fosphenytoin are the first-line options for generalized tonic-clonic status epilepticus. • Benzodiazepines were not identified as being first-line or treatment of choice for the following: complex partial status epilepticus, absence status epilepticus, symptomatic myoclonic and generalized tonic-clonic seizures, complex partial seizures, infantile spasms, Lennox-Gastaut syndrome, benign childhood epilepsy with centro-temporal spikes, childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy.

Conclusions

The anticonvulsant benzodiazepines that are Food and Drug Administration (FDA)-approved for the treatment of various types of seizures include clobazam (ONFI®), clorazepate (Tranxene-T®), clonazepam (Klonopin®) and diazepam (Valium®, Diastat®). The benzodiazepines are believed to exert anticonvulsant activity by enhancing the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.[1-5] Clobazam was approved by the FDA in October, 2011, and only indicated as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome despite being studied throughout Europe for various other forms of epilepsy.[11] Clobazam may be associated with less sedation compared to the other benzodiazepines.[12] Clonazepam is useful for both acute and chronic epilepsies including various myoclonic, atonic and absence seizures that are typically resistant to treatment with other antiepileptic drugs.[13] Clorazepate is only indicated as an adjunctive therapy and its use is limited to refractory partial seizures.[13] Diazepam is available in oral and rectal

formulations and has become the standard outpatient initial therapy for status epilepticus. Clonazepam, clorazepate and diazepam are available generically, while clobazam is a brand-only product.[24]

Clobazam, clorazepate and diazepam are long-acting benzodiazepines while clonazepam is widely considered to have an intermediate duration of action. Clorazepate and diazepam are metabolized to desmethyldiazepam, which is responsible for the anticonvulsant effects of these agents.[14] The benzodiazepines have consistently demonstrated their efficacy for the management of epilepsy in various studies; however, studies generally included a small number of patients and evaluation period was usually short.[25-49] Of important clinical note, the use of benzodiazepines in the management of epilepsy may be limited by the development of tolerance or requiring escalating doses to maintain anticonvulsant activity. Long-term benzodiazepine use may also decrease their effectiveness in acute situations.[50]

The treatment of epilepsy calls for highly individualized care, with a variety of different antiepileptic drugs recommended or considered potential treatment options in each seizure type. According recent clinical guidelines for the management of epilepsy by the National Institute for Clinical Excellence, clonazepam may be considered for absence, myoclonic and idiopathic generalized seizures if a patient has failed first-line treatment options and subsequent adjunctive therapy is ineffective or not tolerated.[15] The International League Against Epilepsy states that clonazepam may be effective for initial monotherapy of newly diagnosed or untreated juvenile myoclonic epilepsy in children.[20] The role of clorazepate is not defined within the current guidelines. Clobazam is recognized as an effective treatment, usually for use in refractory disease when first-line treatments are ineffective or not tolerated. For the treatment of Lennox-Gastaut specifically, sodium valproate should be offered first-line, with lamotrigine offered as adjunctive therapy if sodium valproate is ineffective or not tolerated.[15] For patients with convulsive or non-convulsive status epilepticus diazepam is recommended if lorazepam or intravenous access is unavailable.[21-22]

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