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Epilepsy (E Waterhouse, Section Editor)

The Role of Benzodiazepines in the Treatment of Epilepsy

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Opinion statement

Benzodiazepines are commonly prescribed as anxiolytics, sedatives, and anticonvulsants. They act on the $GABA_A$ receptor by increasing the conductance chloride through ionic channels, promoting a state of central nervous system depression. The clinical properties of benzodiazepines are dependent upon the composition of the different subunits of the $GABA_A$ receptor. Each subunit, in turn, has multiple subtypes that are present throughout the central nervous system, all of which impart different clinical responses. Benzodiazepines are the first-line treatment of status epilepticus. Time to treatment is crucial, and clinical response to benzodiazepines is lost with prolonged status epilepticus. Non-intravenous routes of midazolam should be considered as an equally efficacious alternative to intravenous lorazepam, which is the most commonly administered benzodiazepine for status epilepticus when intravenous access is available. Outpatient therapy with benzodiazepines for the acute treatment of seizures is currently limited to rectal diazepam, but alternative routes of administration are under development. Clobazam and clonazepam are good options for seizure prophylaxis in patients with epilepsy refractory to multiple antiepileptic drugs. Clobazam is preferred due to its affinity for the α2 subunit of the $GABA_A$ receptor, which leads to less potential for sedation. Adverse effects of chronic benzodiazepine use are sedation, tolerance, and potential for addiction and misuse in some patients.

Introduction

Benzodiazepines (BDZ) are widely prescribed as sedatives, anxiolytics, and hypnotics throughout the world. They are also commonly used in the treatment of seizures, utilizing their properties as central nervous system (CNS) depressants to suppress ongoing seizure activity or as an adjunctive treatment to prevent seizures. All BDZs act on the gamma-amino-butyric acid A ($GABA_A$) receptor and potentiate the influx of chloride via ionic channels, imparting a hyperpolarized state. Though the BDZs share a common mechanism, the choice physicians make when treating status epilepticus or epilepsy is largely dependent on pharmacokinetics, side effect

profile, and tolerability. The purpose of this publication is to serve as an update on the most recent evidence in the literature regarding the role of BDZs in the treatment of seizures. Topics reviewed will include a brief pharmacology overview, the use of BDZs in the treatment of status epilepticus and epilepsy, and the disadvantages of BDZs, including the potential for adverse effects, tolerance, and the withdrawal syndrome in the setting of physical dependence and addiction.

Pharmacology

The BDZs are drugs with anticonvulsant, sedative, and anxiolytic properties that work through $GABA_A$ receptors. The $GABA_A$ receptor is composed of five subunits, typically two α, two β, and one either γ or δ subunits. The subunits form a pore in the middle for chloride ion conductance. The receptors are activated by the binding of two GABA molecules in the clefts formed between the α and β subunits; see Fig. 1.

There are multiple subtypes of GABA subunits. There are six subtypes for α subunits, and there are three each for β and γ subunits and one for δ. The combination of different subunits and subtypes gives a wide range of receptors with different properties that are encoded genetically. Different types of neurons express the genes in a unique way to modulate the inhibitory response according to the function. The classical BDZs, such as diazepam predominantly interact with receptors composed of α1β2γ2, α2β2γ2, α3β2γ2, or α5β2γ2. They exhibit no activity on α4β2γ2 or α6β2γ2 receptors and a reduced activity on receptors containing γ1 or γ3 [1, 2] subunits. The overall selectivity of BDZ drugs is not yet sufficient for a selective activation of a single $GABA_A$ receptor subtype. However, studies using point genetic mutations demonstrated that

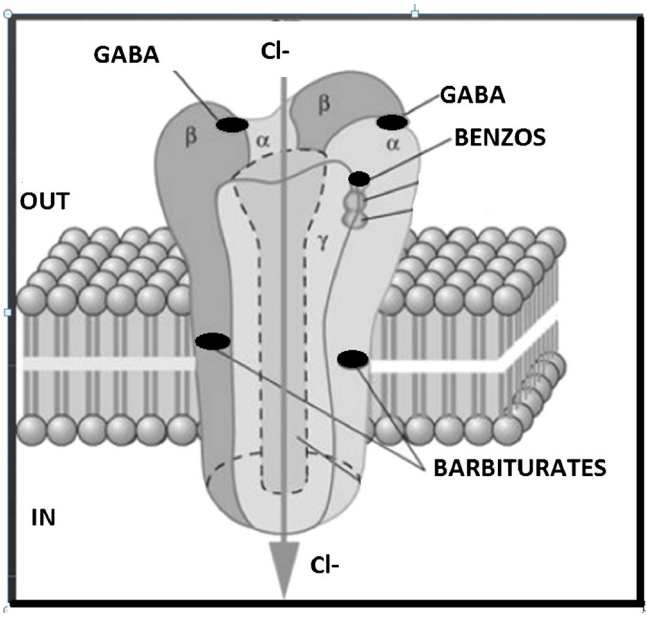

Fig. 1. The $GABA_A$ receptor. Used with permission. Trevor AJ. Sedative-Hypnotic Drugs. In: Katzung BG, Trevor AJ. eds. *Basic & Clinical Pharmacology, 13e*. New York, NY: McGraw-Hill; 2015.

α1βγ2 receptors mediate the sedative, anterograde amnestic, and in part, the anticonvulsant actions of diazepam [3, 4]. Similarly, receptors containing the α3 subtype seem to mediate the anti-absence effects of clonazepam. The α5βγ2 receptors seem to influence learning and memory, as seen in mice that improved spatial memory with knockout of α5 subunits [5]. See Fig. 2.

Benzodiazepines are structurally similar and composed of a benzene ring connected to a seven-membered diazepine ring. Variation of the functional groups attached changes their chemical and therapeutic properties. Most of the BDZs used for epilepsy are 1,4 BDZs, bind to the $GABA_A$ receptor, and potentiate the influx of chloride via ion channels. The most commonly used BDZs as anticonvulsants are diazepam, lorazepam, midazolam, clonazepam, and clorazepate. There is one commercially available 1,5 BDZ, clobazam. Benzodiazepines act through an allosteric mechanism to potentiate the effects of GABA. Benzodiazepines do not open the chloride channel but increase the affinity of the receptor to bind GABA and increase the mean opening time, potentiating the inhibitory response.

The GABA receptors in the postsynaptic membrane induce a phasic inhibition through a short increase of chloride conductance, hyperpolarizing the postsynaptic membrane. In the extrasynaptic sites, during low GABA concentration, the GABA receptors open for a longer time producing a tonic inhibition in response to a low GABA levels. Benzodiazepines do not induce chloride current directly nor do they affect the maximum current amplitude. See Fig. 3.

All BDZs bind to plasma proteins, which has a direct effect on their duration of action. This also has a great effect on their lipid solubility, which varies from 70 to 99 %. Due to their lipid solubility, the BDZs have a relatively fast onset of

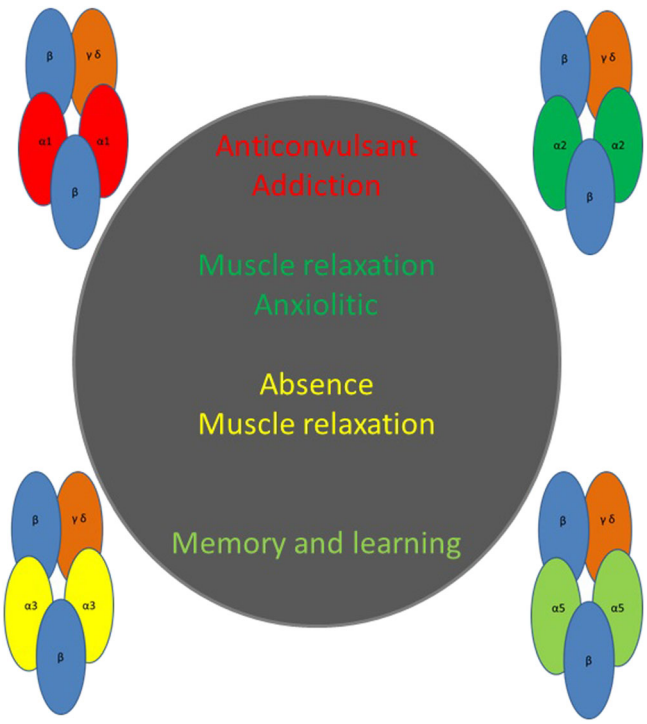

Fig. 2. Different clinical effects of $GABA_A$ receptor subunit subtypes.

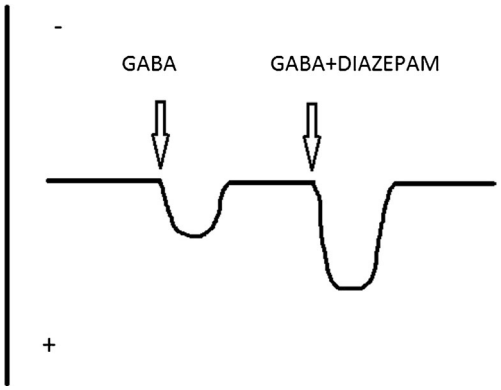

Fig. 3. Chloride channel conductance. Effect of diazepam on chloride conductance with stable GABA concentration.

action when administered. There is also a relatively rapid rate of redistribution into fatty tissues depending on the degree of lipid solubility. Please see Table 1 below for an overview of the relative clinical and pharmacologic properties of the benzodiazepines.

Status epilepticus

Status epilepticus (SE) is one of the most common neurologic emergencies and often the presenting symptom of newly diagnosed seizures. Status epilepticus is diagnosed in the presence of a prolonged seizure greater than 5–10 min or multiple seizures without return to baseline. In the past, SE has been defined as a seizure lasting greater than 30 min or multiple seizures without return to a state of alertness [6]. A temporal definition of SE is less important than the response of SE to treatment. The first-line treatment for SE is a BDZ, most commonly given intravenously or intramuscularly by first responders or in the emergency department.

Table 1. Pharmacologic properties and clinical uses of the benzodiazepines

Drug	Half-life	Lipid solubility	Common routes of administration	Remarks
Diazepam	20–50 h Metabolite: 50–100 h	98–99 %	IV, PO, PR	Long-acting active metabolite is *N*-desmethyldiazepam
Lorazepam	10–20 h	85–93 %	IV, PO, Nasal	First-line IV treatment for SE
Midazolam	2–7 h	Water soluble	IV, IM, Buccal, Nasal	Non-IV formulations are at least as efficacious as IV lorazepam for SE
Clonazepam	30–40 h	85 %	PO	Approved for absence seizures and myoclonus, but effective for multiple seizure types
Clorazepate	20–160 h	97-98 %	PO	Pro-drug to *N*-desmethyldiazepam
Clobazam	36–82 h	80–90 %	PO	Currently approved for LGS, but well-studied and has a role in treatment-resistant epilepsy

Status epilepticus has different "stages" or "phases" which have been described in the literature with varying definitions, leading to ambiguity. Seizures, over time, are thought to become self-sustaining and can progress to SE when untreated. The duration of SE is inversely proportional to its response to treatment with the BDZs. This has been demonstrated by Kapur [7] who showed significant changes in the functional properties of $GABA_A$ receptors, with markedly decreased sensitivity to diazepam noted after 10 min of induced SE. Mechanistically, this is most likely a multifactorial process, including a series of changes at the cellular level such as $GABA_A$ receptor internalization and an increase in NMDA receptor density. Naylor [8] demonstrated the decreased expression $\beta 2/\beta 3$ and $\gamma 2$ subunits of $GABA_A$ receptors in an animal model after 1 h of induced SE. The above explains the critical point in the treatment of SE, which is time to treatment. As SE persists, fewer $GABA_A$ receptors are available as targets for BDZs to stop the seizure. This review will focus on the treatment of seizures using the BDZs, and there are current reviews available on the treatment of pharmacoresistant SE [9, 10•, 11•].

Out-of-hospital treatment of SE with BDZs was established, though not well-studied, at the time of a paper published by Alldredge et al. in 2001 [12]. Intravenous (IV) lorazepam, diazepam, and placebo were compared in the pre-hospital treatment of SE by paramedics in the San Francisco area over a study period of 5 years from 1994 to 1999. Two hundred five patients were enrolled. Overall, it was determined that IV lorazepam was more effective than IV diazepam at terminating status epilepticus (59 versus 42 %) prior to arrival to an emergency department.

The time involved in gaining IV access can significantly delay treatment. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), published in the New England Journal of Medicine in 2012 [13••], compared the efficacy of IV lorazepam and intramuscular (IM) midazolam in the pre-hospital treatment of SE by paramedics in the field. It was a double-blind, randomized trial across multiple centers involving 893 subjects. IM midazolam using an autoinjector was found to be more effective than IV lorazepam in the cessation of seizures when given by paramedics prior to hospital arrival. Seizures were absent in 73.4 % of patients in the IM midazolam group on arrival to emergency departments compared to 63.4 % of patients in the IV lorazepam group. Time to treatment was significantly different in the two groups (1.2 min for IM midazolam versus 4.8 min for IV lorazepam) due to the time taken to gain IV access. Time to cessation of seizures was shorter in the IV lorazepam group (1.6 versus 3.3 min), but the overall time to cessation of seizure activity was similar between the two groups.

Alternative routes of administration other than IM for BDZs have been an area of interest as well. Rectal diazepam gel at pre-determined weight-based doses has been commercially available for home use for some time. Knudsen [14] conducted a study in 1979 with rectal diazepam solution for the acute treatment of convulsions in 44 infants and children with 59 total seizures, finding rectal diazepam to be an effective treatment without significant risk for respiratory depression. Eighty percent of seizures stopped within 5 min of administration. Ten percent of the seizures were responsive to a subsequent dose of IV diazepam, and 10 % were refractory to treatment. Rectal diazepam was also given prophylactically to children with fever greater than 39.5 °C as well with good safety data.

In 1998, Dreifuss [15] published a study on the effectiveness of rectal diazepam gel for acute repetitive seizures in adults and children. Repetitive seizures are often a prelude to impending status epilepticus. Using age-adjusted dosing, 25 children and 20 adults received rectal diazepam versus placebo. Children received a second dose after 4 h from the first, and adults received a third dose 8 h from the second dose, based on previous data for diazepam clearance. Results showed 28 of 45 patients to be seizure-free at 12 h after treatment with rectal diazepam gel versus 11 of 46 patients given placebo.

In older patients, there is significant concern for the inconvenience and socially embarrassing implications of rectal therapy for prolonged seizures and status epilepticus. Buccal, intramuscular, and intranasal routes for the administration of BDZs have been of particular interest.

Buccal midazolam has primarily been studied in children thus far. Scott [16] showed in 1999 in a study of children and adolescents in a residential setting that patients given buccal midazolam had a greater response to treatment than rectal diazepam (75 versus 59 %). There were two patients in this study who had many more seizures than the rest of the participants, one of whom was treated 12 times with each medication. Response within 10 min was achieved 8 of 12 times after therapy with buccal midazolam and 4 of 12 times with rectal diazepam. Overall, no statistically significant differences were noted between the two drugs.

Mpimbaza [17] conducted a similar study among 330 Ugandan children in 2008 and found buccal midazolam to have superior seizure cessation within 10 min when compared to rectal diazepam. The population in this study was much different than in developed countries given the high percentage of patients with malaria as the etiology of their seizures. Fourty-three percent of patients in the diazepam group failed to have seizure cessation after 10 min versus 30.3 % treatment failure in the midazolam group. Interestingly, there was little difference between the two drugs for treating seizures associated with malaria (35.8 versus 31.8 %). For patients without malaria, the diazepam group had a much higher failure rate (55.9) versus 22.5 % in the midazolam group.

Nakken [18•] compared buccal midazolam to rectal diazepam in an adult residential facility for patients with refractory epilepsy. The study showed a statistically significant difference in the time to cessation of seizures in convulsive SE, favoring buccal midazolam (2.8 min) over rectal diazepam (5.0 min). Non-significant differences were reported between the two drugs with regard to convulsive serial seizures, non-convulsive SE, and non-convulsive serial seizures. The study had a relatively low number of patients at 22, but 80 emergency situations were recorded over the course of the study.

Intranasal (IN) routes of BDZ therapy for acute seizures are an active area of research as well. A BDZ given IN allows for drug delivery to the nasal mucosa, which is a highly vascularized area, allowing for rapid absorption. An ideal formulation would minimize the common side effects which most commonly include rhinorrhea, nasal, and pharyngeal irritation. In 2000, Scheepers [19] demonstrated the safety of intranasal midazolam as a rescue medication for patients with refractory epilepsy that regularly required treatment with a rescue BDZ, such as rectal diazepam. Twenty-two patients with refractory epilepsy received 84 treatments with intranasal midazolam for either prolonged seizures, seizure clusters, aggression, or cyanotic episodes. Of the 84 treatments, there were only five treatment failures, defined as recurrent seizure activity within

10 min. An intranasal formulation of midazolam is currently under development [20], as are two intranasal formulations of diazepam [21•, 22]. At this time, IM midazolam and rectal diazepam remain as the most common alternatives to IV therapies for status epilepticus. Their pharmacologic data are detailed in an excellent 2015 review by Leppik [23•].

Benzodiazepines as adjunctive therapy in refractory epilepsy

Use of the BDZs in prophylactic management of refractory epilepsy is controversial due to potential for abuse, dependance, and tolerance. Benzodiazepines are traditionally used as abortive treatments for SE, but they continue to have a role in the treatment of refractory epilepsy. An ideal BDZ for this purpose would be long-acting with few of the traditional side effects of BDZs. The most commonly prescribed oral BDZs for epilepsy are clobazam, clonazepam, clorazepate, diazepam, and lorazepam.

Clobazam

Clobazam is a 1,5 BDZ, with a similar mechanism of action to the other BDZs. It differs in that it binds more selectively to the α-2 subunit of the $GABA_A$ receptor, which is thought to contribute more to the anticonvulsant activity of the BDZs rather than their sedative and hypnotic properties. This is thought to decrease its potential for sedation. This has been shown in animal models. A recent study [24] supported this data, comparing the selectivity of clonazepam, clobazam, and zolpidem in their binding to the $GABA_A$ receptor. Clobazam and its active metabolite, *N*-desmethylclobazam, demonstrated more selectivity for the α-2 subunit, while clonazepam and zolpidem showed more selectivity for the α-1 subunit. Clobazam has been used internationally since its development in 1970 for the treatment of anxiety and subsequently the adjunctive treatment of refractory epilepsy. It is currently approved in the USA as an adjunctive treatment in Lennox-Gastaut syndrome (LGS).

Clinical data has suggested that clobazam should be considered as an adjunctive therapy across a wider spectrum in epilepsy [25] and possibly considered as monotherapy in some cases. In an open-label extension trial, preliminary data in 2012 showed clobazam to have long-term safety and efficacy in the treatment of LGS [26], with an 80 % retention rate and sustained seizure control over 2 years. Recently published results from this trial for clobazam in the treatment of LGS were reported in 2014 [27•]. Two hundred sixty-seven patients were enrolled in this study, which was a combination of the populations from phase II and phase III randomized controlled trials. Of the 267 patients, 207 were able to continue taking clobazam beyond 2 years, because for patients outside the USA, it was mandatory to discontinue the drug at 2 years. The rates of drop seizures and total seizures were monitored in addition to mean dosage. Seventy percent of patients enrolled were able to complete the trial. Twenty-one percent of the patients from the USA were on the drug up to 5 years, and 11 patients were on the drug up to 6 years.

The most common reason for drug discontinuation in this study was caregiver request (12 %), followed by lack of efficacy (6 %) and adverse effects (4 %). Tolerance was not quantified specifically in this study, but it can

reasonably be interpreted that it was not an overwhelming factor due to continued efficacy without significant change in mean dosage over a 3-year period. Of 156 patients with an initial ≥50 % seizure frequency reduction, 74 patients remained at 3 years. Eighty-six percent of this subset had similar efficacy at that point in the study. The mean dosage of clobazam remained largely the same for this patient population throughout the study as well.

Clonazepam

Clonazepam is widely prescribed as an anxiolytic; however, it has been shown to be effective in the treatment of seizures. It is relatively long-acting comparatively to the other BDZs, with a half-life of 30–40 h. Clonazepam is approved in the USA for the adjunctive treatment of LGS for atonic and myoclonic seizures, and in some cases for absence seizures. Clonazepam was studied extensively in the 1970s, and a review by Pinder [28] in 1976 is an excellent resource for a summary of its early clinical trials and pharmacokinetic data. Side effects for clonazepam are characteristic of the BDZs and include ataxia, sedation, and the development of tolerance in about 30 % of patients.

Clorazepate

Clorazepate is an older, less commonly BDZ. This pro-drug is metabolized in the human gastrointestinal tract to desmethyldiazepam [29], sharing a common active metabolite with diazepam. Clorazepate is long-acting and shares the traits of the other BDZs. It was well-studied in the 1970s. It is available in both a single-dose and extended release formulation. Clorazepate is used primarily to treat patients with refractory epilepsy, though less utilized than alternative BDZs [30].

Diazepam and lorazepam

Diazepam and lorazepam are more commonly used for the acute treatment of prolonged seizures or status epilepticus rather than as adjunctive treatment in epilepsy. As previously discussed, they are available in a variety of formulations depending upon their intended use and inpatient versus outpatient setting.

Adverse effects, tolerance, and dependence

The adverse effects of the BDZs are relatively well described, comprising sedation, ataxia, and cognitive impairment most prominently. Benzodiazepines are known for their relative efficacy in the initial phase of treatment, sometimes followed by the development of tolerance, or loss of efficacy over time and at increasing doses. After initiation of therapy, patients often note being sleepy and uncoordinated, but these effects dissipate after several doses. Physical dependence, addiction via the mesolimbic reward system, and an eventual withdrawal syndrome on discontinuation can occur with the BDZs [31]. Cognitive impairment can persist in certain populations after long-term use of BDZs. Though improvement in certain areas of neuropsychiatric testing has been noted, it is apparent that long-term BDZ use can lead to persistent cognitive impairment even after discontinuation [32].

Tolerance can develop to any of the clinical properties of the BDZs, depending on their intended use. Whether prescribed as an anxiolytic, sedative, or

anticonvulsant, BDZs can lose their effect over time, requiring increasing doses to maintain the desired clinical response. The development of tolerance to the different clinical properties of BDZs occurs at different rates. Tolerance has been shown to develop to the sedative effects, followed by the anticonvulsant effects, and in some cases, the anxiolytic effects (in animal models) of BDZs. The mechanisms underlying tolerance are active areas of research. The variability of the temporal development of tolerance to the different effects of the BDZs is thought to be due to a yet to be understood unified mechanism, such as internalization of $GABA_A$ receptors, subunit remodeling, and/or genetic signals [33].

Tolerance rates to the anticonvulsant properties of clonazepam and clobazam in the past have been demonstrated in clinical studies to be between 30 and 50 % [34]. Clobazam, as noted previously, is thought to have less potential for tolerance due to its higher affinity for the α2 subunit of the $GABA_A$ receptor. A large-scale Canadian study group with 877 children and adults noted only 9 % of patients discontinuing the drug as a result of tolerance [35]. Differing definitions of tolerance may account for the variance among the literature. There is evidence to support that the intermittent use of BDZs may circumvent the development of tolerance, though most available data is limited to outpatient rescue therapies for repetitive seizures [36].

Dependence and addiction is an unfortunate characteristic of some of the BDZs and is an active area of research. Abrupt discontinuation in patients who have been maintained on BDZs in the long-term can result in a withdrawal syndrome characterized by insomnia, breakthrough seizures, and psychiatric symptoms. Tapering over several weeks is often necessary to avoid precipitating withdrawal. The α1 subunit of the $GABA_A$ receptor is thought to contribute to the addictive properties of the BDZs, as demonstrated in 2010 in α1 knockout mice versus wild-type mice given the choice for midazolam-containing solutions versus non-midazolam-containing solutions [37]. Abuse is less common among the epilepsy population, and the BZD used as adjunctive therapies are longer-acting and less likely to be used as "party drugs." The subunits involved in the addiction and reward process are likely multifactorial, as other recent papers have shown the α2 and α3 subunits to be important as well [38, 39]. Therapeutic targets for BDZs without potential for dependence or addiction thus remain elusive.

Compliance with Ethical Standards

Conflict of Interest

William A. Kilgo declares that he has no conflict of interest.
Juan G. Ochoa has received speaker fees from Sunovion Pharmaceuticals.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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