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REVIEW ARTICLE

Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability

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Abstract

Status epilepticus (SE) is an acute, life-threatening medical condition that requires immediate, effective therapy. Therefore, the acute care of prolonged seizures and SE is a constant challenge for healthcare professionals, in both the pre-hospital and the in-hospital settings. Benzodiazepines (BZDs) are the first-line treatment for SE worldwide due to their efficacy, tolerability, and rapid onset of action. Although all BZDs act as allosteric modulators at the inhibitory gamma-aminobutyric acid $(GABA)_A$ receptor, the individual agents have different efficacy profiles and pharmacokinetic and pharmacodynamic properties, some of which differ significantly. The conventional BZDs clonazepam, diazepam, lorazepam and midazolam differ mainly in their durations of action and available routes of administration. In addition to the common intravenous, intramuscular and rectal administrations that have long been established in the acute treatment of SE, other administration routes for BZDs—such as intranasal administration—have been developed in recent years, with some preparations already commercially available. Most recently, the intrapulmonary administration of BZDs via an inhaler has been investigated. This narrative review provides an overview of the current knowledge on the efficacy and tolerability of different BZDs, with a focus on different routes of administration and therapeutic specificities for different patient groups, and offers an outlook on potential future drug developments for the treatment of prolonged seizures and SE.

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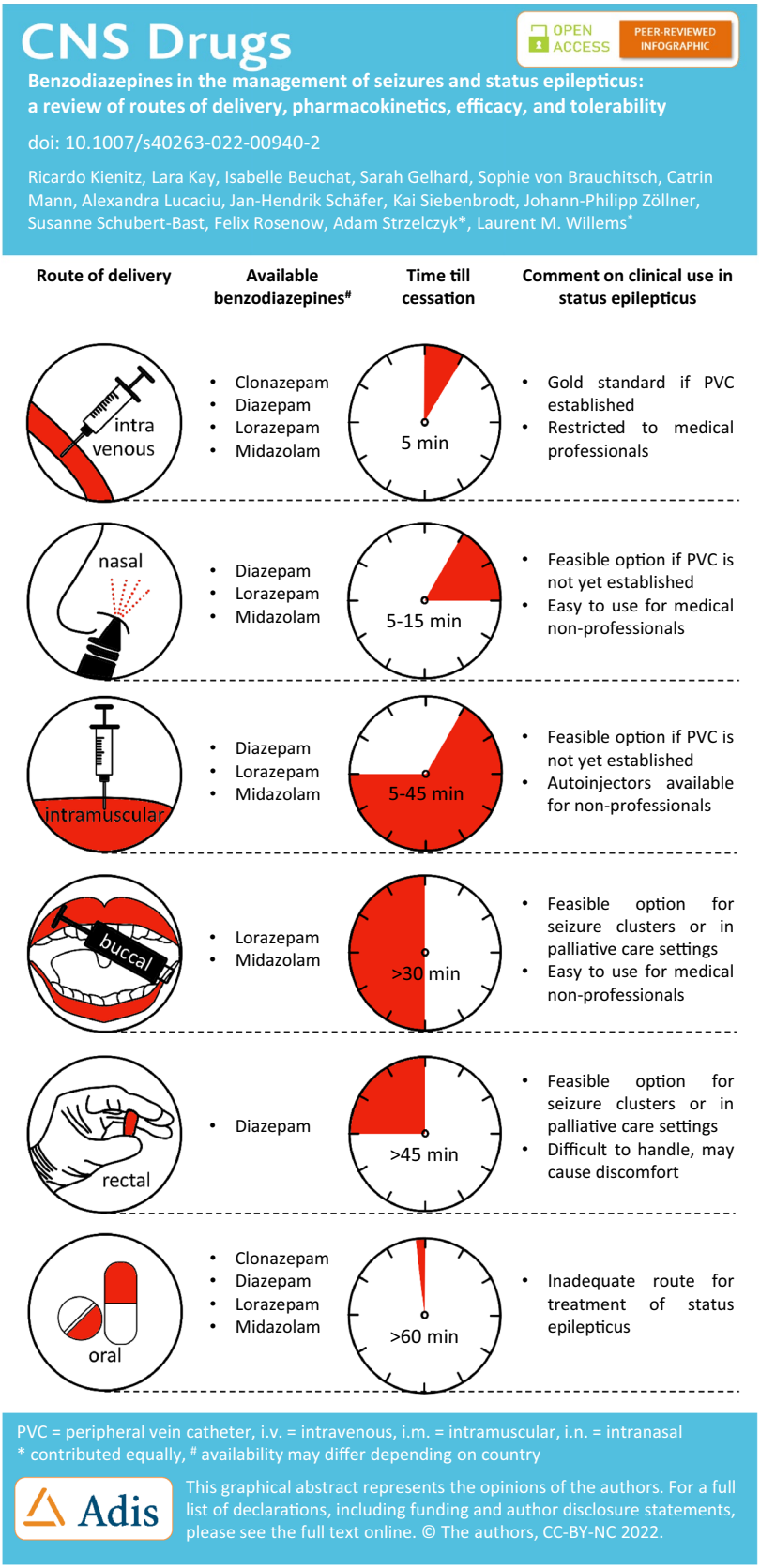
Graphical Abstract



Key Points

Non-intravenous routes for the delivery of benzodiazepines are becoming increasingly important in pre-hospital and in-hospital settings.

Ready-to-use nasal sprays, syringes, rectioles or autoinjectors are particularly suitable for lay use by epilepsy patients or their caregivers.

Somnolence is frequently reported after benzodiazepine administration, while severe side effects, such as respiratory depression and hypoxia, are rare.

The choice of benzodiazepine depends amongst others on individual pharmacokinetic and pharmacodynamic characteristics and available routes of administration.

1 Introduction

The emergency treatment of prolonged epileptic seizures, seizure clusters and status epilepticus (SE) is required to be rapid and efficient, as ongoing epileptic activity may lead to neuronal damage and result in increased morbidity and mortality [1–3]. The ideal anticonvulsant agent for this purpose should be safe, easy to administer, and exhibit a long-lasting anti-seizure effect without relevant side effects. The delineation between prolonged epileptic seizures, seizure clusters and SE is—to some extent—arbitrary and has evolved over the last few decades; however, any rescue medication should prevent seizure recurrence as well as the progression of a seizure or a series of seizures into SE [1, 4].

Benzodiazepines (BZDs), such as lorazepam (LZP), midazolam (MDZ), diazepam (DZP) and clonazepam (CZP), are established first-line drugs for the acute treatment of seizures [5]. BZDs are a family of drugs that exert their effects by allosterically modulating the activity of the ionotropic gamma-aminobutyric acid (GABA)-A receptor in the central nervous system (CNS). These drugs increase the probability that GABA binding to the receptor will open the associated Cl^- channel. Thus, these drugs generally decrease neuronal excitation and exhibit antiseizure, sedative-hypnotic, anxiolytic, muscle relaxant and amnesic properties. As a side effect, BZDs can cause drug dependence, mostly due to recreational misuse or long-term intake against medical advice, cognitive impairment and—when administered in higher doses—can cause respiratory depression.

Available routes of delivery for these drugs include intravenous (i.v.), oral (p.o.), rectal (r.s.), intramuscular (i.m.), buccal, intranasal (i.n.), and even intraosseous [6–10]. Difficulties with achieving i.v. access may lead to a delay in drug administration, rendering the development of alternative suitable routes vital, as responsiveness to BZDs during seizures decays over time [11]. Jaw clenching, hypersalivation and uncontrollable swallowing are major limitations inherent to the p.o. and buccal routes [12], making it difficult to minimize variability in pharmacodynamics due to variable intake [13]. Intramuscular injections can also be challenging in patients with tonic–clonic or hypermotor seizures [7]. While r.s. administration might be hindered by generalized convulsions, it is also becoming less popular due to the social distress and sense of shame it imposes on both patients and caregivers [14].

In comparison, i.n. administration may be a more favorable option, as it can be administered in a significantly shorter amount of time without the need for an i.v. route, and may be preferred by caregivers compared to the r.s. route [15]. Recently approved commercial preparations of MDZ and DZP nasal sprays have become available for the treatment of seizure clusters, and there is growing evidence supporting the use of pharmacy-manufactured MDZ preparations for seizures and SE. However, the use in SE is not yet established.

In this review, we discuss the commonly used BZDs, with a focus on their pharmacodynamics, pharmacokinetics, metabolism and available formulations, and we summarize the published data on their efficacy, safety and routes of delivery in the clinical management of seizures, seizure clusters and SE.

1.1 Status Epilepticus and Seizure Clusters

In 2015, the International League Against Epilepsy published a report on the definition and classification of SE [16]. This SE definition sets two time points (t1, t2), where t1 defines the semiological transition of a seizure to SE and t2 marks the point in time when neurological injury is likely to occur. Typically, the start of SE treatment is based on t1, with the time limit being 5 min for generalized convulsive (tonic–clonic) SE, 10 min for complex focal SE (focal SE with impaired consciousness), and 10–15 min for absence SE [16]. This definition applies to ongoing seizures or a series of discrete seizures between which there is only incomplete recovery of the previous neurological status. SE-induced neuronal damage is assumed to occur later, after a time (t2) of 30 min with generalized convulsive SE (GCSE) and after 60 min with complex focal SE [16]. The 5-min time limit that usually marks the transition from a prolonged seizure to SE dates back to an operational definition proposed by Lowenstein in 1999, aimed at ensuring that patients receive treatment as soon as possible [17]. This approach—equaling seizures longer than 5 min and SE irrespective of

seizure semiology—was amongst others adopted by the German clinical practice guidelines on SE [18].

Using a variety of different methodologies, regions and populations, the incidence of SE has been estimated to be 10–41 per 100,000. The overall mortality rate is 13%, but can reach up to 40% in a super-refractory course of SE [1, 19, 20]. Clinical and experimental data show a correlation between a delayed start of treatment and the reduced likelihood of successful SE termination with the first treatment attempt [11, 21, 22]. Potential underdosing might play a further role in this context [23, 24]. The urgency with which to begin treatment depends on the SE type and appears to be most pressing with GCSE [25].

The *clustering of seizures* in turn is a common clinical phenomenon and describes an increase in seizure frequency during a specific period of time, where the probability of seizure occurrence is affected by the occurrence of a previous seizure [26]. A recent review found the prevalence of seizure clusters to be between 13 and 76% for outpatient studies and 18% and 61% for inpatient video-EEG monitoring studies likely involving a high percentage of therapy-resistant epilepsy [26], while a cohort study using the United Kingdom General Practice Research Database estimated the age-adjusted prevalence at 2.5/10,000, with a peak in the 0–4 years age group (5.9/10,000) [27]. Despite being a common phenomenon, seizure clusters still lack a clear definition. Previous studies looking into acute treatment (with DZP) defined them as a characteristic episode of multiple complex partial or generalized convulsive seizures occurring within a 24-h period in adults or a 12-h period in children, with a pattern distinguishable from the patient's usual seizure pattern, and with an onset readily recognizable by a caregiver that will predict further seizures [28, 29]. Other studies have used a minimum number of seizures as a criterion (e.g., at least three seizures within 24 h, or within 4 h during video-EEG monitoring) [30–32].

While the mechanisms leading to seizure clusters are not yet well understood, well-described catamenial phenomena (i.e., a worsening of seizures in relation to the menstrual cycle) may result in perimenstrual seizure clusters [33, 34]. A better understanding of the prediction, occurrence and clustering of seizures will likely result from big data approaches, which may help to better define the clinical course and dynamics of seizure clusters [35, 36].

2 Characteristics of Individual Benzodiazepines

In the following sections we discuss the characteristics of the most commonly used individual benzodiazepines—lorazepam, midazolam, diazepam and clonazepam.

2.1 Lorazepam

LZP is a BZD with a fast onset of anticonvulsant action: It begins to act about 1–3 min after i.v. injection and has a short-to-intermediate duration of action. Additionally, LZP has sedative-hypnotic and anti-anxiety effects. Common doses for the treatment of SE in adults are 2–4 mg in the pre-hospital phase [37]. The American Epilepsy Society recommends a LZP dose of 0.1 mg/kg (a maximum single dose of 4 mg), which may be repeated [38]. In adults and children, i.v. LZP is established as efficacious at stopping seizures lasting at least 5 min [38], but due to the faster time for administration, i.m. MDZ has superior effectiveness in adults with convulsive SE when an i.v. access is not established [38].

2.1.1 Pharmacodynamics, Pharmacokinetics and Metabolism

LZP is readily absorbed after sublingual, p.o. and i.m. administration, and the bioavailability for all routes of administration exceeds 94%. The preferential route of administration for seizures or SE, however, is i.v. injection, as peak plasma concentrations are reached significantly slower when using other routes (at least 1 h after p.o. or sublingual use) [39]. LZP is highly bound to plasma proteins (91%) [40] and only unbound drug fraction diffuses into the CNS. LZP remains mostly in the intravascular compartment, as its lipophilicity is lower than that of DZP and the volume of distribution (V_d) is thus comparatively low (1.3 L/kg body weight) [39, 40]. This leads to prolonged clinical effects of LZP after a single dose by a rebalancing of bound and free drug fractions, even though "paradoxically" the elimination half-life is shorter than that of DZP [41]. A slower redistribution from the CNS to other tissues due to its relatively lower lipophilicity than, for example, DZP might further contribute to the prolonged clinical effect. This also means that LZP does not significantly accumulate in body fat after repeated administrations. Hepatic one-step, non-oxidative conjugation at the 3-hydroxy group to LZP-glucuronide is rapid, after which this non-active metabolite is predominantly excreted renally [42]. The duration of action is about 10–20 h and the elimination half-life is 8–25 h [39, 40].

2.1.2 Available Formulations

LZP is available as a tablet (0.5 mg, 1 mg and 2 mg tablets) or a concentrate (2 mg/ml) for oral use, and as a solution for i.v. injection (2 mg/ml and 4 mg/ml). In Canada and Europe, a sublingual tablet is also available (0.5 mg, 1 mg and 2.5 mg tablets). In the setting of comfort care, LZP may be used subcutaneously or rectally, but this is off-label. There is currently no manufactured form of LZP for

i.n. administration. There is some evidence that it might be efficacious in SE termination, at least in children [43]. However, nasal administration is off-label.

2.1.3 Clinical Efficacy

Before the US Food and Drug Administration (FDA) approved LZP on 30 September 1977, in 1975 a phase II trial of i.v. LZP showed promising results controlling seizures in 11 patients with EEG-confirmed SE [44]. Soon after the market introduction of LZP, Walker et al. [45] performed a non-randomized prospective trial in patients with SE, resulting in a seizure control rate of 88%. The first randomized, double-blind trial, which was designed to compare the efficacy of LZP and DZP, was published in 1983 [46] and demonstrated a higher percentage of seizure control with LZP compared to i.v. DZP. Pivotal results came from the first randomized and double-blind trial by Treiman et al. [47] in 1988, which demonstrated a superior efficacy of LZP over phenobarbital (PB) and at least equal efficacy to phenytoin (PHT ± DZP) as a first-line treatment for SE. Subsequently, further trials were designed to study the benefits of outpatient administration of LZP. Alldredge et al. [22] conducted a large placebo-controlled trial, showing that LZP at a dose of 2 mg led to seizure termination more frequently than placebo or DZP following i.v. administration by trained emergency medical technicians. However, in the largest preclinical trial to date, Silbergleit et al. [48] found that, in comparison to i.m. MDZ, the i.v. administration of LZP is more time-consuming due to venous access placement, resulting in inferiority despite high response rates in both groups. Another drawback of LZP is the need for refrigeration, limiting its use in ambulances. In the paediatric setting, LZP has been compared in controlled trials with DZP, demonstrating equal [49, 50] or higher efficacy [51]. Compared to i.m. MDZ, i.v. LZP showed a similar rate of seizure cessation [52]; albeit, this particular randomized trial was underpowered and was based on a re-analysis of [48].

In sum, LZP is frequently singled out among the BZDs for its rapid onset of action and effective seizure control when used as a first-line treatment for SE and given i.v. in adequate dose. It should be noted that, due to concerns for respiratory depression, the administration of insufficient doses with resulting limitations in efficacy is quite common. While the guidelines recommend a dose of 0.05–0.1 mg/kg [38], a prospective study of adult patients with SE demonstrated that a lower dose was administered in 84–95% of cases [53].

Tables 1 provide a detailed overview of the studies discussed in this section.

2.2 Midazolam

MDZ has a relatively short half-life of only 1–4 h. This drug exhibits anticonvulsant, sedative-hypnotic, anxiolytic, muscle relaxant and amnesic properties [54]. Following its first FDA approval in 1985, MDZ was mainly used to promote preoperative sedation, anxiolysis and anesthesia induction. More recently, newer forms of administration have extended its use to treating prolonged seizures, seizure clusters and SE. In contrast to other BZDs, MDZ formulations are available with a wide range of administration routes including p.o. (tablet and syrup), i.v., i.m., r.s., buccal and i.n. However, officially approved indications vary across the administration routes.

2.2.1 Pharmacodynamics, Pharmacokinetics and Metabolism

MDZ is generally readily absorbed after administration. However, the exact time to peak plasma concentrations (T_{max}) and bioavailability differ significantly between administration routes (p.o.: 1–2 h, 40–50%; i.v. < 5 min; i.m.: 45 min, > 90%; r.s.: 30 min, 50% (off-label); buccal: 30 min, 75%; i.n.: 7–15 min, 44%) [55–62]. When comparing to i.v. administration, i.n. administration reaches maximal plasma concentrations only slightly slower with lower maximal plasma levels. At a physiological pH, MDZ is bound to plasma proteins (97%) in part due to its lipophilia; however, at a lower pH, it becomes hydrophilic, allowing for water-based solutions. MDZ crosses the placenta and is also excreted into human milk [61]. Compared to other BZDs, MDZ has a rather short half-life of 1.5–3.5 h [63]. This drug is primarily metabolized in the liver by cytochrome P450 3A4 (CYP3A4), and its metabolites, mainly 1-hydroxymidazolam, are excreted in the urine [63]. MDZ, like other BZDs, may potentiate the action of other CNS depressants and alcohol.

2.2.2 Available Formulations

MDZ is available as a tablet (7.5 mg/tablet) or syrup (2 mg/ml) for p.o. use in adult and paediatric patients, respectively, mainly for sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures, or before anesthesia induction. A solution for i.v. injection (1 mg/ml, 5 mg/ml) is available for promoting preoperative sedation, anxiolysis, anesthesia induction or amnesia. A solution for i.m. injection (5 mg/ml) is approved for the treatment of SE in adults. Rectal use has also been reported in several studies but is not officially approved. In 2019, MDZ was approved as a nasal spray (Nayzilam®) by the FDA for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, repetitive seizures) that are

Table 1 Summary of studies on the use of lorazepam for status epilepticus

Delivery route	Study design	*n*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	Ref.
Intravenous									
LZP	OLS, SC	11	≥ 6	SE	2.5–5	100	–	–	[44]
LZP	OLS, SC	25	5–81	SE, RS	4–8	88	12	Respiratory depression (4)	[45]
LZP	OLS, SC	9	16–60	SE	4	88	–	–	[191]
LZP	OLS, MC	31	2–18	SE	0.05–0.1[a]	81	0	–	[192]
LZP	OLS, SC	77	< 12	SE	0.1[a]	79	–	–	[193]
LZP vs. i.v. CZP	OLS	61	≥ 18	SE	4–10	51–63	100	Drowsiness (100)psychomotor agitation (12)	[147]
LZP vs. i.v. DZP	RCT, DB, SC	78	≥ 18	SE	4	89	13	Respiratory depression	[46]
LZP vs. i.v. DZP	ReS, SC	44	0–18	SE, RS	0.03–0.22[a]	82	25	Respiratory depression	[194]
LZP vs. i.v. DZP	RCT, DB, MC	273	0.25–17	CSE	0.1[a]	72.9	–	Sedation (67)respiratory depression (37)	[50]
LZP vs. i.v. DZP	RCT, OLS, SC	48	1–11	CSE	0.13[a]	65	19	Admission to ICU	[49]
LZP vs. i.v. LEV	RCT, OLS	79	1–75	CSE, NCSE, RS	0.1[a]	75.6	–	Lethal course (43)respiratory depression (48)hypotension (8)	[195]
LZP vs. i.v. DZPvs. i.v. placebo	RCT, DB, SC	205	≥ 18	SE, RS	2 (LZP) 5 (DZP)	59	11	Respiratory depression	[22]
LZP vs. i.v. DZP + PHT	RCT, OLS, SC	178	1–12	CSE	0.1[a]	100	4	Respiratory depression	[121]
LZP vs. i.v. MDZ vs. i.v. CZP	PS, MC	177	≥ 16	SE, RSE	0.1[a]	Inferior to CZP or MDZ	–	–	[53]
LZP vs. i.v. DZP + PHT vs. i.v. PHT vs. i.v. PB	RCT, DB, MC	384	58.6 ± 15.6 (CSE) 62 ± 15.1 (NCSE)	CSE, NCSE	0.1[a]	65	–	Hypotension (26) respiratory depression (10) cardiac arrhythmia (7)	[47]
LZP (i.v. and rectal) vs. i.v. DZP	PS, RCT, OLS, SC	102	< 18	S, RS, SE	–	76	3	Respiratory depression	[51]
LZP vs. rectal DZP	PS, MC	182	0.2–16	CSE	0.1[a]	Superior to DZP	–	–	[196]
LZP vs. i.m. MDZ	RCT, DB, MC	893	1–94	SE	4	63,4	–	Respiratory depression (14) hypotension (14)	[48]
LZP vs. i.m. MDZ	Secondary analysis	120	< 18	SE	4–10	71.6	–	Respiratory depression (15)	[52]

RCT randomized controlled trial, *OLS* open-label study, *SC* single-centre, *MC* multicentre, *DB* double-blind, *PS* prospective study, *ReS* retrospective study, *CO* cross-over, *HV* healthy volunteer, *S* seizure, *RS* repetitive seizure, *SE* status epilepticus, *RSE* refractory status epilepticus, *TEAE* treatment-emergent adverse event, *i.v.* intravenous, *i.n.* intranasal, *i.m.* intramuscular, *p.o.* oral, *s.l.* sublingual, *MDZ* midazolam, *LZP* lorazepam, *CZP* clonazepam, *DZP* diazepam, *PHT* phenytoin, *CBZ* carbamazepine

[a] Milligram per kilogram body weight (mg/kg BW)

distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older [64, 65]. Nayzilam® is licensed for administration by a non-healthcare professional in patients actively seizing when and where a seizure cluster occurs. Intranasal MDZ solutions can also be formulated by pharmacies [66–68].

In Europe, MDZ is also European Medicines Agency (EMA) approved for buccal use (Buccolam®, oromucosal solution: 2.5 mg/0.5 ml, 5 mg/1 ml, 7.5 mg/1.5 ml, 10 mg/2 ml) for the treatment of prolonged, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years). The reason for the exclusive paediatric-use marketing authorization is that it is a special approval procedure. Thus, only i.m., buccal and i.n. administrations are officially approved for the treatment of seizures.

2.2.3 Clinical Efficacy

Due to a long history of approval, the release of MDZ in 1985, and the different approval modalities for drugs at that time, there are no phase I or II clinical trials on the i.v. use of MDZ. There are, however, several studies that have assessed the efficacy of i.v. MDZ as a bolus dose followed by a continuous infusion to terminate refractory SE (RSE) [69–71]. More recent studies have focused on other routes of administration, including i.m., buccal and i.n. Regarding i.m. administration, the first evidence stems from 1992 when Chamberlain et al. [72] showed that children with prolonged motor seizures received medication sooner and had a faster cessation of seizures when administered i.m. MDZ compared to i.v. DZP. It was subsequently shown that MDZ is also effective in terminating SE (in combination with oral PHT or carbamazepine [CBZ]) [73]. More recently, it was reported that i.m. MDZ is not inferior to i.v. LZP with regard to prehospital SE [48], which was followed up by studies showing that i.m. MDZ can act faster than r.s. DZP [74] in terminating motor activity during SE in children, and that fewer children receiving i.m. MDZ had recurrent seizures, were intubated or required ICU care compared to i.v. LZP [52].

In 1999, it was also shown that the buccal administration of MDZ is at least as effective as r.s. DZP in terminating prolonged seizures in children and young adults [75]. In addition, buccal MDZ is effective in terminating prolonged seizures in children [76] and can terminate serial seizures or SE faster and with fewer adverse events than r.s. DZP in adults [77].

The latest MDZ formulation is a nasal spray. It has been shown that i.n. MDZ reaches dose-dependent maximal plasma concentrations after ~ 8–14 min, with sneezing and local irritation reported as the most common side effects [58, 78]. Two recent phase III studies have assessed the efficacy of 5–10 mg i.n. MDZ to terminate seizures and showed the drug to be effective in approximately 54% of seizure clusters within 10 min (placebo response rate 34%) [79, 80]. Intranasal administration of MDZ has also been compared to DZP and it was found that i.n. MDZ was equally as effective as i.v. DZP in controlling seizures in children [81]. While the treatment was initiated faster in the MDZ group, the seizures were controlled slightly faster with i.v. DZP when the time needed to establish an i.v. line was excluded. Subsequent studies showed that i.n. MDZ resulted in a faster onset of action and a faster termination of seizures compared to i.v. DZP in prolonged (febrile) seizures in children [15, 82]. Two additional studies showed no significant differences in efficacy between i.n. MDZ and r.s. DZP for terminating prolonged seizures in both adults [83] and children [14] when administered by caregivers. Importantly, i.n. MDZ was generally preferred by caregivers and patients over r.s. DZP in these settings due to the ease of administration. A retrospective study showed that i.n. MDZ was comparable to i.v. LZP for seizure termination and prevention of seizure clusters in the adult epilepsy monitoring unit [84]. Use of i.n. MDZ for the treatment of SE was demonstrated in a open-label pharmaco-EEG study showing SE termination in 57% of the cases at an average time of 5 min [66].

Open questions include whether i.n. MDZ can reduce the transformation of seizures into a status epilepticus, the number of applications without increasing adverse events, and whether the availability of MDZ spray increases the rate of BZD administrations by emergency medical services [85].

Tables 2 provide a detailed overview of the studies discussed in this section.

2.3 Diazepam

DZP is a BZD with a relatively long half-life compared to other drugs in this class. DZP is approved by the FDA and EMA for the treatment of anxiety, acute alcohol withdrawal, skeletal muscle spasms and convulsive disorders, such as SE. In addition, it is commonly used off-label for numerous other conditions including insomnia, restless legs syndrome, and pre-/post-operative sedation [86]. DZP is available as an oral tablet, oral solution, as preparations for i.v. or i.m. use and, since 2020, as a ready-made solution with a one-way applicator for i.n. administration.

2.3.1 Pharmacodynamics, Pharmacokinetics and Metabolism

DZP interacts with alcohol and many different classes of drugs, including analgesics, antibiotics, anticonvulsants and antidepressants. In addition, oral contraceptives can inhibit the biotransformation of DZP, thereby increasing its effects and possibly increasing the incidence of break-through bleeding [87]. However, DZP should be avoided in pregnant

Table 2 Summary of studies on the use of midazolam for status epilepticus

Delivery route	Study design	*n*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	Ref.
Intravenous									
MDZ	PS, OLS	19	16–87	RSE	0.2[a] bolus then, 1 µg/kg/min	94.7	21	Pharyngeal hypersecretion	[69]
MDZ vs. i.v. propofol	ReS	20	17–81	RSE	2–12 bolus, then 0.05–0.8[a] /h	67	–	–	[70]
Intramuscular									
MDZ vs. i.v. LZP	RCT, DB, MC	102	0–102	SE	10	73.4	–	Endotracheal intubation (14) hypotension (3)	[48]
MDZ vs. i.v. LZP	Secondary Analysis	120	0–17	SE	5–10	68.3	Inferior to LZP	Intubation hospitalization ICU care	[52]
MDZ vs. rectal DZP	RCT	100	0–16	SE	0.3[a]	96	0	–	[74]
MDZ + p.o. PHT vs. p.o. CBZ	PS, OLS	38	–	SE	15	84	–	Drowsiness	[73]
Buccal									
MDZ	OLS, SC	19	0–15	S, SE	0.3[a]	100 (AS), 50 (SE)	–		[76]
MDZ (s.l.)	OLS, SC	10	23–47	HV	10	–	–	–	[13]
MDZ vs. rectal DZP	PS	22	25–68	SE	15.5	83.3	21	Tiredness ataxia	[77]
MDZ vs. rectal DZP	RCT, OLS, SC	18	5–19	S	10	75	–	Mild decrease in blood pressure	[75]
Intranasal									
MDZ	OLS	175	12–62	RS	5–10	55	40–57	Nasal discomfort somnolence headache	[80]
MDZ vs. placebo	RCT, DB	292	12–65	RS	5	54	2)	Nasal discomfort somnolence	[197]
MDZ vs. i.v. MDZ	OLS, CO, SC	6	27–47	HV	5	–	–	Temporary nasal irritation	[58]
MDZ vs. i.v. LZP	ReS, SC	50	38.6 (SD 14.0)	S, RS	3 MDZ or 1–2 LZP	No difference	30.4 MDZ	Somnolence	[84]
MDZ vs. i.v. DZP	RCT	70	0–15	S	0.2[a]	Inferior to DZP	0	–	[81]
MDZ vs. rectal DZP	PS, RCT, SC	358	< 18	S	0.2[a]	Not inferior to DZP	–	Respiratory insufficiency (6) intubation (2)	[14]
MDZ vs. rectal DZP	PS, OLS	24	25–69	RS, SE, RSE	10	82		Drowsiness (68) local irritation 29)	[83]

RCT randomized controlled trial, *OLS* open-label study, *SC* single-centre, *MC* multicentre, *DB* double-blind, *PS* prospective study, *ReS* retrospective study, *CO* cross-over, *HV* healthy volunteer, *S* seizure, *RS* repetitive seizure, *SE* status epilepticus, *RSE* refractory status epilepticus, *TEAE* treatment-emergent adverse event, *i.v.* intravenous, *i.n.* intranasal, *i.m.* intramuscular, *p.o.* oral, *s.l.* sublingual, *MDZ* midazolam, *LZP* lorazepam, *CZP* clonazepam, *DZP* diazepam, *PHT* phenytoin, *CBZ* carbamazepine

[a]Milligram per kilogram body weight (mg/kg BW)

women as there is evidence for an increased risk of harmful effects on the human fetus or neonate without causing malformations [88].

With a V_d of 0.95 to 2.01 L/kg, DZP is a widely distributed compound showing a bioavailability of 93–100% after p.o. administration, 90% after r.s. administration, and 97% after i.n. administration [89–92]. Peak plasma levels are reached after 30–90 min following p.o. administration, 30–60 min after i.m. injection, 10–45 min after r.s. administration, 45 min after i.n., administration, and < 5 min after i.v. delivery. With chronic dosing, steady-state levels are reached after 5–14 days [89–92]. The half-life of DZP is 24–48 h due to an extended redistribution into the muscle and fat tissue after initial adsorption [90]. However, the half-life and free fraction of DZP increases in aged populations due to reduced carrier albumin serum levels and a high plasma protein binding of > 98% [93, 94]. The metabolization of DZP is mediated by hepatic CYP450 enzymes and glucuronidation for the renal elimination of several metabolites; however, marginal amounts of unmetabolized DZP can be found in the urine [95].

2.3.2 Available Formulations

DZP is available as a tablet (2 mg, 5 mg and 10 mg tablets) or a concentrate (10 mg/ml) for oral use, as a rectal suppository (10 mg/suppository), as rectal enema (5 mg/vial, 10 mg/vial; also as a rectal gel in an administration device), and as solution for i.v. injection (5 mg/ml, available as a clear water solution and as a lipid emulsion). In the USA, an FDA-approved ready-to-use DZP nasal spray has been available since 2020 under the trade name VOLTOCO® (5 mg/0.1 ml, 7.5 mg/0.1 ml and 10 mg/0.1 ml) for seizure clusters or repetitive seizures in patients aged 6 years or older [89].

2.3.3 Clinical Efficacy

For i.n. use, there are four phase I studies in healthy volunteers showing a feasible pharmacokinetic profile for DZP [96–99]. Another study in heathy volunteers revealed that i.m. administration of DZP resulted in a more rapid and less variable drug absorption compared to r.s. delivery [100]. Overall, three phase II studies for DZP were identified that compared rectal gel to i.n. [92] or i.m. administration using an auto-injector [101, 102] for the treatment of repetitive seizures.

For phase III studies, two double-blinded, multicentre, randomized controlled trials and one single-centre open-label trial were found, which revealed significant increases in seizure-free intervals in patients with seizure clusters using a DZP auto-injector. The seizure termination rate in these studies was approximately 78% [103, 104]. The efficacy of p.o., i.v. or r.s. DZP at doses of 0.2–0.5 mg/kg, or up to 20 mg, for the termination of seizures, seizure clusters or SE in general has been extensively demonstrated [22, 28, 29, 105–115]. Subsequently, several studies have compared the efficacy of DZP and valproate (VPA) for terminating SE and showed a response rate of 56–85% for DZP and 50–80% for VPA [116, 117]. Additional studies comparing the i.v. use of DZP to LZP or MDZ revealed a SE cessation rate of 72–100% [46, 50, 51, 118, 119]. However, in some studies, multiple doses were required to finally gain seizure control [120]. Other studies comparing the combination of i.v. DZP plus PHT with i.v. LZP or PB treatment showed a cessation of seizures or SE in 56–100% of cases for DZP [40, 121, 122]. Further studies have compared the efficacy of DZP with i.m. MDZ, revealing a seizure control rate of 88–91% for i.m. and i.v. DZP, respectively [72, 123, 124], and a 94% rate for the r.s. delivery of DZP [74]. Comparative studies examining the differences between i.n. or buccal/sublingual MDZ or LZP and DZP showed a cessation rate of 65–93% for i.v. DZP [15, 125–130], and 45–100% for the r.s. administration of DZP [12, 75, 77, 83, 131–138]. In addition, several reports have revealed no differences in efficacy between i.n. MDZ or LZP and DZP [14, 139]. For a detailed overview of the mentioned studies please refer to Table 3.

With regard to the safety and tolerability of DZP, frequent substance-specific treatment-emergent adverse events (TEAEs) have been identified, including somnolence, sedation, drowsiness, vomiting, hyperactivity, tiredness, hypotension and ataxia [77, 83, 107, 113, 120, 124, 135]. Several severe TEAEs have also been reported, mostly due to respiratory depression that, in some cases, required mechanical ventilation [50, 72, 117, 118, 121]. In addition, different TEAEs have been reported that are specific to the individual routes of administration. For example, injection site pain for i.m. [103, 104], thrombophlebitis for i.v. [123], and nasal discomfort for i.n. administration [92, 101, 102].

2.4 Clonazepam

CZP has been used for over 40 years to treat seizures, paediatric and adult SE, chronic epilepsy (including severe childhood epilepsy, such as Lennox-Gastaut syndrome, absence or myoclonic seizures), and—in the USA—panic disorders. Evidence supporting the efficacy of CZP for SE is still scarce, mainly consisting of uncontrolled case series. Therefore, even if widely used in Latin America and in many European countries, CZP is still not recommended by the latest European or American SE guidelines [38, 140]. Various formulations and routes of delivery for CZP exist. However, their availability varies among countries. For example, i.v. formulations are not available in the USA, while disintegrating tablets are not accessible in Europe.

Most of the existing data regarding CZP efficacy for the treatment of SE or seizure clusters are based on i.v.

Table 3 Summary of studies on the use of diazepam for status epilepticus

Delivery route	Study design	*N*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	References
Intravenous									
DZP	SC	15	16–73	RS, SE	5–40	82	–	–	[114]
DZP	RCT, MC	21	0–2	RS	–	87	–	Respiratory arrest	[111]
DZP infusion	ReS, SC	62	1–12	RSE	0.017 mg/kg/min	86		Hypotension, respiratory depression	[113]
DZP vs. i.v. VPA	RCT, SC	20	0–12	RSE	10	85	–	Respiratory depression	[117]
DZP vs. i.v. VPA	PS	66	41[d]	SE	2 × 0.2[b] in 10 min	56	–	–	[116]
DZPvs. i.v. LZP	RCT, DB, SC	78	–	S	5	76	–	Respiratory depression	[46]
DZP vs. i.v. LZP	RCT, DB, MC	140	3–18	SE	0.2[b]	72	–	Respiratory depression	[50]
DZP vs. i.v. LZP	RCT, MC	273	0–17	SE	–	Not superior	–	Respiratory depression	[139]
DZP vs. i.v. LZP vs. i.v. placebo	RCT, DB, SC	205	≥ 18	SE	5	Superior to placebo	–	Respiratory complications, circulatory complications	[22]
DZP vs. i.v. LZP and rectal DZP vs. rectal LZP	RCT, SC	53	3.3–6.6[c]	SE	0.3–0.4[b]	85 (i.v.) 37 (rectal)	15	Respiratory depression	[51]
DZP + PHT vs. i.v. LZP vs. i.v. PH	RCT, DB, MC	570	58.6[c]	SE	0.15[b]	56	–	Hypoventilation, cardiac arrhythmia	[47]
DZP + PHT vs. i.v. LZP	RCT, SC	88	1–12	SE	0.2[b] (+ 18[b] PHT)	100	–	Respiratory depression	[121]
DZP vs. i.v. MDZ	RCT, SC	19	2–12	RSE	0.5[a]	90	–	Respiratory depression	[118]
DZP vs. i.v. MDZ	RCT	120	Children	S	0.3–0.5[b]	100	–	–	[119]
DZP vs. i.v. MDZ vs. i.v. LZP	RCT, SC	120	0–14	S	0.3[b]	73	–	Somnolence, sedation	[198]
DZP + PHT vs. PB + PHT	RCT, SC	36	43.8[c]	SE	2/min	Inferior to PB	–	Respiratory failure	[122]
DZP vs. i.n. MDZ	RCT, SB, SC	35	0–15	S	0.2[b]	Superior to MDZ	–	–	[81]
DZP vs. i.n. MDZ	RCT, SC	60	0–15	S	0.3[b]	Inferior to MDZ	–	–	[127]
DZP vs. i.n. MDZ	RCT, SC	50	1–12	S	0.3[b]	65	–	–	[15]
DZP vs. i.n. MDZ	RCT, SC	125	–	S	0.3[b]	Inferior to MDZ	–	–	[130]
DZP vs. i.m. MDZ	RCT, SC	115	0–12	S	0.2[b]	–	11	Thrombophlebitis	[123]
DZP vs. i.m. MDZ	RCT, SC	32	0–14	S	0.5[b]	88	–	Vomiting, hyperactivity	[124]
DZP vs. i.m. MDZ	RCT, SC	11	0–10	SE	0.3[b]	91	9	Respiratory depression	[72]

Table 3 (continued)

Delivery route	Study design	*N*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	References
DZP vs. buccal MDZ	RCT, SC	120	0–12	S	0.3[b]	93.3	–	–	[128]
DZP vs. buccal MDZ	RCT, SC	92	0–14	S	0.3[b]	70	42	Respiratory failure	[129]
Intramuscular									
DZP	RCT, DB, MC	234	≥ 2	RS	5, 10, 15, 20[a]	Reduction of time to next seizure	42	Injection site pain (17), injection site hemorrhage (5)	[103]
DZP	RCT, MC	234	2–83	RS	5, 10, 15[a]	78	75	Injections site pain (11), injections site hemorrhage(6)	[104]
DZP vs. i.m. rectal gel	SC, OLS	24	18–55	HV	10	i.m. superior to rectal	–	Pain, discomfort, drowsiness	[100]
DZP vs. DZP rectal gel	RCT, DB, SC, CO	48	18–40	RS	5, 10, 15[a]	–	22	Injection site discomfort	[101]
Rectal (gel or solution)									
DZP	ReS, SC	50	34.7[c]	RS	0.2[b]	90		Somnolence	[107]
DZP	SC	39	16–65	RS	20, 30	29–72		Drowsiness	[108]
DZP	SC	17	–	RS	0.5[b]	66		Respiratory difficulties, dizziness	[115]
DZP	OLS	149	2–76	RS	0.2–0.5[b]	77	–	Sedation	[109]
DZP vs. placebo	RCT, DB, MC	96	≥ 18	RS	0.2[b]	–	–	–	[105]
DZP vs. placebo	RCT, DB	125	2–60	RS	0.2–0.5[b]	Superior to placebo	–	–	[28]
DZP (rectal or p.o.) vs. placebo	RCT, DB, SC	40	18–60	RS	20	Superior to placebo	–	–	[110]
DZP vs. placebo	RCT, DB, MC	158	> 2	RS	0.2–0.5[b]	55	–	Somnolence	[29]
DZP vs. placebo	PS, DB	133	2–17	RS	5	Superior to placebo	–	Somnolence	[112]
DZP vs. i.m. MDZ	RCT, SC	100	0–16	SE	0.5[b]	94	–	–	[74]
DZP vs. buccal MDZ	RCT, MC	110	0–15	S	2.5–10	45	6	Respiratory depression	[12]
DZP vs. buccal MDZ	RCT, SB, SC	165	0–12	S	2.5–10	57	–	Respiratory depression	[131]
DZP vs. buccal MDZ	RCT, SC	39	5–22	S	10	59	–	–	[75]
DZP vs. buccal MDZ	RCT, MC	98	0–12	S	0.5[b]	82	–	–	[132]
DZP vs. buccal MDZ	RCT, SC	43	0–12	S	0.3–0.5[b]	85	–	–	[133]

Table 3 (continued)

Delivery route	Study design	*N*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	References
DZP vs. buccal MDZ	RCT, SC	22	25–82	S	5	83	–	Tiredness, ataxia	[77]
DZP vs. buccal MDZ	RCT, SC	34	0–18	S	0.5[b]	100	–	–	[136]
DZP vs. sublingual LZP	RCT, MC	436	0–10	S	0.5[b]	79	–	–	[137]
DZP vs. i.n. MDZ	RCT, SC	45	0–13	S	0.3[b]	60	–	–	[134]
DZP vs. i.n. MDZ	RCT, SC	46	0–12	S	0.3[b]	89	–	Vomiting, drowsiness, hypoxia	[135]
DZP vs. i.n. MDZ	PS, SC	21	25–69	S	10	89	–	Drowsiness	[83]
DZP vs. i.n. MDZ	RCT, SB, MC	358	3–11	S	0.3–0.5[b]	Not superior	–	Respiratory failure (1)	[14]
DZP vs. i.n. MDZ	RCT, MC	358	–	RS	0.3–0.5[b]	–	–	–	[138]
Intranasal									
DZP	Pilot study	24	18–45	HV	10	–	–	–	[96]
DZP	Pilot study	8	28.3[c]	HV	5, 10	–	–	–	[98]
DZP	MC	78	18–65	S	0.2[b]	–		Nasopharyngeal signs	[92]
DZP vs. i.v. MZD	Pilot study	4	20–24	HV	5	–	–	–	[99]
DZP vs. rectal gel DZP	OLS, CO	24	18–50	RS	5, 20 [a]	–	32–48	Nasal redness, nasal discomfort	[102]
DZP vs. i.v. DZP	Pilot study	9	20–30	HV	20 (i.n.) 2 (i.v.)	–	–	–	[97]

RCT randomized controlled trial, *OLS* open-label study, *SC* single-centre, *MC* multicentre, *DB* double-blind, *PS* prospective study, *ReS* retrospective study, *CO* cross-over, *HV* healthy volunteer, *S* seizure, *RS* repetitive seizure, *SE* status epilepticus, *RSE* refractory status epilepticus, *TEAE* treatment-emergent adverse event, *i.v.* intravenous, *i.n.* intranasal, *i.m.* intramuscular, *p.o.* oral, *MDZ* midazolam, *LZP* lorazepam, *DZP* diazepam, *VPA* valproate, *PHT* phenytoin, *PB* phenobarbital

[a] Absolute

[b] Milligram per kilogram body weight (mg/kg BW)

[c] Average

administration studies [53, 141–147]. Anecdotal evidence exists regarding the wafer formulation (orally disintegrating tablets) [148], and only phase I and II trials have been conducted for i.n. [149], r.s. [150], i.m. [151], oral droplets [152] or subcutaneous [153] formulations.

2.4.1 Pharmacodynamics, Pharmacokinetics and Metabolism

CZP is more lipophilic than LZP, but less so than DZP, with consequently less redistribution compared to the latter drug. Its protein binding is 86%, which is somewhat lower than for other BZDs. After i.v. administration, CZP reaches the brain within 1 min, and its distribution follows a two-compartment model with a half-life from 0.7 to 3.4 h and a V_d from 1.5 to 4.4 L/kg [40]. After p.o. administration, CZP is completely absorbed with an absolute bioavailability of ~90% (T_{max} is achieved within 1–4 h) [154].

In a preclinical study, i.n. CZP administration using nanocarriers was demonstrated to be safe and effective [149], and oral droplet administration (with CZP dissolved into droplets of propylene glycol) has been shown to achieve therapeutic levels within 10–15 min [152].

Rectal administration (11 healthy children with previous febrile convulsion, six aged 1.4–4.7 years at a dose of 0.05 mg/kg, and 5 aged 1.4–4.1 years at a dose of 0.1 mg/kg) showed plasma concentrations indicating a rapid absorption (T_{max} 10 min–2 h, mean 30 min) [150]. One open-label study investigating the pharmacokinetics of i.v., i.m. and p.o. CZP (2 mg) reported a slower absorption rate after i.m. administration compared to p.o. administration (T_{max} 3.1 h vs. 1.7 h) [151].

Subcutaneous injection of CZP (microspheres) demonstrated complete absorption with a slow-release pharmacokinetic profile [153]. CZP has a long half-life of 30–40 h and undergoes extensive metabolism, primarily by CYP3A4, with no formation of active metabolites. Due to its extensive CYP450 metabolism, several drug interactions exist. For example, CYP450 inducers, such as PHT, CBZ, lamotrigine (LTG) or PB, can cause a 38% decrease in CZP plasma levels. Similarly, CYP inhibitors, such as antifungal agents, may impair CZP metabolism [154, 155]. CZP can be kept at ambient temperature and can be administered as a rapid i.v. bolus (0.015 mg/kg, over ≤ 30 s).

2.4.2 Available Formulations

CZP is available as a tablet (0.5 mg and 2 mg tablets), orally disintegrating tablet and concentrate (2.5 mg/ml) for oral use and as solution for i.v. injection (1 mg/ml).

2.4.3 Clinical Efficacy

Since the first clinical publication by Gastaut in 1971 [142], few clinical trials have been conducted to evaluate the efficacy of CZP for SE. In addition to the trials described below, eight uncontrolled case series from the 1970s (a total of 385 patients) reported CZP to be effective in approximately 80–90% of patients [144]. In the initial publication, Gastaut and colleagues reported SE termination, without unfavorable side effects, in 38/39 SE episodes treated with i.v. CZP (1–8 mg) [142]. In children, an early study (17 children, age 2 weeks to 15 years) reported SE cessation after i.v. CZP (0.25–0.75 mg) in all cases without significant side effects [141].

More recently, two retrospective studies suggested that i.v. CZP may not be inferior—and may even be superior—to other BZDs [53, 145]. A retrospective multicentre study including 177 adult patients reported the prescription of CZP as a first-line treatment in 72 (41%) SE patients, with 82 (46%) and 23 (13%) using LZP and MDZ, respectively. Interestingly, only 85% of the patients received BZDs as a first-line treatment and 59% were prescribed an insufficient dosage [53]. A single-centre retrospective assessment of 167 SE episodes described i.v. CZP as the most effective treatment (50% response rate) for terminating GCSE compared to i.v. DZP (18%), i.v. LZP (29%) or i.m. MDZ (12%) [145]. Even if not designed to evaluate CZP efficacy, a randomized double-blind trial (SAMUKeppra) evaluating i.v. levetiracetam (LEV; 2.5 g) plus i.v. CZP (1 mg) versusplacebo plus i.v. CZP in outpatient GCSE treatment offered good insights regarding CZP efficacy [143]. No advantage was found with the addition of LEV over CZP alone. Convulsions stopped after 15 min in 84% (57/68) of patients receiving CZP alone [143]. Regarding non-i.v. formulations, a retrospective study investigating the efficacy of CZP wafers for the acute treatment of prolonged seizures in children and young adults (2–25 years) reported seizure termination in 38/56 (68%) patients [148]. In 19/56 (34%) patients, seizure termination was reported within 1 min, perhaps partially corresponding to a spontaneous termination.

In conclusion, although class I evidence is currently lacking, i.v. CZP, which is already widely used, constitutes a good option for first-line SE treatment. Regarding alternative routes of administration, p.o. administration (CZP wafers) and i.m. administration is not recommended due to its slower absorption rate, and—despite promising phase I–II studies—i.n. and r.s. formulations are not yet available.

Tables 4 provide a detailed overview of the studies discussed in this section.

Table 4 Summary of studies on the use of clonazepam for status epilepticus

Delivery route	Study design	*n*	Age (years)	SE types	Dosage (mg)	Seizure control (%)	TEAE rate (%)	Frequent TEAE (%)	Ref.
Per os									
CZP	ReS, SC	56	2–25	RS, SE	0.25, 0.5, 1 or 2	68	–	–	[148]
Intravenous									
CZP	–	16	–	SE	1	88	–	–	[199, 200]
CZP	–	17	–	SE	1–6	82	–	–	[201]
CZP	–	194	–	SE	0.5–10	81 (19 multiple doses)	–	Respiratory depression, somnolence	[202]
CZP	PS, OLS, SC	8	–	SE	2	100	–	Drowsiness, ataxia	[203]
CZP	PS, OLS, SC	65	–	SE	1–4	83	–	Respiratory depression, somnolence	[204]
CZP	PS, OLS, SC	40	< 18	SE	0.5–2	75	–	–	[205]
CZP	–	13	0.15–15	SE	0.4–3	77	–	–	[206]
CZP	–	32	–	SE	2	84	–	–	[207]
CZP	ReS, OLS, SC	17	0–15	SE	0.25–0.75	100	–	–	[141]
CZP	OLS	24		SE, RS	1–2	100 (focal aware), 66 (focal unaware) 50 (GTC)	42	Respiratory depression, drowsiness	[146]
CZP (bolus vs. perfusion)	ReS, OLS, SC	37	–	SE	1–8	97	–	–	[142]
CZP vs. i.v. LZP vs. i.v. LZP + CZP	OLS	61	≥ 18	SE	1	76	–	Drowsiness, psychomotor agitation	[147]
CZP vs. i.v. DZP vs. i.v. LCM vs. i.v. LEV vs. i.v. LZP vs. i.v. MDZ vs. i.v. PHT vs. i.v. VPA	ReS, SC	167	63.1 (SD 17.4)	S, SE, RSE	1.2 (SD 1) –5.5 (SD 5.3)	50	–	–	[145]
CZP vs. i.v. LZP vs. i.v. MDZ	PS, OLS, MC	177	≥ 16	SE, RS	0.015[a]	56.96 (endpoint: not RSE)	–	–	[53]
CZP + placebo vs. i.v. CZP + LEV	RCT, DB	205		S, RS	1	84	19	Respiratory failure, cardiac failure	[143]

RCT randomized controlled trial, *OLS* open-label study, *SC* single-centre, *MC* multicentre, *DB* double-blind, *PS* prospective study, *ReS* retrospective study, *S* seizure, *RS* repetitive seizure, *SE* status epilepticus, *RSE* refractory status epilepticus, GTC generalized tonic clonic sizure, *TEAE* treatment-emergent adverse event, *i.v.* intravenous, *p.o.* oral, *MDZ* midazolam, *LZP* lorazepam, *CZP* clonazepam, *VPA* valproate, *PHT* phenytoin, *LCM* lacosamide, *LEV* levetiracetam

[a]Milligram per kilogram body weight (mg/kg BW)

2.5 General Considerations

We would like to point out that, although the previously discussed established pharmacokinetic and pharmacodynamic measures provide a good overview of how a drug acts, additional factors might contribute to complex drug behaviors. For instance, time of maximum concentration in plasma after IV administration does not necessarily correspond to the time of maximum pharmacologic effect, for example due to the delay in diffusion across the blood-brain barrier [156–158]. Furthermore, the half-life of a drug might not necessarily correspond to the duration of action (as mentioned above), which, for example, also depends on the size of the dose and the extent of peripheral tissue distribution during the initial distribution phase.

2.6 Group-Specific Side Effects

All benzodiazepines can—due to their action as a $GABA_A$-receptor agonists—cause amnesia, sedation, respiratory depression and coma. Therefore, after administration, monitoring of the patient´s clinical status, especially vigilance breathing, and protective reflexes is mandatory. In case of a severe respiratory depression, protective intubation usually involving muscle relaxants can be necessary, which in turn hinders further evaluations of the patient's clinical status, neurological assessment and seizure detection without EEG. Furthermore, consequent admission to the intensive care unit might increase the risk of ventilation-associated pneumonia, which in turn can promote refractory SE and lead to poorer outcome [159–161]. Though, it should be mentioned that SE per se can also cause severe respiratory depression.

As side effects depend on dose and time of action, choice of an adequate initial dose and of a short-acting drug are important factors (e.g., MDZ i.v. or the newer formulations). The benzodiazepine effect can further be counteracted by the BZD antagonist flumazenil.

Of the discussed benzodiazepines, all but LZP are mainly metabolized via CYP450 enzymes and glucuronidation for the renal elimination of metabolites. LZP in turn is metabolized by hepatic one-step, non-oxidative conjugation after which the non-active metabolite is predominantly excreted renally. This might make LZP a preferential choice in patients with liver disease. Dose adjustments should be made according to product labels.

3 Novel Administration Routes and Other Benzodiazepines

New routes of drug administration, such as the intrapulmonary route, are currently being investigated for the treatment of epilepsy and other disorders [162, 163]. Due to a large surface area, and high permeability and blood flow in the lung, rapid systemic drug effects are possible with inhalation therapies [164]. Therefore, intrapulmonary administration for the treatment of SE seems promising. In 1994, Xi et al. treated 120 patients with seizures in a single-blind trial with inhalable DZP and showed a significant effect on seizure control [165]. Dhir and colleagues also showed that MDZ and a propofol prodrug are highly effective antiseizure drugs when administered intrapulmonarily in a preclinical model [166, 167]. Currently, intrapulmonary administration of alprazolam delivered via the Staccato delivery system is being developed as a rapid epileptic seizure termination therapy. This drug delivery system vaporizes the drug through a heating package that is activated by breathing through the system. The drug vapor condenses into aerosol particles and is delivered into the lungs by normal breathing.

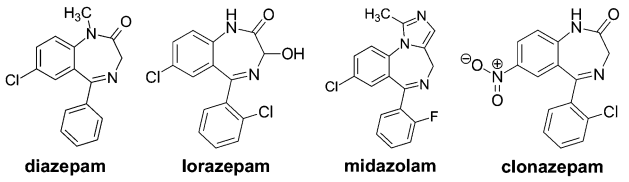


Fig. 1 Overview of the structural forms of the benzodiazepines diazepam, lorazepam, midazolam and clonazepam, which are discussed in this review. Even though the benzodiazepines are structurally very similar and closely related, their different pharmacological and pharmacokinetic properties result in relevant differences that are of particular importance when considering various delivery routes. All structural forms displayed have been released into the public domain by their creators

Alprazolam is a 1,4-benzodiazepine and also an allosteric modulator of $GABA_A$-receptors. This drug was approved by the FDA for the treatment of anxiety and panic disorders in 1981 and is available for p.o. administration [168]. Alprazolam does not have an indication for seizure therapy at present, but preclinical studies suggest that it does have a potent antiseizure effect [164]. After p.o. administration, peak concentration in the plasma is reached in 1–2 h and is proportionate to the dose. Single doses usually range from 0.5–3 mg and result in peak levels of 8–37 ng/ml. Alprazolam has an intermediate onset of action (function of rate of absorption) compared to other BZDs and mean plasma elimination half-life of ~6–15 h [169, 170]. In a phase 1 study, 1 mg of inhaled alprazolam reached a peak concentration of 48 ng/ml in smokers and 26.72 ng/ml in non-smokers after 1.8 min [171]. In vitro, alprazolam is mostly bound to serum albumin (80%). It is mainly metabolized by CYP3A4, which means that pharmacological interactions must be considered. The two main metabolites of alprazolam are 4-hydroxyalprazolam and α-hydroxyalprazolam, both of which have low plasma concentrations in comparison to alprazolam and do not contribute to the pharmacological effects of this drug.

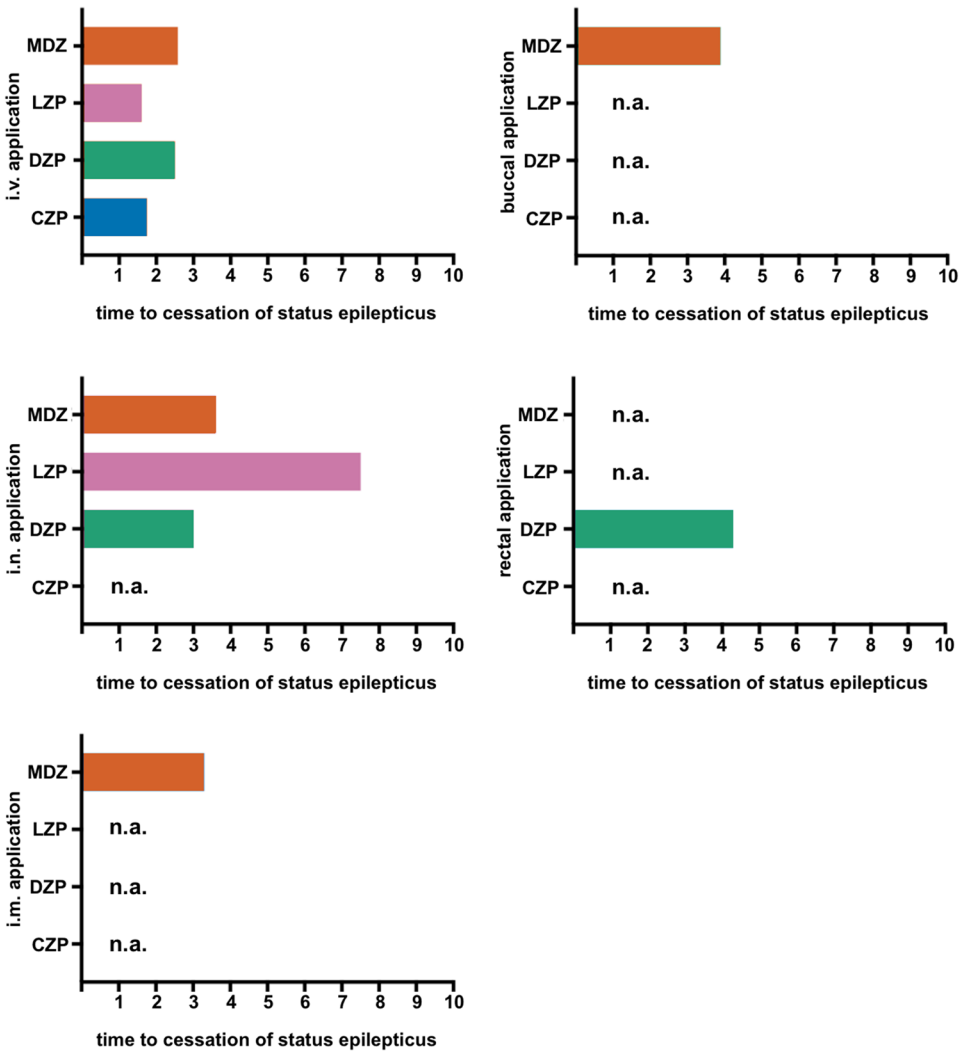


Fig. 2 Mean time from drug administration to cessation of status epilepticus (SE) in minutes is displayed for different delivery routes, based on literature research, as far as available (n.a. = not available). Intravenous (i.v.) administration showed the fastest onset of action with a latency of less than 3 min, followed by intranasal (i.n.) and intramuscular (i.m.) administration, as well as buccal and rectal delivery. Due to the heterogeneous patient populations and study settings, the displayed values should only serve as a basic guidance [48, 50, 51, 146, 186–190]. *MDZ* midazolam, *LZP* lorazepam, *DZP* diazepam, *CZP* clonazepam

Alprazolam and its metabolites are excreted primarily in the urine [171]. In a phase IIa study, five patients with a diagnosis of photoparoxysmal response on EEG received alprazolam intrapulmonarily via the Staccato system in 0.5–2 mg doses after intermittent photic stimulation [164]. The number of photic stimulation frequencies that produced a photoepileptiform response was measured after inhalation. Staccato alprazolam reduced the number of photic stimulation frequencies at 2 min compared to placebo, and the effect stopped after 4 h for the 0.5 mg dose and after 6 h for the 1 and 2 mg doses. Alprazolam plasma concentrations were dose related and reached 31.5 ± 3.14 ng/ml within 2 mins after the inhalation of 2 mg [164].

Potential limitations include the patient's compliance, insufficient spontaneous breathing during seizures, or reduced transpulmonary diffusion capacity. The results of a phase IIb randomized, double-blind, inpatient study and phase III studies exploring the efficacy and safety of Staccato alprazolam for the acute termination of a predictable seizure pattern are currently pending.

4 Special Therapeutic Aspects for Infants and Children

4.1 Particular Features of the Pharmacokinetics of Benzodiazepines (BZDs) in Children

As with many other drugs, the pharmacokinetics of BDZs vary with age. This is mainly due to the maturation of the hepatic microsomal oxidizing system over the 6 months after birth. Consequently, the pharmacokinetics of hepatic metabolized pharmaceuticals in children less than 6 months of age are significantly different from adults. Cytochrome P450-catalyzed metabolism tends to be low at birth but exceeds adult values by 2–3 years of age. Thereafter, CYP-catalyzed metabolism decreases again, reaching adult levels

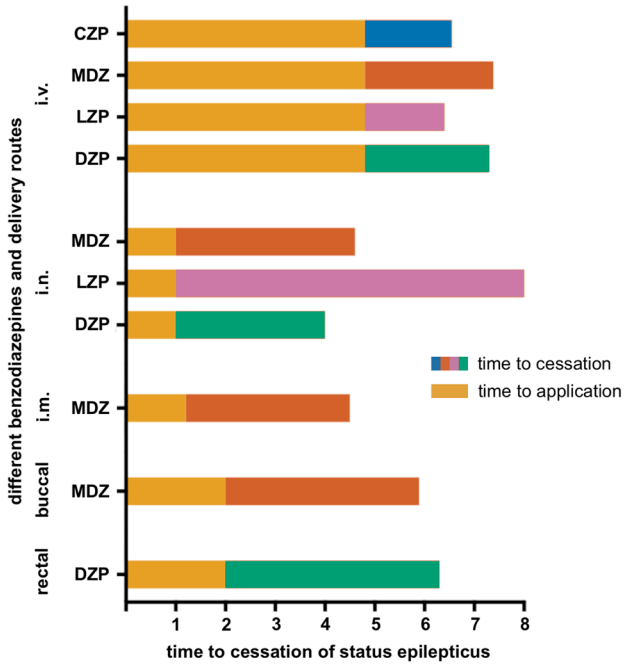


Fig. 3 Time from therapy administration to cessation of status epilepticus (SE) is displayed to help decide on the clinical use of different delivery routes for benzodiazepines in SE, based on published preparations and process times for drug administration via intravenous injection (i.v.), intramuscular injection (i.m.), rectal, intranasal (i.n.) and buccal administration [48]. For i.v. administration, it was assumed that no peripheral indwelling venous catheter had yet been established analogous to Silbergleit et al. [48]. *MDZ* midazolam, *LZP* lorazepam, *DZP* diazepam, *CZP* clonazepam

around puberty [172]. Metabolism via glucuronidation tends to be low in neonates, reaching adult levels by the age of 3–4 years. Overall, pharmacokinetics continue to differ from adults until around age 12 years. The dosages used and substances preferred therefore vary depending on the patient's age. Currently, available data regarding the efficacy and safety of BZDs in neonates are still insufficient.

DZP has a long half-life in neonates and should be avoided until hepatic metabolic pathways have matured at the age of approximately 6 months [173]. Doses of BZDs given to children must be calculated on a mg/kg basis. For children 6 months to 5 years of age, the initial dose of MDZ should be 0.05–0.1 mg/kg. A total, slowly titrated dose up to 0.6 mg/kg may be necessary to achieve the desired endpoint. For children 6–12 years of age, the initial dose should be 0.025–0.05 mg/kg, with a total dose up to 0.4 mg/kg [174]. LZP pharmacokinetics in children are similar to the adult pharmacokinetic parameters except for increased clearance. Therefore, uniform paediatric dosing (0.1 mg/kg, to a maximum of 4 mg) can be used to achieve serum concentrations of 50–100 ng/ml in children with SE, which have been previously associated with effective seizure control [175, 176].

4.2 Rescue Medications in Paediatric Epilepsy Patients

Rescue medications for lay use are frequently prescribed for paediatric epilepsy patients. The availability of such preparations differs between the USA and the EU. Oromucosal MDZ (Buccolam®) is a BZD approved by the EMA—but not by the FDA—for the treatment of paediatric patients aged 3 months to < 18 years with prolonged, convulsive seizures [177]. The ready-to-use, prefilled oral syringes containing a MDZ solution (in a concentration of 5 mg/ml with different volumes to provide an age-appropriate dose) are administered in fixed doses depending on the patient's age. The recommended doses are 2.5 mg (in patients aged 3 months to < 1 year), 5 mg (in patients aged 1 year to < 5 years), 7.5 mg (in patients aged 5 years to < 10 years), and 10 mg (in patients aged 10 years to < 18 years) [178]. Oromucosal MDZ (0.2–~0.5 mg/kg or 10 mg) is at least as effective as r.s. DZP (~0.5 mg/kg or 10 mg), and as effective as i.v. DZP (0.3 mg/kg) with regard to response rate (cessation of seizures) in paediatric patients in randomized, controlled trials [12, 75]. DZP rectal gel is approved by the EMA for epilepsy patients weighing a minimum of 10 kg (a patient age of approximately 1 year), and FDA approval exists for the treatment of occasional episodes of increased seizures that are different from a patient's usual seizure pattern in patients with epilepsy that are 2 years of age and older [179]. The recommended dose for DZP rectal gel is 0.2–0.5 mg/kg depending on age. The ready-for-use rectal delivery system is provided in unit doses of 2.5, 5, 7.5, 10, 12.5, 15, 17.5 and 20 mg DZP, and the prescribed dose is obtained by rounding upward to the next available dose. DZP nasal spray (VOLTOCO®, FDA approved for epilepsy patients aged 6 years and older) and MDZ nasal spray (Nayzilam®, FDA approved for epilepsy patients aged 12 years and older) are not yet approved in the EU (Fig. 1).

5 Conclusion: Comparing Different BZDs and Delivery Routes for Status Epilepticus

Over the last several decades, different BZDs have been established as first-line therapies for SE, each of which has its own pharmacological characteristics with advantages and disadvantages [180]. Here, the comparably long half-life of DZP especially stands out [181]. As it has been shown that interrupting SE as soon as possible reduces the chance of developing RSE and improves outcomes, ensuring rapid treatment in acute care is at least as important, if not more important, than the BZD choice [182]. Fortunately, several delivery routes for BZDs have now been established, which are suitable for both lay users and medical staff [9]. To provide an overview of the available treatment options

Table 5 Comparison and dosing of frequently used benzodiazepines for the treatment of status epilepticus

Drug	Pharmacokinetics				Dosing and delivery route specific aspects						
	$V_{distribution}$ (l/kg)	PB (%)	Half-life [a] (h)	Clearance (ml/min/kg)	Delivery routes	BA (%)	T_{max} [b] (min)	Initial dose (mg/kg BW)	Initial dose (mg)	Dose repetition (min)	Max. dose (mg)
Lorazepam (LZP)	0.8–1.3	90	8–20	0.7–1.2	i.v.	100	10	0.1	2–4	5–10	8
					i.n.	77	30	–	–	–	–
					i.m.	100	80	–	–	–	–
					s.l.	94	120	–	–	–	–
Midazolam (MDZ)	4.2–6.6	98	2–3	4–9	i.v.	100	4.5	0.2	10	5–10	10
					i.n.	78	10–15	–	5–10	no	–
					i.m.	91	20	–	10	no	–
					buccal	75	15–90	–	5–10	no	–
Diazepam (DZP)	0.8–1.4	99	40–60	0.5	i.v.	100	1	0.15–0.2	5–10	5	20
					i.n.	70–90	60–90	–	–	–	–
					i.m.	100	60	0.1–0.2	5–10	–	30
					r.s.	80–100	30–74	0.2–0.5	10–30	no	20
Clonazepam (CZP)	3	86	17–55	0.42	i.v.	90	< 10	0.015	1–2	5–10	2
					i.m.	93	3.1	–	–		

Modified after [9, 151, 181, 183–185]

i.v. intravenous, *i.n.* intranasal, *i.m.* intramuscular, *s.l.* sublingual, *r.s.* rectal, *mg/kg BW* milligram per kilogram body weight, *h* hour, *BA* bioavailability, *PB* protein binding

[a]Elimination half-life

[b]T_{max} after administration of a single dose

and delivery routes, Fig. 2 displays this information according to the type of administration, and Fig. 3 displays this according to the duration of action, considering the time required to establish access. The relevant pharmacokinetic and pharmacodynamic properties of the different BZDs are presented in Table 5, including delivery route-specific dosing recommendations for adult patients.

Due to a short T_{max} of between 90 and 150 s and the reliability of correct administration, i.v. administration of MDZ, LZP or DZP remains the gold standard in the professional medical setting [9, 151, 181, 183–185]. The i.v. administration of CZP in SE care is still a additional alternative [185]. However, establishing a peripheral vein catheter in patients with poor venous conditions or during motor seizures can be challenging. A quick but risky alternative in patients with poor venous conditions could be an intraosseous approach, which—due to its invasive nature—carries the risk of infection, fracture or osteomyelitis [38]. Data from the RAMPART study showed that the time to successful administration of BZDs via the i.m. route was significantly shorter than by the i.v. route [48]. Even if seizure termination after i.v. administration was shorter compared to i.m. injection, the resulting overall time from the start of treatment to the termination of convulsions was similar [48]. Despite their almost complete bioavailability, the T_{max} of 20, 60 and 80 min after i.m. injection described for MDZ, DZP and LZP injections are absorbed slowly, and might be therefore less, suitable for the acute treatment of SE [9]. To ensure a fast and safe administration of medication, even in difficult situations, i.n. administration has become widely accepted (MDZ, LZP and DZP). In addition to BZD administration via mucosal atomization devices or specifically formulated nasal sprays, commercially available applicators have been approved for DZP and MDZ in the USA for the treatment of seizure clusters or SE [64, 65, 89]. With a bioavailability of ~70–90% and a T_{max} between 30 and 60 min, the nasal route seems inferior to i.v. and i.m. administration for LZP and DZP [183]. However, with a T_{max} of < 15 min and a bioavailability of 44%, the i.n. administration of MDZ appears to be a feasible alternative, especially due to the comparably short and uncomplicated administration. In a pharmaco-EEG study, a relevant effect of MDZ after i.n. administration could already be measured after 4 min, which preceded the clinical end of the seizure by ~ 1 min [66]. For lay use, there are also BZD formulations available that can be administered either rectally or buccally. Buccal MDZ can easily be applied into the cheek pouches using prefabricated disposable syringes. With a bioavailability of 75% and a T_{max} between 15 and 90 min, this delivery route is mainly used in the treatment of seizure series or clusters, but there is a risk of aspiration and the pharmacokinetics can vary greatly depending on mucosal absorption. Therefore, the comprehensive use of buccal MDZ in professional emergency care does not appear to be reasonable. In addition, DZP is available for rectal use as rectioles, which are mainly used in paediatrics. Here, again, a T_{max} of 30–74 min limits this administration in the professional medical setting, despite almost complete bioavailability. Based on a disproportionately long T_{max} of approximately 120 min, sublingual LZP is not an adequate therapeutic option for the acute treatment of SE. Other new delivery routes, such as intrapulmonary administration, appear promising but require further studies before clinical use. To ensure further therapeutic management including prevention of potential RSE and for safety reasons, the establishment of a peripheral venous catheter for the repeated administration of BZDs at the earliest possible time seems indispensable.

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Code availability Not applicable.

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Authors' contributions AS developed the idea for this review. AS and RK drafted the concept. All authors performed the literature search and data analysis. AS, RK and LMW drafted the graphical abstract and the final manuscript. All authors contributed substantially to the final manuscript. All authors approved the final manuscript for submission. All authors agree to be accountable for the work.

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