Basic & Clinical Pharmacology & Toxicology

BCPT Basic & Clinical Pharmacology & Toxicology

FOCUSED REVIEW OPEN ACCESS

Could Flumazenil Be Used Pre-hospital by Intramuscular Injection for Coma due to Mixed Drug Overdose Not Responding to Naloxone?: A Systematic Review of the Evidence

Ilinca Farcas[1] | Lisa Schölin[2] | Michael Eddleston[2]

[1]Department of Chemistry, University of Oxford, Oxford, UK | [2]Centre for Pesticide Suicide Prevention, and Pharmacology, Toxicology and Therapeutics, Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

Correspondence: Michael Eddleston (m.eddleston@ed.ac.uk)

Received: 4 December 2024 | **Revised:** 24 January 2025 | **Accepted:** 30 January 2025

Funding: Lister summer studentship (for IF) from the Lister Institute of Preventive Medicine.

Keywords: antidote | benzodiazepine overdose | flumazenil | intramuscular | intravenous

ABSTRACT

Background/Rationale: Benzodiazepine-involved overdose deaths are increasing. Flumazenil is rarely used due to fear of seizures; however, the risk benefit may favour its use. Flumazenil is licensed for intravenous (IV) use, but intramuscular (IM) treatment would be required pre-hospital.

Objective: To identify and synthesise pre-clinical and clinical data on the parenteral IM flumazenil safety and efficacy.

Methods: PubMed, Google Scholar, Cochrane and Scopus searches without any language restriction. Adverse effect studies were limited to systematic reviews and large cohort studies ($n > 100$), IM administration efficacy to studies in large animal (mammalian, excluding reptiles and birds) and humans.

Results: Two systematic reviews reported adverse effects from IV or IM flumazenil in clinical use and combined retrospective/prospective patient cohort. Seizures were uncommon (< 2%) including mixed overdoses. Seven studies (four animal, three human) reported on IM flumazenil. Animal studies indicated IM flumazenil efficacy. In a canine cross-over study, IM flumazenil reversed midazolam sedation moderately slower than IV. Two clinical observational studies reported sedation reversal with IM flumazenil, whereas a cross-over study found no IM flumazenil response at 15 min.

Conclusion: IM flumazenil data are sparse, but it may be effective and safe. Clinical research is urgently needed to determine whether pre-hospital IM flumazenil can prevent benzodiazepine-involved overdose deaths.

1 | Introduction

The United Nations estimates that 292 million people worldwide (5.6% of 15- to 64-year-olds) used drugs in 2015 and 64 million suffer from a drug use disorder [1]. According to data from 2019, 128 000 individuals died from drug use disorders, with 70% of deaths due to the effects of opioids [2].

Unintentional drug overdoses killed 4390 people in the United Kingdom in 2021 [3, 4]. Over the last 8 years, there has been a major increase in the number of these deaths that are associated with benzodiazepines, particularly in Scotland where 918/1330 [69.0%] of deaths in 2021 involved benzodiazepines according to formal post-mortems (Figure 1) [3], particularly with potent non-licensed benzodiazepines such as etizolam and alprazolam

Summary

- Drug-related deaths involving benzodiazepines are increasing.
- Flumazenil is an antidote that could be used to treat overdoses by injection into a person's muscle (intramuscularly [IM]) but is only licensed for injection into a person's veins.
- Intramuscular antidote for opioid overdose is effective and flumazenil could be used the same way, if safe.
- We looked at animal and human studies measuring risks (adverse outcomes) and efficacy (how well it worked).
- The literature is limited but shows IM flumazenil effectively reverses benzodiazepines with few reports of adverse events.
- Studies in patients are needed to determine if this antidote could be given to people outside of hospital.

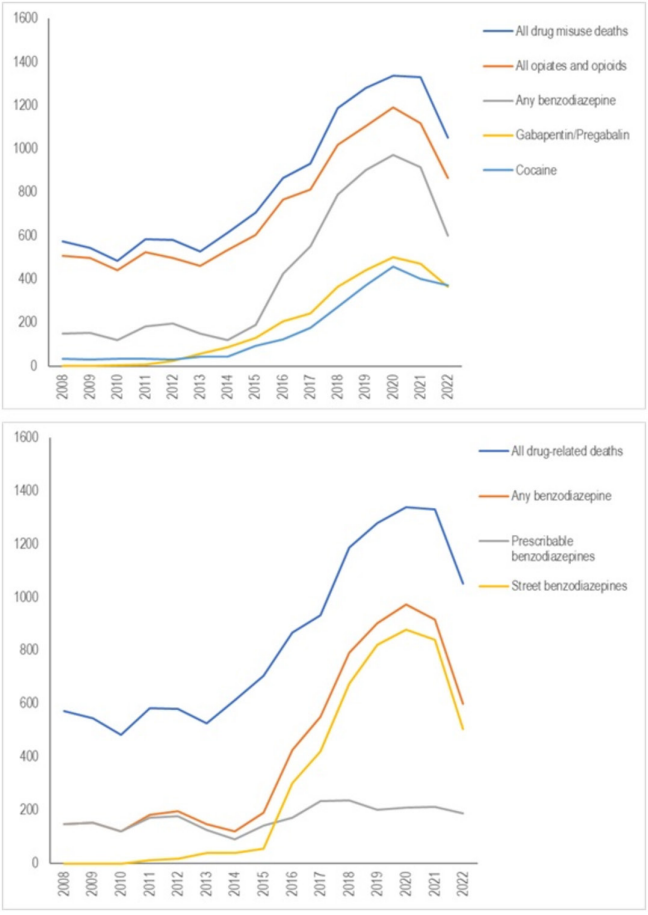

FIGURE 1 | Top: Number of drug misuse deaths in Scotland in 2008–2022, by implicated drugs. Bottom: Number of drug misuse deaths in Scotland in 2008–2022 by implicated benzodiazepine. *Source:* National Records Scotland [2] (Open Government Licence 3.0).

[5–7]. Etizolam is usually taken in high doses as its short-lived effects encourage people to take repeated doses [8, 9]. Compared to other European countries, Scotland has the highest rate of drug-related deaths. According to the most recent data, Scotland's rate of drug-induced deaths (the European Union Drug Agency, formerly European Monitoring Centre for Drugs and Drug Addiction, definition) was 277 per million population (2023 data), far higher than the second highest country (Ireland, 97 per million population, 2020 data). The overall rate for the 27 European Union countries plus Türkiye and Norway was 20 per million; however, due to differences in how data are recorded, comparisons need to be made with caution [10].

Benzodiazepines cause respiratory depression [11], and synergy between benzodiazepines and opioids may be causing many deaths. An antidote for benzodiazepines is available—flumazenil [12] (Box 1 and Table 1)—akin to naloxone for opioid overdose, which is established as a pre-hospital intramuscular (IM) antidote for first-response professionals and trained bystanders and shown to save lives [19–21]. However, flumazenil is little used in clinical practice due to a perceived risk of causing seizures after mixed medicine overdoses including benzodiazepines [22].

Most unintentional deaths from drug use occur before hospital admission or before presentation to pre-hospital medical services [26]. It is possible that pre-hospital flumazenil will save lives if benzodiazepines are causal in the pathway to death and if it can be used safely by ambulance paramedics or trained community members at first contact with patients after drug overdose. Pre-hospital use will require an alternative route to intravenous administration, such as IM. Unfortunately, flumazenil is not licensed for this route [22]. In addition, there are

Box- Pharmacology of flumazenil

Flumazenil, a 1,4-imidazobenzodiazepine, is a specific competitive central-acting benzodiazepine ($GABA_A$) receptor antagonist [23]. It interacts with the receptor's extracellular surface (between the α and γ_2 units, close to where benzodiazepines bind). The effects of non-benzodiazepine agonists acting via the $GABA_A$ receptor, such as zopiclone and triazolopyridazine, are also antagonised by flumazenil [24].

It is licensed for the reversal of benzodiazepine sedative effects in anaesthesia, clinical procedures and intensive care by the intravenous (IV) route [22, 25]. The initial IV dose is 200 mcg, given over 15 s; if there is no response at 1 min, 100 mcg can be given every 1 min (q1min) as required. The usual total dose is 300–600 mcg with a max of 1 mg per course. Benzodiazepine sedative effects are reversed rapidly (within 1–2 min) after IV administration. Depending on differences in elimination time between agonist and antagonist, sedative effects can recur [13]. Other routes of administration have been clinically used (Table 1). Log Kow (log P) is 1.0; oral bioavailability is 0.17% [13].

Flumazenil is 50% bound to plasma proteins, particularly albumin [13]. During distribution, the flumazenil plasma concentration decreases with a half-life of 4–15 min; the distribution volume under steady-state conditions (Vss) is 0.9–1.1 L/kg [13]. Elimination is mainly by hepatic metabolism. An inactive carboxylic acid metabolite is the most important metabolite. Elimination is rapid, with a half-life of 40–80 min. Radiolabelled flumazenil is completely eliminated within 72 h, with 90%–95% appearing in the urine and 5%–10% in the faeces [13]. We were unable to find any papers reporting IM pharmacokinetics.

TABLE 1 | Summary of dosing for clinical routes of administration to adults.

Route of administration	Dose	Observations
Licensed recommendation		
Intravenous	0.2–0.3 mg over 15 s [13]	If the required level of consciousness is not regained within 60 s, further doses of 0.1 mg can be administered and repeated at 60 s intervals, to a total dose of 1 mg (anaesthesia) or 2 mg (intensive care)
Unlicensed (individual) recommendations		
Intranasal	0.025–0.04 mg/kg [14]	Maximum of 0.1–0.2 mg
Oral	30–100 mg [15]	Maximum of 600 mg. Doses of 20–25 mg have been given 3–5 times daily over several days to prevent coma relapse [12]
Subcutaneous	1 mg/h [16, 17]	Not found to be effective in addition to IV flumazenil [16]. Has been used for sustained infusions to treat benzodiazepine dependence [17]
Sublingual	0.4–1.6 mg [18]	

Note: The table presents information on licensed IV dose and recommended doses in the literature for unlicensed routes. The intramuscular route has no recommended dose and so is not presented in the table.

currently no data on the number of patients who die after adequate pre-hospital naloxone administration, patients who might benefit from pre-hospital flumazenil.

We here review evidence from both animal and human studies for the safety and efficacy from IM administration.

2 | Methods

We searched PubMed, Google Scholar, Cochrane and Scopus databases using the terms 'flumazenil' and either 'adverse effects' or 'intramuscular'. Eligible studies reported information on the adverse effects (AEs) of parenteral (IV or IM) flumazenil and effectiveness by the IM route. There was no restriction by language. Studies describing AEs of parenteral (IV or IM) flumazenil use in patients were limited to systematic reviews and large cohorts of benzodiazepine intoxicated patients including abstracts of case series. We included PhD theses if they met inclusion criteria and were retrievable in full text. Studies describing IM administration were limited to large animal (mammalian) pre-clinical studies and clinical studies. Two authors (I.F. and M.E.) independently selected articles addressing the IM use of flumazenil by initially reading the abstract and then the full article when relevant. PRISMA guidelines were not followed for this review.

3 | Results

We found 10 papers addressing AEs of parenteral flumazenil and efficacy of IM flumazenil (Figure 2).

3.1 | AEs of IM Flumazenil Administration

AEs associated with IM flumazenil were only reported in one clinical study, which compared IM with IV flumazenil and placebo in male and female patients aged 18–60 years undergoing dental or maxillofacial surgery (for whom the presence of benzodiazepine tolerance was not reported) [27]. Of 15 patients receiving IM flumazenil, five experienced chills, and four became agitated, in comparison to seven and five out of 15 patients receiving IV flumazenil respectively. In the control group (who received saline solution), four out of 15 patients experienced chills, but none became agitated. The only seizure occurred in a patient in the IV group who also was taking the tetracyclic antidepressant maprotiline.

3.2 | AEs of IV Flumazenil Administration

As the data on AEs after IM administration were minimal, we also looked for data on safety following IV administration because AEs by either route may be similar. We identified two systematic reviews [28, 29] reporting AEs from parenteral flumazenil administration in clinical use, as well as a combined retrospective/prospective cohort of patients ($n = 731$) receiving flumazenil 0.5 mg IV on presentation to hospital [30].

Penninga et al. [28] extracted data on 498 patients treated with flumazenil (with 492 controls) in 13 trials ($N = 990$). Three randomised controlled trials (RCTs) had exclusion criteria related to benzodiazepines: known or suspected benzodiazepines overdose, known therapeutic use of benzodiazepines and known hypersensitivity to benzodiazepines. One RCT excluded patients with evidence of alcohol or tricyclic antidepressant ingestion, and eights RCTs excluded patients with organ injury, including kidney, liver and/or brain injury (including epilepsy). No information was provided in the papers on the presence of benzodiazepine tolerance.

Across all trials included in Penninga et al.'s systematic review [28], 720 patients (72.4% of all patients) had overdosed with benzodiazepines. Ten studies provided information about single- versus multi-drug overdose for 596 patients, of whom 205 (34.4%) were exposed to a single benzodiazepine and 391 (65.6%) were exposed to multiple substances including ethanol, anxiolytics (e.g., barbiturates), opioids and tricyclic antidepressants [28].

Flumazenil regimens differed among trials in this review [28]. All studies administered flumazenil IV with an initial dose varying

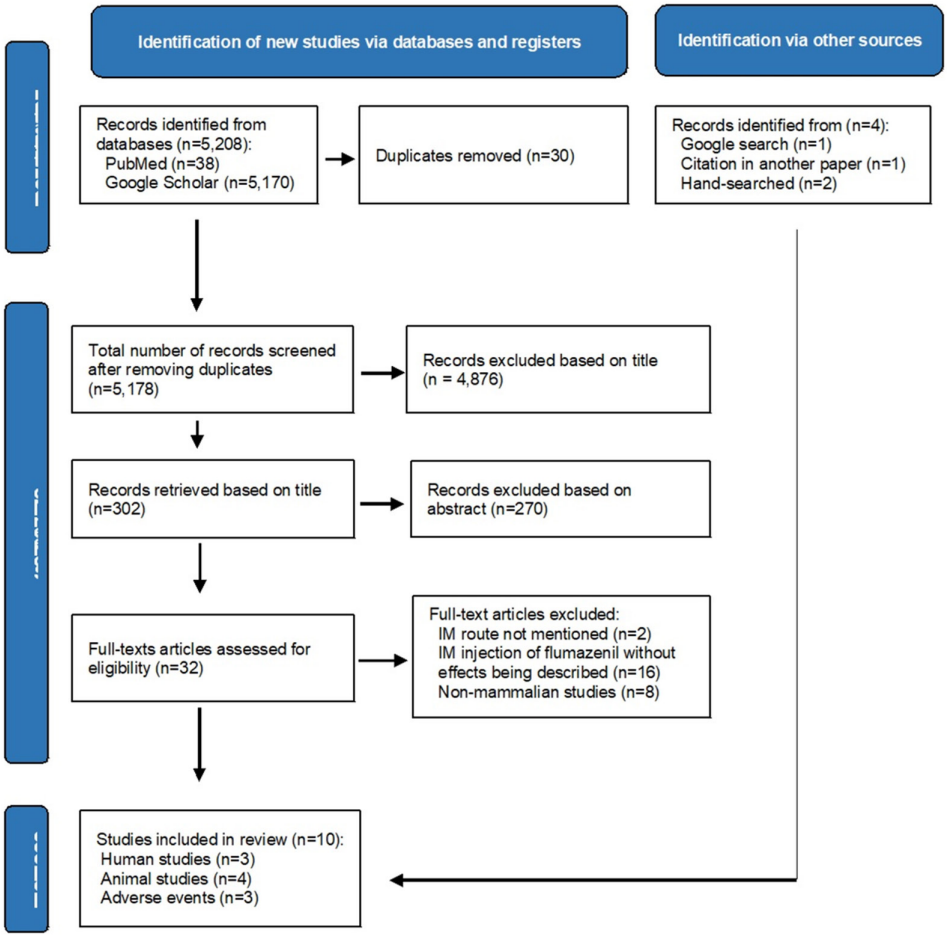

FIGURE 2 | Prisma flow chart—selection of eligible studies.

from 0.1 to 2.5 mg (total dose 1.0–10.0 mg). Average flumazenil dose varied from 0.77 to 7.1 mg. Nine studies reported observation times of between 10 min and 24 h (median 5 h). AEs were more common in the flumazenil group (138/498) compared with the placebo group (47/492) (risk ratio: 2.85; 95% confidence interval [CI]: 2.11–3.84; $p < 0.00001$). Serious adverse effects (SAEs) were also more common with flumazenil than with placebo (12/498 vs. 2/492; risk ratio: 3.81; 95% CI: 1.28–11.39; $p = 0.02$). The most common AEs in the flumazenil group were agitation and gastrointestinal symptoms. The most common SAEs were supraventricular arrhythmias and/or tachycardia (7 flumazenil patients and 2 control patients). Seizures occurred in three (0.6%, 95% CI 0.12%–1.75%) flumazenil patients and no control patients. No patients died during the blinded phase of the RCTs. It is unclear from the data reported whether the patients with SAEs had co-ingested other substances.

Ramos Rodriguez in an unpublished thesis [29] identified seven papers reporting case series of flumazenil use for which adverse reactions were reported, including that by Penninga et al.'s [28] and Sivilotti's narrative review [24]. The papers included 8214 patients of which at least 1438 received flumazenil (56 on multiple occasions in one clinical study). A total of 340 AEs were identified in these cohorts and in two narrative reviews, with agitation (15.9% of AEs), nausea and vomiting (15.6%) and anxiety (14.1%) being most frequently documented. Seizures were reported on only three occasions in the cohort of 1438 patients. Seizures were often associated with the co-ingestion of tricyclic antidepressants [29].

Rasimas et al. [30] reported a case series of 731 patients (519 retrospective, 212 prospective; 38% with mixed overdoses) receiving 0.5 mg flumazenil over 30 s to treat sedation, many on presentation to hospital. They excluded patients who were 'notably hyper-reflexic, myoclonic, or tachycardic (physical findings they considered inconsistent with sedative toxicity)'. They noted no cases of arrhythmias or seizures. In the prospective component, 12/212 patients (5.7%) developed only mild AEs [30].

3.3 | Efficacy of Intramuscular Administration of Flumazenil

We identified 38 papers related to IM administration in PubMed and 5170 in Google Scholar. We did not identify papers with Cochrane or Scopus. Additional records identified on Google ($n = 1$), via citation (n = 1) or hand-searching ($n = 2$) were considered. Duplicates ($n = 30$) and papers not addressing flumazenil administration ($n = 4912$) were eliminated by abstract review (Figure 2), leaving 302 publications. Initial assessment of full papers revealed 36 possibly eligible papers; papers were then excluded on the basis of unspecified route of administration

($n = 2$), lack of documentation of flumazenil reversal times ($n = 13$) and inclusion of non-mammalian species (n = 2). We ultimately identified seven studies (four animal [31–34] (Table 2) and three human [27, 35, 36] (Table 3)) that addressed IM flumazenil administration related to efficacy, AEs, re-sedation and/or time to recurrence of sedation. None of the papers reported pharmacokinetics from IM administration.

3.3.1 | Large Animal Studies of IM Flumazenil

Heniff et al. [31] conducted a randomised controlled cross-over canine study (animal weight 20–25 kg) given thiopental (19 mg/kg) and midazolam (0.1 mg/kg followed by 0.2 mg/kg) comparing time to reversal of respiratory depression for flumazenil (0.5 mg) administered by different routes (IV, IM, sublingual [SL] or per-rectum, vs. no treatment [control]). The IV route had the fastest time to reversal (mean 120 [±24.5] s), followed by SL (262 [±94.5] s). The IM route had the third fastest time to reversal (310 [±133.7] s), but the highest variation in mean recovery time [31] (Figure 3). Recovery time in the single control animal was 1620 s.

In a non-randomised three-arm observational study, Walzer and Huber [33] studied cheetahs anaesthetised with tiletamine-zolazepam (4.2 mg/kg) and compared flumazenil (0.031 ± 0.006 mg/kg) and sarmazenil (0.1 mg/kg) with no antidote. The stand-up recovery time for flumazenil (40.3 ± 22.3 min), given about 30 min after initial anaesthesia, was longer than for sarmazenil (17 ± 8.5 min) but substantially shorter than without antidote (105 min).

In an observational field study, Bodley et al. [32] studied Weddell seals sedated with 100–130 mg midazolam before comparing time to reversal of sedation for seals receiving IM flumazenil and those not receiving flumazenil. The study was not randomised, and there were likely systematic differences between groups. The flumazenil dose (0.5 mg) used was very low per kilogram for these heavy animals (weight 240–370 kg) compared to the dose used in other studies. The mean (standard deviation) recovery times for animals receiving IM flumazenil ($n = 9$) was longer (5.3 ± 3.2 min) than for animals not receiving flumazenil ($n = 2$, 4 min).

Lu et al. [34] conducted a randomised controlled cross-over study in pigs anaesthetised with tiletamine-zolazepam (3 mg/kg), xylazine (1.2 mg/kg) and tramadol (1.6 mg/kg). They compared time to recovery of head up in animals receiving flumazenil (0.1 mg/kg), atipamezole (0.12 mg/kg) or naloxone (0.03 mg/kg), and combinations of these medicines, versus placebo. The mean (standard deviation) recovery times for animals receiving IM flumazenil ($n = 9$) was 65.0 ± 20 min versus 87.0 +/− 188 min in control animals, suggesting that non-benzodiazepine elements of the anaesthetic mix was causing sedation.

3.3.1.1 | AEs in IM Animal Studies. Only one animal study mentioned the occurrence of AEs. In the study of pigs receiving zolazepam, Lu et al. [34] mentioned limb rigidity in some animals receiving flumazenil but did not provide data on comparative incidence in different groups.

3.3.2 | Clinical Studies of IM Flumazenil

Three eligible human studies (two randomised and one non-randomised) were identified. They assessed the recovery of patients using the Glasgow coma score (GCS) [35, 36] or the Alert/Verbal/Pain/Unresponsive (AVPU) [37] scale [27] (Table 3).

An abstract by Passeron et al. [35] described an observational study of the clinical use of IV or IM flumazenil administered for benzodiazepine overdose in 19 patients. Recovery in GCS was monitored for up to 4 h after administration. The dose and route varied across four groups. Two groups received IM flumazenil (Table 3). Doses were either (i) 0.5 mg flumazenil IV every min until consciousness had returned followed by 2.5 mg IM ($n = 2$) or (ii) injection of 2.5 mg IM, repeated as required if sedation recurred ($n = 5$). Both patients receiving the first regimen regained consciousness (time not presented); all five patients receiving the second regimen regained consciousness within 10 min, but three required further doses due to re-sedation. There was no control group in this study.

An RCT by Bonnet, Roche, and du Cailar [27] assessed reversal times based on the AVPU scoring system for IV versus IM flumazenil (both 0.015 mg/kg) and placebo control for flunitrazepam-induced sedation. Data are provided at 15 and 60 min after antidote administration. At 15 min, IV flumazenil had led to almost full recovery (mean score 2.8 out of 3.0 for alertness), although patients receiving IM flumazenil or control were responsive to pain stimuli only (scores 1.2 and 0.8 out of 3.0, respectively). At 60 min, scores for the three groups did not differ (all about 2.0 out of 3.0, consistent with response to voice) due to the effect of IV flumazenil wearing off.

Esparza Medina [36] conducted a prospective controlled study. Rapid recovery times were reported for elective surgery patients receiving IM flumazenil 0.5 mg ($n = 20$, 23 min [no variance reported]) compared to patients receiving placebo ($n = 20$, 180 min). Consciousness was evaluated based on an adapted GCS using a maximum score of 20. This coma score has been not previously been reported in the literature, making the evaluation of the consciousness state unreliable. Patients with known substance use were excluded.

4 | Discussion

The Scottish drug death crisis involving opioid and highly potent benzodiazepine combinations means that pre-hospital IM administration of flumazenil needs to be considered as one approach to preventing deaths. Our review indicates that the key hazard of concern—seizures—appears to be uncommon, occurring in less than 2% of patients receiving IV flumazenil. None were reported to have developed status epilepticus unresponsive to therapy; no deaths were noted. The studies cited here did not report whether patients were dependent on benzodiazepines before they received flumazenil. However, Penninga et al.'s [28] review included many patients who had taken an overdose, some of whom would be expected to using benzodiazepines regularly and therefore dependent. Not knowing how many patients were dependent is a limitation of this study and our conclusions.

TABLE 2 | Study characteristics of animal studies.

Study, year of publication	Species	Sample size	Study design	Anaesthesia cocktail	Flumazenil preparation	Dose and volume (IM unless stated)	Observation times	Results	Adverse events
Heniff et al. [31], 1997	Dogs (*Canis familiaris*)	*N* = 10 for IV, IM, SL, PR Placebo = 1 Wt: 20–25 kg	Randomised, controlled, cross-over study comparing IV, IM, SL and PR routes of FZ to reverse midazolam-induced respiratory depression	Thiopental (19 mg/kg IV) then midazolam (0.1 mg/kg [up to 2 doses] followed by 0.2 mg/kg [up to 5 doses])	Not specified	0.2 mg/kg followed by 0.3 mg/kg after 30 s Volume: not described	Every 30 s until recovery	Mean recovery time (s): • IV = 120 ± 24.5 • SL = 262 ± 94.5 • IM = 310 ± 133.7 • PR = 342 ± 84.4 Control = 1620	Not reported
Walzer and Huber [33], 2002	Cheetah (*Acinonyx jubatus*)	*N* = 4 Wt: not specified	Comparative observational study of FZ and SAR for reversing tiletamine-zolazepam-induced anaesthesia	Tiletamine-zolazepam (4.2 mg/kg)	0.1 mg/mL (Roche)	0.031 ± 0.006 mg/kg	Every 60 s	Head-up recovery time (min): • FZ = 5.0 ± 1.9 • SAR = 5.25 ± 1.5 • Control = [estimated from text] 39 +/− 28.4[a]	None observed
Bodley, van Polanen, and Gales [32], 2004	Weddell seals (*Leptonychotes weddellii*)	*N* = 11 FZ *n* = 9 No FZ *n* = 2 Wt (mean): 334 ± 64 kg	Observational study of the effects of FZ to reverse isoflurane and midazolam-induced anaesthesia	Midazolam (100–130 mg) Approximate dose 0.3–0.5 mg/mg	0.1 mg/mL (Roche)	0.5 mg 0.001 mg/kg Volume: 0.01 mL/kg	Constant until recovery	Mean recovery time was 5.3 ± 3.2 min (*n* = 9) Control: 4 min (*n* = 2)	None observed
Lu et al. [34], 2011	Chinese experimental miniature pigs (*Sus domesticus*)	*N* = 8 Wt (mean): 57.5 kg	Randomised cross-over study of ATI, FZ and/or NAL to reverse Tiletamine-zolazepam (plus xylazine/tramadol)-induced anaesthesia	Tiletamine-zolazepam (3.0 mg/kg), XL (1.2 mg/kg), TR (1.6 mg/kg)	Not specified (Lingkang)	0.1 mg/kg Volume: not described	0, 3, 5, 7, 10, 15, 30, 45, 60, 75, 90 and 120 min	Head up time (min): • FZ = 65 ± 20 • ATI-NAL = 15 ± 15 • ATI-FZ-NAL = 6 ± 1 Control = 87 ± 188	Not reported

Abbreviations: ATI, atipamezole; FZ, flumazenil; HR, heart rate; IM, intramuscular; IV, intravenous; NAL, naloxone; PR, per rectum; RR, respiratory rate; SAR, sarmazenil; SL, sublingual; TR, tramadol; TZ, tiletamine-zolazepam; XL, xylazine.

[a]The time from antidote administration to head up position in the control group was not presented in the paper as no antidote or placebo was given (to give $t = 0$ for antidote time). However, the paper reported time from benzodiazepine administration to heads up for all groups, and it was possible to obtain an estimate of the time to heads up as if a placebo had been given.

TABLE 3 | Study characteristics of human studies of IM flumazenil.

Study, year of publication	Sample size	Patient group, age, gender	Study design	Anaesthetic	Flumazenil preparation	IM dose (volume)	Observation times	Results	Adverse events
Passeron et al. [35], 1987	$N=7$ 2 relevant protocols: 1. IV, then IM ($n=2$) 2. IM only ($n=5$)	Non-systematic observational study of IV or IM flumazenil. Route chosen according to severity 1. IV, then IM = both patients had GCS 8/15 2. IM only = five patients had GCS 12/15	Evaluation of recovery of patients hospitalised with BZD overdose	Not relevant Overdosed benzodiazepines not identified	Anexate (flumazenil) 0.1 mg/mL (Hoffman-La Roche)	IV then IM: 0.5 mg every 1 min until recovery of GCS, then 2.5 mg IM IM: 2.5 mg, repeated for re-sedation as required	Every 1 min for 10 min, then 30, 60, 120, 180 and 240 min	Recovery time: • IV then IM = 2–5 min • IM = 10 min [3/5 required further dose(s)]	No adverse events with IM flumazenil (one with IV flumazenil due to co-ingested maprotiline)
Bonnet, Roche, and du Cailar [27], 1991	$N=45$ IV $n=15$ (mean wt 66.7 ± 7.5 kg) IM $n=15$ (64.0 ± 8.3 kg) Control $n=15$ (62.5 ± 7.4 kg)	Dental or max fax surgery, aged 18–60 years IV: 10 male, 5 female, IM: 9 male, 6 female, Control: 9 male, 6 female	Prospective randomised controlled study of IM and IV FZ to reverse flunitrazepam-induced anaesthesia	Pre-medication Flunitrazepam 1 mg IM Induction: flunitrazepam (0.04 mg/kg with fentanyl and droperidol), followed by 0.011 mg/kg/h maintenance	Not specified	0.015 mg/kg (mean total dose by wt:0.96 mg) Volume: not described	15, 60 and 120 min Sedation scoring system ~uses AVPU A = 3 V = 2 P = 1 U = 0	Sedation level (app. Mean score) at 15 min: • IV 2.8[a] • IM 1.2 • Control: 0.8 Sedation level (app. mean score) at 60 min: • IV 2.1 • IM 2.0 Control: 1.9	IM: • Chills $n=5$ • Agitation $n=4$ IV: • Chills $n=7$ • Agitation $n=5$ Control: • Chills $n=4$ • Agitation = 0
Esparza Medina [36], 1996	$N=40$ Cases $n=20$, controls $n=20$	Elective surgery, aged 25–45 years Cases: 5 male, 15 female Controls: 2 male, 18 female	Prospective controlled study of IM FZ vs. no FZ to reverse flunitrazepam-induced anaesthesia (no report of randomisation)	Premedication cases: midazolam $n=9$, triazolam $n=11$ Controls: midazolam $n=6$, triazolam $n=14$ Flunitrazepam 5 mcg/kg, then 35 mcg/kg	Not specified	0.5 mg	0, 10, 30, 60, 90, 120 and 180 min	Recovery time (to a GCS [modified by Teasdale] score of 16/20): • IM = 23 min Control = > 180 min	None reported

Abbreviations: AVPU, Alert/Verbal/Pain/Unresponsive scoring system; BZD, benzodiazepine; FZ, flumazenil; max fax, maxillofacial surgery; GSC, Glasgow Coma Scale.
[a]This study did not involve assessing animals between 15 and 60 min so full recovery may have occurred transiently during this time and not been detected.

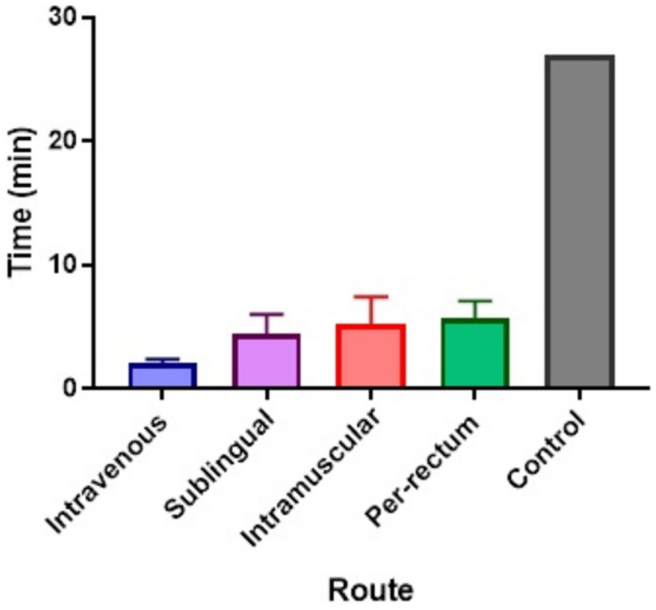

FIGURE 3 | Time to reversal of midazolam-induced respiratory depression in a canine study of different administration routes for flumazenil. Data are from Heniff et al. [31], reproduced with permission.

However, overall, the quality of data to support IM use is currently poor. Human studies of IM flumazenil are few because its indication is reversal of iatrogenic benzodiazepine overdose, which usually occurs around a procedure in patients with IV access, making IM administration irrelevant. IM administration of 2.5 mg flumazenil to five patients with GCS 12/15 appears to have reversed sedation in an early study [35], but the study has only been reported in abstract format, meaning that information on study design and outcome is missing. Less promisingly, a study of 0.015 mg/kg flumazenil (1.05 mg for a 70 kg adult) for flunitrazepam sedation showed a good response to IV administration at 15 min but no response to IM administration [27]. No dose response was assessed, so it is possible that a higher dose would have been effective. However, 1 mg is usually an effective IV dose; it is possible that the response was delayed past 15 min (no measurements of sedation were made between 15 and 60 min). The most recent clinical study reported a mean time to response for the IM route of 23 min (vs. 180 min for placebo), supporting efficacy with a delay to peak effect [35]. However, the clinical usefulness of a route that takes more than 15 min to work will need to be assessed formally in clinical trials.

Previously, Weinbroum, Halpern, and Geller in their review of flumazenil [38] had noted that they found IM flumazenil to be effective in their clinical practice, citing two publications (one a meeting abstract [39] and the other a submitted paper [40]). However, review of both papers revealed no mention of IM administration; they were therefore excluded from the data analysis and the basis for Weinbroum's positive views on IM flumazenil is unclear.

The data on safety are reassuring. Some of the studies included in the major systematic review of safety [28] recruited patients dependent on benzodiazepines and/or patients taking a benzodiazepine overdose. Despite this, the rate of SAEs was low. Most seizures were associated with the use of tricyclic antidepressants such as amitriptyline. Status epilepticus was not reported, suggesting that even if seizures do occur they are likely to be transient and responsive to benzodiazepine treatment. One concern is that early narrative reviews suggest that IV flumazenil doses greater than 1 mg are associated with seizures [12, 41], a dose that might be necessary for effective IM therapy. However, if accurate, this dose threshold may be associated with a high Cmax and rapid antagonism following fast IV administration, differing from the relatively lower peak concentration and slower time to peak following IM injection.

The half-life of flumazenil is relatively short after IV dosing, at 40–80 min, contrasting with much longer half-lives for many benzodiazepines, for example, etizolam (10–14 h [42]) and diazepam (up to 48 h; 100 h for the active metabolite). Therefore, there is a need for observation after dosing, with consideration of further doses of flumazenil; such a wearing off of flumazenil's effect was noted in the Bonnet, Roche, and du Cailar study, where IV flumazenil's benefit at 15 min had reduced by 60 min. A pilot study suggests good efficacy and safety from an infusion of flumazenil once respiratory depression has been reversed with bolus doses [43]. Doses of 0.5 mg flumazenil every 1–2 h have also been given to sustain a response [30]. IM administration may result in more prolonged absorption and therefore longer half-lives and effect. Clinical studies are required to address the pharmacokinetics of IM administration.

A series of pharmacokinetic and clinical studies to determine whether pre-hospital administration of IM flumazenil could save lives are needed. Initial studies will need to focus on finding an effective and safe dose, with transient seizures occurring in less than 2%–3% of patients; studies will best be performed in emergency departments that are familiar with respiratory support and management of seizures. A dose response study is essential to identify both a dose that works for most cases and the time to effect. The dose would not be required to wake the person up fully; the main target of effect will be respiratory rate. Clinical trials will be needed to address how quickly IM flumazenil should work—will improved GCS at 15 min be adequate or would 5 min be preferable? Although other routes such as intranasal and sublingual may be effective, community familiarity with IM naloxone may allow its uptake if effective to be quicker.

Initial studies should exclude patients with epilepsy on antiepileptic medication and those with previous head injury. However, we believe that they should not exclude patients with benzodiazepine dependence because it is these patients that are at high risk of overdose and who may benefit from flumazenil. Identification of a safe and effective dose should initiate pragmatic pre-hospital clinical trials with ambulance services and then trained community members. Information on previous epilepsy and head injury may not be available to such people using IM flumazenil, unless they are wearing something like a medic alert bracelet.

Take-home IM naloxone is widely available in Scotland and has been shown to be effective at preventing deaths [19–21]. However, there is currently no good evidence about the proportion of people who die from opioid/benzodiazepines mixed overdoses after receiving adequate doses of pre-hospital naloxone. These represent individuals who could potentially benefit from provision of

pre-hospital flumazenil. We are currently seeking these data for Scotland. However, it is clearly possible that the benzodiazepine component of mixed overdoses is not relevant for lethality and that use of flumazenil will have no effect on saving lives. The solution to the drug death crisis may simply be much earlier administration of effective doses of naloxone. However, until the RCTs are done, we will now know whether flumazenil is useful and people with lived experience will continue to question why we do not use a potentially effective antidote.

4.1 | Limitations

Published pre-clinical and clinical reports of IM flumazenil use are of limited quality and quantity. We only identified four mammalian pre-clinical studies and three clinical studies. All studies were small and offered limited evidence on the safety and efficacy of this route. Safety data were taken from systematic reviews of IV use of flumazenil, which may differ from AEs of IM administration. RCTs included in the systematic review were small with fewer than 500 patients in total receiving IV flumazenil. Not all the RCTs included patients relevant to IM use of flumazenil such as patients with benzodiazepine dependence or taking overdoses. The AE reviews did not present data on the presence of co-ingestants in the patients who had seizures after receiving flumazenil. Many of the publications were not published in full and were only available as abstracts or university theses for this review, reducing confidence in the data presented.

4.2 | Conclusion

We found limited data suggesting that IM flumazenil may be an effective and safe route of administration that could be used for pre-hospital treatment of poisoned patients. There is an urgent need to initiate a clinical research programme to determine whether pre-hospital flumazenil is a valid approach to preventing deaths from unintentional drug overdose.

Acknowledgements

We thank Rebecca McDonald, Nick Bateman, Matt Reed and Marco Sivilotti for their critical review of the manuscript and the Lister Institute for their funding of IF's summer scholarship. The Centre for Pesticide Suicide Prevention is funded by a grant from Open Philanthropy, at the recommendation of GiveWell.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1. United Nations Office on Drugs and Crime, "World Drug Report 2024. Global Overview of Drug Demand and Supply," (Vienna: United Nations Office on Drugs and Crime, 2024). Accessed January 14, 2025, https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2024.html.

2. United Nations Office on Drugs and Crime, "World Drug Report 2023. Global Overview of Drug Demand and Supply," (Vienna: United Nations Office on Drugs and Crime, 2023). Accessed January 14, 2025, https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2023.html.

3. National Records of Scotland, "Drug-Related Deaths in Scotland in 2023," (Edinburgh: National Records of Scotland, 2023). Accessed January 14, 2025, https://www.nrscotland.gov.uk/publications/drug-related-deaths-in-scotland-in-2023/.

4. Office for National Statistics, "Deaths Related to Drug Poisoning in England and Wales: 2021 Registrations," (Newport, UK: Office for National Statistics, 2022). Accessed November 7, 2024, https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2021registrations.

5. R. Robertson, A. McAuley, and C. Matheson, "Benzodiazepines: The Time for Systematic Change Is Now," *Addiction* 116 (2021): 2246–2247.

6. European Monitoring Centre for Drugs and Drug Addiction, "Drug-Related Deaths and Mortality in Europe: Update From the EMCDDA Expert Network," (Lisbon: EMCDDA, 2021). Accessed November 7, 2024, https://www.drugsandalcohol.ie/34173/1/EMCDDA_drug-related_deaths_2021.pdf.

7. A. McAuley, C. Matheson, and J. R. Robertson, "From the Clinic to the Street: The Changing Role of Benzodiazepines in the Scottish Overdose Epidemic," *International Journal on Drug Policy* 100 (2022): 103512.

8. C. Fracasso, S. Confalonieri, S. Garattini, and S. Caccia, "Single and Multiple Dose Pharmacokinetics of Etizolam in Healthy Subjects," *European Journal of Clinical Pharmacology* 40 (1991): 181–185.

9. S. Nielsen and A. McAuley, "Etizolam: A Rapid Review on Pharmacology, Non-medical Use and Harms," *Drug and Alcohol Review* 39 (2020): 330–336.

10. European Union Drug Agency, "European Drug Report 2024, Annex Table 6," (Lisbon: European Union Drug Agency, 2024). Accessed January 14, 2024, https://www.euda.europa.eu/publications/european-drug-report/2024/annex-tables_en#edr24-annex-tables-table-6.

11. D. J. Greenblatt, "Pharmacology of Benzodiazepine Hypnotics," *Journal of Clinical Psychiatry* 53, no. Suppl (1992): 7–13.

12. A. A. Weinbroum, R. Flaishon, P. Sorkine, O. Szold, and V. Rudick, "A Risk-Benefit Assessment of Flumazenil in the Management of Benzodiazepine Overdose," *Drug Safety* 17 (1997): 181–196.

13. M. A. Claeys, F. Camu, I. Schneider, and E. Gepts, "Reversal of Flunitrazepam With Flumazenil: Duration of Antagonist Activity," *European Journal of Anaesthesiology* 2 (1988): 209–217.

14. A. M. Bailey, R. A. Baum, K. Horn, et al., "Review of Intranasally Administered Medications for Use in the Emergency Department," *Journal of Emergency Medicine* 53 (2017): 38–48.

15. G. Roncari, W. H. Ziegler, and T. W. Guentert, "Pharmacokinetics of the New Benzodiazepine Antagonist Ro 15-1788 in Man Following Intravenous and Oral Administration," *British Journal of Clinical Pharmacology* 22 (1986): 421–428.

16. T. J. Luger, R. F. Morawetz, and G. Mitterschiffthaler, "Additional Subcutaneous Administration of Flumazenil Does Not Shorten Recovery Time After Midazolam," *British Journal of Anaesthesia* 64 (1990): 53–58.

17. M. Faccini, R. Leone, S. Opri, et al., "Slow Subcutaneous Infusion of Flumazenil for the Treatment of Long-Term, High-Dose Benzodiazepine Users: A Review of 214 Cases," *Journal of Psychopharmacology* 30 (2016): 1047–1053.

18. N. Katz, G. Pillar, E. Peled, A. Segev, and N. Peled, "Sublingual Flumazenil for the Residual Effects of Hypnotics: Zolpidem and Brotizolam," *Clinical Pharmacology in Drug Development* 1 (2012): 45–51.

19. S. M. Bird, A. McAuley, S. Perry, and C. Hunter, "Effectiveness of Scotland's National Naloxone Programme for Reducing Opioid-Related Deaths: A Before (2006-10) Versus After (2011-13) Comparison," *Addiction* 111 (2016): 883–891.

20. T. Kerensky and A. Y. Walley, "Opioid Overdose Prevention and Naloxone Rescue Kits: What We Know and What We Don't Know," *Addiction Science & Clinical Practice* 12 (2017): 4.

21. S. M. Bird and A. McAuley, "Scotland's National Naloxone Programme," *Lancet* 393 (2019): 316–318.

22. British Medical Association and Royal Pharmaceutical Society of Great Britain, "British National Formulary Number 79 (March 2020)," (London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2020).

23. S. D. Harding, J. L. Sharman, E. Faccenda, et al., "The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: Updates and Expansion to Encompass the New Guide to IMMUNOPHARMACOLOGY," *Nucleic Acids Research* 46 (2018): D1091–D1106.

24. M. L. Sivilotti, "Flumazenil, Naloxone and the 'Coma Cocktail'," *British Journal of Clinical Pharmacology* 81 (2016): 428–436.

25. Hameln Pharma Ltd, "Summary of Product Characteristics: Flumazenil 100 Micrograms/ml Solution for Injection/Infusion," Electronic Medicines Compendium, (Leatherhead, UK: Datapharm Ltd, 2020).

26. National Drug & Alcohol Research Centre, "Trends in Overdose and Other Drug-Induced Deaths in Australia, 1997–2020," (Sydney: NDARC, UNSW, 2022). accessed November 7, 2024, https://www.unsw.edu.au/research/ndarc/resources/trends-drug-induced-deaths-australia-1997-2020#:~:text=The%20preliminary%20estimated%20rate%20of,sharply%20in%20the%20early%202000s.

27. M. C. Bonnet, B. Roche, and J. du Cailar, "Antagonism of the Sedative Effects of Flunitrazepam Used as a Hypnotic Agent in Neuroleptanalgesia Using Flumazenil Administered by i.v. and i.m. Routes [French]," *Cahiers d'Anesthésiologie* 39 (1991): 23–27.

28. E. I. Penninga, N. Graudal, M. B. Ladekarl, and G. Jürgens, "Adverse Events Associated With Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication--A Systematic Review With Meta-Analyses of Randomised Trials," *Basic & Clinical Pharmacology & Toxicology* 118 (2016): 37–44.

29. L. M. Ramos Rodriguez, "Adverse Effects of Flumazenil: A Systematic Review [Spanish]," (Thesis, San Cristobal de La Laguna: Universidad de La Laguna, 2021). accessed November 7, 2024, https://riull.ull.es/xmlui/handle/915/27143#:~:text=Entre%20ellos%20se%20incluyen%3A%20cefaleas,%2C%20resedaci%C3%B3n%2C%20aspiraci%C3%B3n%20y%20muerte.

30. J. J. Rasimas, V. Kivovich, K. K. Sachdeva, and J. W. Donovan, "Antagonizing the Errors of History: Bedside Experience With Flumazenil," *Toxicology Communications* 4 (2020): 25–39.

31. M. S. Heniff, G. P. Moore, A. Trout, W. H. Cordell, and D. R. Nelson, "Comparison of Routes of Flumazenil Administration to Reverse Midazolam-Induced Respiratory Depression in a Canine Model," *Academic Emergency Medicine* 4 (1997): 1115–1118.

32. K. Bodley, T. van Polanen Petel, and N. Gales, "Immobilisation of Free-Living Weddell Seals *Leptonychotes weddellii* Using Midazolam and Isoflurane," *Polar Biology* 28 (2005): 631–636.

33. C. Walzer and C. Huber, "Partial Antagonism of Tiletamine-Zolazepam Anesthesia in Cheetah," *Journal of Wildlife Diseases* 38 (2002): 468–472.

34. D. Z. Lu, H. G. Fan, M. Kun, et al., "Antagonistic Effect of Atipamezole, Flumazenil and Naloxone Following Anaesthesia With Xylazine, Tramadol and Tiletamine/Zolazepam Combinations in Pigs," *Veterinary Anaesthesia and Analgesia* 38 (2011): 301–309.

35. D. Passeron, J. L. Peschaud, J. Kienlen, and J. du Cailar, "Preliminary Study of a Benzodiazepine Antagonist (Flumazenil) in Toxicology [French]," *Annales Françaises d'Anesthèsie et de Rèanimation* 6 (1987): 26A.

36. J. Esparza Medina, "Utility of Intramuscular Flumazenil in Patients Sedated With Flunitrazepam in Regional Anesthesia [Spanish]," (Thesis, Mexico DF: Universidad Nacional Autonoma de Mexico, 1996). accessed November 2024, https://ru.dgb.unam.mx/bitstream/20.500.14330/TES01000234661/3/0234661.pdf.

37. C. A. Kelly, A. Upex, and D. N. Bateman, "Comparison of Consciousness Level Assessment in the Poisoned Patient Using the Alert/Verbal/Painful/Unresponsive Scale and the Glasgow Coma Scale," *Annals of Emergency Medicine* 44 (2004): 108–113.

38. A. Weinbroum, P. Halpern, and E. Geller, "The Use of Flumazenil in the Management of Acute Drug Poisoning — A Review," *Intensive Care Medicine* 17, no. Suppl 1 (1991): S32–S38.

39. E. Geller, D. Niv, A. Weinbrum, A. Silbiger, P. Halpern, and P. Sorkine, "The Use of Flumazenil in the Treatment of 34 Intoxicated Patients," *Resuscitation* 16, no. Suppl (1988): S57–S62.

40. A. Weinbroum, V. Rudick, P. Sorkine, et al., "Use of Flumazenil in the Treatment of Drug Overdose: A Double-Blind and Open Clinical Study in 110 Patients," *Critical Care Medicine* 24 (1996): 199–206.

41. W. H. Spivey, "Flumazenil and Seizures: Analysis of 43 Cases," *Clinical Therapeutics* 14 (1992): 292–305.

42. T. Fukasawa, N. Yasui-Furukori, A. Suzuki, Y. Inoue, T. Tateishi, and K. Otani, "Pharmacokinetics and Pharmacodynamics of Etizolam Are Influenced by Polymorphic CYP2C19 Activity," *European Journal of Clinical Pharmacology* 61 (2005): 791–795.

43. A. S. Razavizadeh, N. Zamani, P. Ziaeefar, S. Ebrahimi, and H. Hassanian-Moghaddam, "Protective Effect of Flumazenil Infusion in Severe Acute Benzodiazepine Toxicity: A Pilot Randomized Trial," *European Journal of Clinical Pharmacology* 77 (2021): 547–554.