BMJ Mental Health

Chronotherapeutic considerations of benzodiazepine administration for agitation management in the emergency department

Emily Rudisell,[1,2] Kyle Weant,[2] Alessandra Porcu [1]

[1]Department of Drug Discovery and Biomedical Sciences, University of South Carolina, Columbia, South Carolina, USA
[2]Department of Clinical Pharmacy and Outcome Sciences, University of South Carolina, Columbia, South Carolina, USA

Correspondence to
Dr Alessandra Porcu, Department of Drug Discovery and Biomedical Sciences, University of South Carolina, Columbia, South Carolina, USA; aporcu@mailbox.sc.edu

Received 12 June 2024
Accepted 19 February 2025

To cite: Rudisell E, Weant K, Porcu A. *BMJ Ment Health* 2025;**28**:1–7.

ABSTRACT

Objective Agitation in the emergency department (ED) affects up to 2.6% of encounters, posing significant risks to patients and caregivers. This review investigates the impact of circadian rhythms on benzodiazepine (BZD) pharmacokinetics and pharmacodynamics, focusing on how dosing time influences outcomes in managing acute agitation.

Methods A comprehensive literature search was performed using PubMed and Google Scholar (updated April 2024) to identify studies on BZD use in adult ED patients for acute agitation. Search terms included "antipsychotic agents," "lorazepam," "midazolam," "diazepam," and "emergency service." Studies focusing solely on substance intoxication were excluded. Priority was given to double-blind clinical trials, while open-label studies were included if no double-blind data were available. Referenced citations from identified publications were also reviewed.

Results Twenty-nine studies met the inclusion criteria: 16 randomised, double-blinded placebo-controlled trials, 5 prospective open-label studies and 8 retrospective reviews. Of these, 22 studies either did not report the time of day of patient recruitment or recruited patients over a year-long time frame. Four studies that specified the time of day of patient recruitment suggested a possible circadian variation in BZD sedation efficacy. Additionally, three studies that reported recruitment months revealed potential seasonal patterns in sedation requirements and efficacy.

Conclusions Circadian rhythms appear to influence BZD metabolism and therapeutic effects, which could have implications for optimising treatment strategies. Aligning BZD dosing schemes with biological timing may enhance treatment outcomes and minimise adverse effects. Further research is needed to validate these findings and develop personalised chronopharmacotherapy strategies for acute agitation in the ED.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several studies have shown circadian fluctuations in drug metabolising enzyme activity, affecting the pharmacokinetics of medications like diazepam, however little is known regarding the clinical implications of these alterations.

WHAT THIS STUDY ADDS

Among the 29 human studies analysed, only four reported enrolment times. When we compared sedation efficacy with time-of-day enrolment among those studies, substantial variation in sedation efficacy was noted that varied by enrolment time frame.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Future research should focus on confirming the significance of dosing time in benzodiazepine administration and exploring how integrating knowledge of circadian rhythms into treatment protocols can improve patient outcomes.

INTRODUCTION/BACKGROUND

The increasing prevalence of visits to the emergency department (ED) for behavioural conditions, including mental health and substance use disorders, underscores the importance of addressing acute agitation, a severe manifestation of these conditions that can lead to violent behaviour.[1 2] These episodes, occurring approximately 1.7 million times annually in US emergency settings, pose significant challenges in management, risking the safety of both patients and ED staff. While physical restraints are commonly used, they come with documented risks such as physical trauma and respiratory compromise.[3 4]

Pharmacological management, including the use of sedatives, is crucial in providing an alternative to physical restraints for addressing acute agitation. However, this approach does carry its own set of risks, with up to 37% of cases experiencing complications such as respiratory compromise and even fatalities in rare circumstances.[5] Therefore, it is of paramount importance to identify effective and safe interventions in the ED setting. A plethora of evaluations has compared various pharmacologic interventions, often demonstrating the superiority of certain combination therapies over monotherapy.

Benzodiazepines (BZDs), commonly used in the pharmacological management of acute agitation, act on the γ-aminobutyric acid (GABA) receptors to exert their effects.[6] The GABAergic system, which modulates anxiety-related behaviours, exhibits significant diurnal and circadian variations, potentially influencing the efficacy of BZDs.[7] Additionally, circadian rhythms impact the pharmacokinetics and pharmacodynamics of medications, including BZDs like diazepam, by affecting drug-metabolising enzyme activity.[8–10]

While immediate administration of BZDs is essential for managing severe agitation in

the ED, optimising the dose based on the time of day may enhance therapeutic outcomes by aligning with the circadian regulation of the GABA system. Although adjusting dosing times is often impractical in the fast-paced ED setting, understanding these circadian influences can help identify periods of reduced efficacy or heightened risk, which may necessitate an alteration in the dose administered. This knowledge enables targeted monitoring and informed clinical decisions, potentially improving patient outcomes and minimising adverse effects. Furthermore, insights into circadian variations in BZD efficacy have broader implications for other healthcare settings where medication timing can be more readily modified, allowing for tailored therapeutic strategies that optimise efficacy and safety.

Effective management of acute agitation in the ED thus requires a multifaceted approach that integrates prompt pharmacological intervention with an awareness of circadian influences on medication efficacy. Standardised, evidence-based practices are essential to ensure safe and effective treatment outcomes in this critical care environment.

OBJECTIVE

This review aims to analyse and discuss existing clinical data regarding the utilisation of BZDs for managing agitation in the ED, specifically focusing on elucidating the impact of dosing time on patient outcomes.

STUDY SELECTION AND ANALYSIS

A comprehensive literature search of BZD medication therapy use in adult patients in the ED for the treatment of acute agitation was conducted using PubMed and Google Scholar (update: April 2024) to identify primary literature. Studies were excluded if the population only included patients suffering from substance intoxication. Search terms included “antipsychotic agents”; “lorazepam”; “midazolam”; “diazepam”; “emergency service”. Published reports on double-blind clinical trials were included in this review. Open-label studies of a given medication were included if no published double-blind studies were identified. In addition, referenced citations from publications identified in the search were also reviewed.

FINDINGS

Twenty-nine studies were identified that met the search criteria. Sixteen studies were randomised, double-blinded placebo-controlled trials, 5 were prospective open-label studies and 8 were retrospective reviews. Twenty-two of the studies identified did not report the time of day of patient recruitment or recruited patients over at least a year’s time frame. Studies that reported specific times of day or specific months of the year that patients were recruited were analysed in more detail (table 1).

Studies with time-of-day enrolment reporting

Barbic *et al*[11] randomised 80 patients who presented to the ED to receive either intramuscular (IM) ketamine 5 mg/kg (n=40) or

Table 1 Studies reporting monthly or hourly dosing time

Source	Study design	Study population	Intervention	Dose timing information provided	Results
Bieniek *et al*[12]	Randomised, controlled trial (n=20)	Patients with acutely agitated behaviour in the psychiatric ED	▶ Intravenous lorazepam ▶ Intravenous haloperidol+lorazepam	Hourly (0700–1500)	▶ Intravenous haloperidol+lorazepam was significantly more effective at achieving target sedation
Nobay *et al*[13]	Randomised, controlled trial (n=111)	Patients requiring chemical restraints for violence and severely agitated behaviour in the ED	▶ IM midazolam ▶ IM lorazepam ▶ IM haloperidol	Hourly (0800–2300)	▶ Midazolam had a significantly shorter time to onset of sedation and more rapid time to arousal than lorazepam or haloperidol
Barbic *et al*[11]	Randomised, controlled trial (n=80)	Patients requiring behavioural control in the ED for severe psychomotor agitation	▶ IM ketamine ▶ IM midazolam+haloperidol	Hourly (0800–0000)	▶ IM ketamine had a significantly shorter time to adequate sedation than the combination group
Gomez and Dopheide[15]	Retrospective analysis (n=388)	Patients administered an antipsychotic for agitation in the psychiatric ED	▶ IM haloperidol ▶ Oral second-generation antipsychotics ▶ Concomitant benzodiazepines	Monthly (July–August)	▶ Coadministration of lorazepam with oral second-generation antipsychotics occurred in 39% of patients ▶ No significant differences in time to redosing between groups
Klein *et al*[16]	Observational cohort (n=737)	Patients receiving IM medication to treat agitation in the ED	▶ IM haloperidol ▶ IM ziprasidone ▶ IM olanzapine ▶ IM midazolam	Monthly (June–October)	▶ IM midazolam achieved more effective sedation at 15 min compared with the other groups
TREC Group[14]	Randomised, controlled trial (n=301)	Patients with aggression or agitation requiring sedation in the psychiatric ED	▶ IM midazolam ▶ IM haloperidol+promethazine	Monthly (June–December) 95% of patients presenting between 0800 and 0000	▶ Midazolam was more rapidly sedating than haloperidol+promethazine
Martel *et al*[17]	Randomised, controlled trial (n=144)	Patients requiring sedation for acute undifferentiated agitation in the ED	▶ Intravenous droperidol ▶ Intravenous ziprasidone ▶ Intravenous midazolam	Monthly (October–April)	▶ Droperidol or ziprasidone required rescue medications to achieve sedation less frequently than those sedated with midazolam

ED, emergency department; IM, Intramuscular.

haloperidol 5 mg plus midazolam 5 mg (n=40) for the treatment of psychomotor agitation. Of the 80 patients enrolled, 46.3% had a known prior psychiatric history. Patients were enrolled between June and March from 0800 to 0000 and sedation was assessed using the Richmond Agitation Score. The median time to sedation was found to be significantly faster in those receiving ketamine compared with the combination group. At 30 min, 80% of patients in the midazolam group were considered adequately sedated. 13% of patients in the ketamine group and 15% in the combination group required rescue medications. No significant differences were found between the two groups with regards to adverse effects. In addition, no data were presented regarding when patients specifically presented within the enrolment time window.

Bieniek *et al*[12] conducted a randomised double-blind study comparing patients who received intravenous lorazepam 2 mg (n=11) or haloperidol 5 mg plus lorazepam 2 mg (n=9) for the treatment of acutely agitated behaviour in a psychiatric ED. The majority of the population (90%) had a prior psychiatric history. Response to therapy was assessed using the Overt Aggression Scale, visual analogue scales reflecting agitation and hostility, and the Clinical Global Impressions severity scale. Patients who presented to the ED between 0700 and 1500 were evaluated. The time of year of patient enrolment was not presented. At 60 min following injection, the combination group of haloperidol combined with lorazepam demonstrated significantly more efficacy than lorazepam alone (100% vs 55%; p=0.03, respectively). No adverse effects were reported in either group. No data were presented regarding when patients specifically presented within the enrolment time window.

Nobay *et al*[13] randomised 111 violent or severely agitated patients who presented to the ED to IM midazolam 5 mg (n=42), lorazepam 2 mg (n=27) and haloperidol 5 mg (n=42). Adult patients, 48.6% having a prior psychiatric history, were enrolled from 0800 to 2300 over a 2-year period and efficacy was assessed using the Modified Thomas Combativeness Scale. The midazolam group had a significantly shorter time to onset of sedation (p<0.05) and more rapid time to arousal than the other two agents (p<0.05). 20% of patients in the two BZD arms required rescue medications compared with 19% in the haloperidol group (p=0.66). No data were presented regarding when patients specifically presented within the enrolment time window.

The TREC Collaborative Group[14] conducted a randomised trial in three psychiatric EDs of 301 aggressive or agitated patients, 72.8% of whom had a prior psychiatric history, randomised to receive either IM midazolam 7.5–15 mg (n=151) or haloperidol 5–10 mg plus IM promethazine 25–50 mg (n=150). Patients were enrolled between June and December, with 95% presenting between 0800 and 0000. Midazolam resulted in significantly faster sedation than the combination group both at 20 min and 40 min. At 20 min, 89% of the patients in the midazolam group were tranquil or asleep, compared with 93% at 40 min. No significant differences were noted between the groups with regards to adverse effects. No data were presented regarding when patients specifically presented within the enrolment time window.

Studies with only monthly enrolment reporting

Gomez and Dopheide[15] retrospectively reviewed 388 patients administered antipsychotics for agitation over two summer months. Time to repeat dosing and ED length of stay were compared among IM haloperidol, other IM antipsychotics and oral antipsychotics. No significant difference in repeat dosing time was observed, but oral antipsychotics reduced ED stay significantly (p=0.038). Klein *et al*[16] found IM midazolam superior to IM antipsychotics for rapid sedation among 737 patients during summer months. Martel *et al*[17] noted that those patients who received IM droperidol or ziprasidone required significantly fewer rescue medications than those who received IM midazolam (p<0.05) for agitation in winter months.

DISCUSSION

Visits to the ED for behavioural conditions are becoming increasingly common, with mental health and substance use disorders accounting for one in every eight visits.[18] Among these, the most severe cases often involve acute agitation, characterised by excessive psychomotor activity that has the potential to escalate into violent and disruptive behaviour.[1 2] These agitation episodes occur approximately 1.7 million times annually in emergency settings. Managing these patients presents a complex challenge, with potential safety risks for both patients and ED staff.[19] While physical restraints are frequently employed in the ED, they carry significant dangers. Risks such as physical trauma, respiratory depression and even asphyxiation leading to cardiac arrest are well-documented consequences of restraint use.[3 4] Additionally, the administration of sedatives as chemical restraints, commonly used to manage agitation, poses its own set of risks. Indeed, up to 37% of cases treated with sedatives experienced complications including respiratory compromise, QT interval prolongation, paradoxical agitation and even death.[20] Therefore, the management of agitation in the ED is a critical and complex aspect of patient care in the ED. Several studies have highlighted the importance of pharmacological management of agitation in the ED, emphasising the need for safe and effective interventions.[21]

Chronopharmacology is a field of science focusing on studying the effect of biological rhythms on pharmacotherapy, that is, a branch of pharmacology studying the dependencies between the timing of drug administration and its effect.[9 22 23] This consideration is crucial in the broad rationalisation of pharmacotherapy to ensure maximum effectiveness and safety. Recommending optimal drug dosing at various administration times, particularly for drugs with narrow therapeutic ranges, holds promise in maximising medication efficacy and minimising adverse drug events. Despite similar drug exposure, varying dosing times can lead to significant differences in drug effects, indicating the involvement of additional mechanisms beyond simple drug exposure.[9 24] Some factors to be considered in chronopharmacotherapy include consideration of the effect of biological rhythms on the pharmacokinetic disposition of the drug in the body as well as expression or function of drug targets, which will be discussed below.

Biological rhythms are recurring daily phenomena found in most organisms, orchestrating complex physiological processes across molecular, phenotypic and behavioural levels.[25] These rhythms synchronise internal circadian mechanisms with environmental cues, enabling adaptation and maintenance of bodily functions. Various physiological parameters exhibit rhythmicity, including sleep–wake patterns, hepatic metabolism, renal and cardiovascular function.[26] Drug pharmacokinetics, such as absorption, distribution, metabolism and elimination, exhibit circadian rhythms.[9] Therefore, the efficacy and toxicity of many drugs are subjected to circadian rhythms (ie, dosing time-dependency) with a variability of up to 10-fold,[8] although the underlying mechanisms are unknown. Evidence from several drug classes showed that circadian pharmacokinetics can be

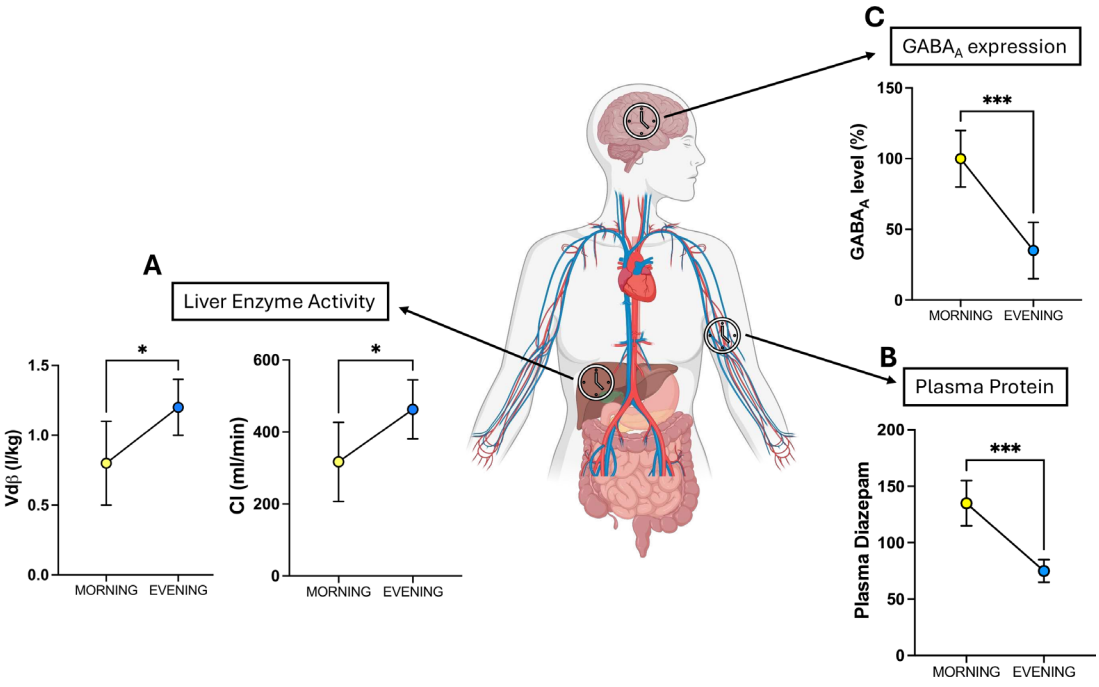

Figure 1 Molecular clocks regulate physiological processes that might affect intravenous benzodiazepine efficacy and safety. (A) Midazolam intrinsic clearance (Cl) and volume of distribution during elimination phase (Vdβ) adapted from Klotz and Ziegler.[47] (B) Plasma diazepam data adapted from Naranjo *et al*.[10] (C) γ-aminobutyric acid (GABA$_A$) level (%) adapted from Li *et al*.[39]

translated to chronotoxicity and chronoefficacy. For example, chronotoxicity of acetaminophen has been attributed to diurnal hepatic expression of CYP2E1 enzyme (high expression in the nighttime and low expression in the daytime).[27 28] Studies in vitro have also established several other CYP genes as potential targets of the circadian system, including CYP3A4,[29] which metabolises lorazepam, triazolam, brotizolam and midazolam and partially diazepam. Therefore, circadian regulation of CYP3A4 can profoundly influence the pharmacokinetics and pharmacodynamic actions of BZD, contributing to time-dependent effects (figure 1A). These rhythms impact BZD disposition and actions, potentially altering therapeutic outcomes and toxicity based on dosing timing.

To date, very few studies have been performed to investigate the circadian changes in drug distribution to tissues from systemic blood circulation. The variation in protein binding, particularly the proportion of unbound proteins, due to circadian oscillation, is considered a contributing factor to the time-dependent dosing dynamics of drug distribution.[30 31] Diazepam and its metabolite, N-desmethyldiazepam, are highly bound to plasma albumin.[32 33] Only 1.33+0.21% (mean+s.d.) of diazepam is in the unbound form in the plasma over the range of concentration normally encountered in therapy and the drug elimination is reported to be dependent on free fraction.[32 34] Changes in diazepam free fraction may, therefore, cause important variations in disposition and effects. The fraction of unbound diazepam is lower at 0.5 hour after intravenous dosing in the morning, and a negative correlation is observed between the fraction of unbound and total plasma level[35] (figure 1B). Therefore, diurnal alteration in protein binding contributes to time-dependent changes in the rate of diazepam distribution and has both pharmacokinetic and clinical importance.[10] According to these observations, defining the best dosing time for BZD administration may result in better pharmacokinetic profiles, improved therapeutic effect and less side effects. This would help guide practitioners in knowing when dose increases or dose reductions may be most appropriate to yield targeted levels of sedation.

Circadian variations in expression or function of drug targets might represent a main source of drug chronoefficacy in addition to circadian pharmacokinetics, particularly for allosteric modulators. BZDs act as allosteric modulators on type-A receptors for the inhibitory neurotransmitter GABA (GABA$_A$). BZD binding prolongs chloride currents through GABA$_A$ receptors to increase the duration and strength of GABA inhibitory signals.[36] The number of GABA$_A$ receptors on the surface of neurons is a critical determinant of the efficacy of synaptic inhibition.[37 38] Interestingly, preclinical data showed daily fluctuation in the degradation of GABA$_A$ receptors (figure 1C). This fluctuation directly impacts the rhythm of GABA sensitivity, which regulates the excitability of neurons that are responsible for promoting wakefulness.[39] These findings suggest that the timing of BZD administration could significantly influence their effectiveness in inducing sedation.

As many other brain components and functions, the GABAergic system exhibits robust daily and circadian variations in many parameters, including fluctuations in GABA levels, GABA$_A$ receptor affinity, turnover and postsynaptic activity[7] (figure 2A,B). Such neurochemical rhythms correlate with diurnal and circadian changes in behaviours directly associated with the GABA$_A$ receptor, like the anxiety-related behaviour and locomotor activity.[40] When administered intravenously at a dose of 5 mg/kg, Flumazenil, a competitive antagonist at the BZD-binding site on the GABA$_A$ receptor, resulted in a notable 60% increase in anxiety responses in rats during the dark phase.[40] This effect coincided with the period of heightened chloride uptake and increased binding affinity to GABA$_A$ receptors[7] (figure 2B). Conversely, when the same dose was administered during the light phase, it still elicited a significant 46% enhancement in anxiety responses, yet without impacting general locomotion.[40] The findings from preclinical studies indicate that

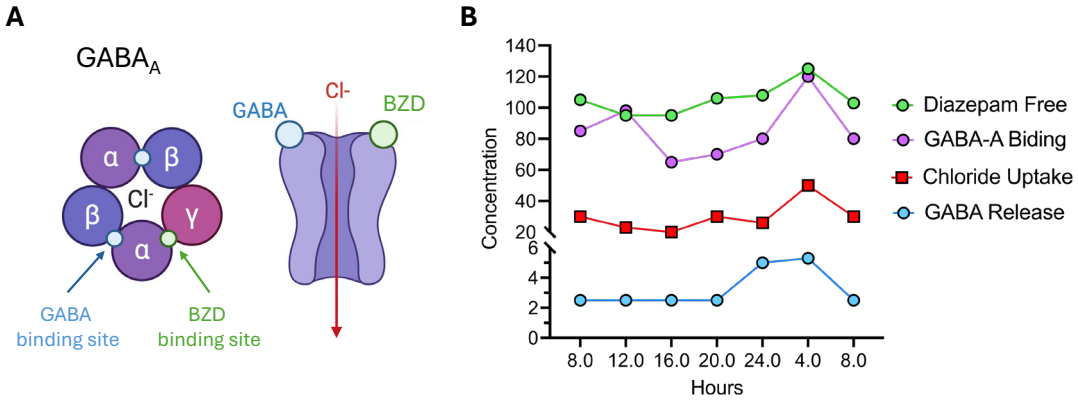

Figure 2 Diurnal variation of GABAergic system and diazepam-free content. (A) Schematic representation of a GABA$_A$ receptor: subunit arrangement, GABA and benzodiazepine (BZD) binding sites. (B) Graph shows diurnal changes in a 24-hour cycle in GABA release (^{3}H-GABA release, fractional release x 10), $^{36}Cl^-$ uptake (nmol/mg protein) and GABA binding affinity (mM^{-3}x10) from rats adapted from Cardinali and Golombek[7] (figure 1) and diazepam free fraction from humans adapted from Naranjo *et al*[10] (figure 2). GABA, γ-aminobutyric acid.

the safety profile of BZD could be optimised by administering a low dose when GABA$_A$ receptor affinity, GABA release and chloride uptakes reach their peak in the 24-hour cycle (between 24–4 hours, dark phase). The peak of free-diazepam also appears to be between 24–4 hours in humans (figure 2B),[10] suggesting that dose-timing BZD administration to align with the circadian rhythm of GABA system could enhance therapeutic efficacy while minimising adverse effects. This chronopharmacological approach presents a promising strategy to enhance the therapeutic benefits of BZD by capitalising on natural circadian fluctuations in receptor dynamics and in drug bioavailability. Aligning BZD administration with these biological rhythms may reduce the risks of tolerance, dependence and other adverse effects associated with unsynchronised dosing schedules. These findings highlight the potential of chronopharmacology to personalise BZD therapy based on individual circadian profiles. Future research should focus on elucidating the contributions of diurnal variations in GABA synthesis, receptor subunit composition and drug metabolism to the time-dependent effects of BZD in both preclinical and clinical settings.

Among the 29 human studies analysed, only four reported enrolment times (table 1). Interestingly, when we compared sedation efficacy with time-of-day enrolment, patients entering the ED in the morning or afternoon exhibited a 55% sedation efficacy with lorazepam alone[12] (figure 3). However, patients entering the ED between 0800 and 2300 showed almost 100% sedation efficacy with midazolam alone, with 20% of these patients requiring rescue medications.[13 14] We hypothesise that the inclusion of a group that received BZD administration at night may have helped yield greater efficacy due to the peak in chloride uptake and GABA content during this later time frame (figure 2B). Future studies could further investigate this hypothesis by conducting controlled trials comparing the sedative effects of BZDs administered at different times of the day, with particular attention to variations in patient outcomes. Such studies would contribute valuable insights into optimising medication administration timing for enhanced therapeutic outcomes in emergency settings.

The circadian rhythm plays a fundamental role in regulating sleep propensity and arousal.[41 42] Sleep propensity, defined as the innate tendency to initiate sleep, typically increases during the biological night, whereas the arousal rhythm diminishes, facilitating sleep onset.[43] BZD administration coincident with the natural peak of sleep propensity may potentiate the sedative effects of the drug. Specifically, BZD-induced sedation could be amplified by the broad soporific effects of the circadian system, which promotes sleep during the biological night. This additive or potentially multiplicative interaction between BZD and the circadian rhythm could account for the enhanced efficacy of BZD observed at these time points in figure 3. Understanding this interaction is crucial for interpreting results related to the dose-timing of BZD administration and provides a biological basis for the observed potentiation of drug effects. This insight highlights the importance of integrating circadian timing in future pharmacological studies, particularly when optimising the timing of BZD administration.

Environmental conditions can change drastically over the course of the year and thus require an adequate physiological response from the human body.[44] The circadian system of many species is responsive to seasonal changes in the natural light–dark cycle. While previous studies have suggested seasonal adaptations in the GABAergic neurotransmitter system,[45] recent

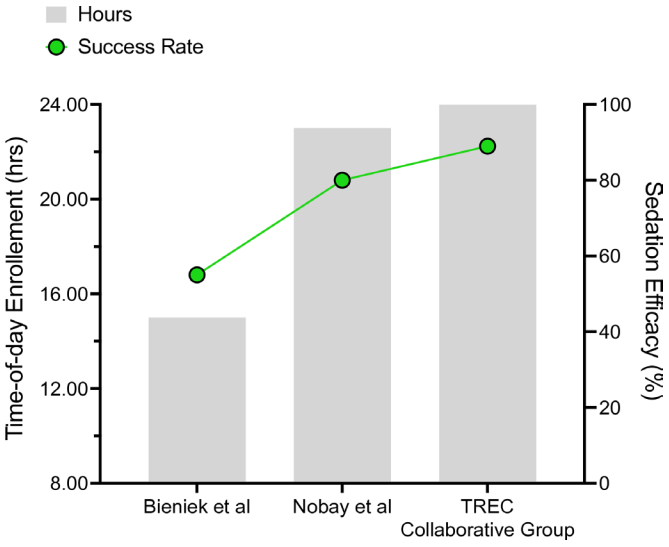

Figure 3 Bar graphs showing the time-of-day of enrolment and a line graph demonstrating sedation efficacy (%) with benzodiazepine therapy. Data adapted from Bieniek *et al*, Nobay *et al*, TREC Group.[12–14]

MRI research has indicated stable levels of GABA throughout the year in healthy individuals.[46] Interestingly, our retrospective review revealed distinct patterns in sedation requirements and efficacy based on the time of year patients were enrolled in the ED (table 1). Patients enrolled from October to April and sedated with droperidol or ziprasidone required rescue medications less frequently compared with those sedated with midazolam.[16] Conversely, patients enrolled from June/July to December showed that midazolam achieved more rapid and effective sedation at 15 min compared with haloperidol+promethazine and other groups.[17] However, research on seasonal variations in brain function and structure remains limited, often constrained by small sample sizes, cross-sectional study designs or focusing on only a few regions of interest. Further investigations with larger and more comprehensive studies are warranted to elucidate the extent and implications of seasonal variations in brain function and GABA system.

CONCLUSIONS AND FUTURE PERSPECTIVES

Chronotherapy has demonstrated significant potential in optimising the efficacy of medications while minimising their toxicity.[8] For BZDs, dosing time emerges as an important variable that may influence pharmacokinetics and therapeutic outcomes. Circadian rhythms intricately regulate various factors affecting the pharmacokinetics and pharmacodynamics of BZDs, presenting challenges in interpreting findings from both animal and human studies. While immediate administration of BZDs is critical in ED settings to manage severe agitation, understanding how circadian timing affects drug efficacy can provide valuable insights. This knowledge could identify periods when BZDs are less effective or associated with greater risks, guiding improved patient monitoring strategies. To advance this field, future studies should incorporate assessments of agitation scales and behavioural responses at different times of day, even within the constraints of acute care environments like the ED. Preclinical research is also essential to elucidate the chronopharmacological profiles of specific BZDs, helping to refine their time-dependent efficacy and safety profiles. Such research could inform personalised dosing strategies in settings where medication timing is modifiable, translating preclinical findings into improved patient outcomes. Ultimately, a deeper understanding of chronopharmacotherapy for BZDs could revolutionise their use across diverse clinical contexts, paving the way for evidence-based strategies to optimise their therapeutic potential.

Limitations

An exhaustive search of PubMed and Google Scholar identified seven studies reporting enrolment timing, with three noting specific months and four providing time-of-day information. Of these, three included both day and nighttime hours, while one reported only daylight hours (0700–1500). Factors contributing to agitation and their impact on dosing, treatment success, and adverse effects were not thoroughly assessed. Variability in the definition of 'acute agitation' and the use of multiple assessment scales limited comparisons across studies.

X Kyle Weant @kyleweant

Contributors KW and AP conceived the study. ER, KW and AP performed the reference search. KW and AP drafted the manuscript and designed the figures and tables. KW and AP are the guarantors.

Funding This work was supported by the College of Pharmacy, Department of Drug Discovery and Biomedical Sciences at the University of South Carolina and by NIH-NCCIH (grant no. AT010903) to AP.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Part of a topic collection; not commissioned; internally peer-reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Alessandra Porcu http://orcid.org/0000-0003-3891-3027

REFERENCES

1 Capp R, Hardy R, Lindrooth R, *et al*. National Trends in Emergency Department Visits by Adults With Mental Health Disorders. *J Emerg Med* 2016;51:131–5.
2 Nordstrom K, Zun LS, Wilson MP, *et al*. Medical evaluation and triage of the agitated patient: consensus statement of the american association for emergency psychiatry project Beta medical evaluation workgroup. *West J Emerg Med* 2012;13:3–10.
3 Zun LS. A prospective study of the complication rate of use of patient restraint in the emergency department. *J Emerg Med* 2003;24:119–24.
4 Karger B, Fracasso T, Pfeiffer H. Fatalities related to medical restraint devices-asphyxia is a common finding. *Forensic Sci Int* 2008;178:178–84.
5 Korczak V, Kirby A, Gunja N. Chemical agents for the sedation of agitated patients in the ED: a systematic review. *Am J Emerg Med* 2016;34:2426–31.
6 Sieghart W. Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes. *Pharmacol Rev* 1995;47:181–234.
7 Cardinali DP, Golombek DA. The rhythmic GABAergic system. *Neurochem Res* 1998;23:607–14.
8 Dong D, Yang D, Lin L, *et al*. Circadian rhythm in pharmacokinetics and its relevance to chronotherapy. *Biochem Pharmacol* 2020;178:114045.
9 Dobrek L. Chronopharmacology in Therapeutic Drug Monitoring-Dependencies between the Rhythmics of Pharmacokinetic Processes and Drug Concentration in Blood. *Pharmaceutics* 2021;13:1915.
10 Naranjo CA, Sellers EM, Giles HG, *et al*. Diurnal variations in plasma diazepam concentrations associated with reciprocal changes in free fraction. *Br J Clin Pharmacol* 1980;9:265–72.
11 Barbic D, Andolfatto G, Grunau B, *et al*. Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial. *Ann Emerg Med* 2021;78:788–95.
12 Bieniek SA, Ownby RL, Penalver A, *et al*. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998;18:57–62.
13 Nobay F, Simon BC, Levitt MA, *et al*. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. *Acad Emerg Med* 2004;11:744–9.
14 TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003;327:708–13.
15 Gomez S, Dopheide J. Antipsychotic Selection for Acute Agitation and Time to Repeat Use in a Psychiatric Emergency Department. *J Psychiatr Pract* 2016;22:450–8.
16 Klein LR, Driver BE, Miner JR, *et al*. Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department. *Ann Emerg Med* 2018;72:374–85.
17 Martel M, Sterzinger A, Miner J, *et al*. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med* 2005;12:1167–72.
18 Theriault KM, Rosenheck RA, Rhee TG. Increasing Emergency Department Visits for Mental Health Conditions in the United States. *J Clin Psychiatry* 2020;81:20m13241.
19 Holloman GH Jr, Zeller SL. Overview of Project BETA: Best Practices in Evaluation and Treatment of Agitation. *WestJEM* 2012;13:1–2.
20 Yap CYL, Taylor DM, Kong DCM, *et al*. Risk Factors for Sedation-related Events During Acute Agitation Management in the Emergency Department. *Acad Emerg Med* 2019;26:1135–43.
21 Zeller SL, Nordstrom KD, Wilson MP. *The diagnosis and management of agitation*. Cambridge University Press, 2017.
22 Ballesta A, Innominato PF, Dallmann R, *et al*. Systems Chronotherapeutics. *Pharmacol Rev* 2017;69:161–99.
23 Institute of Medicine, National Research Council, Division of Behavioral and Social Sciences and Education. *Depression in parents, parenting, and children: opportunities to improve identification, treatment, and prevention*. National Academies Press, 2009.

24 Ayyar VS, Sukumaran S. Circadian rhythms: influence on physiology, pharmacology, and therapeutic interventions. *J Pharmacokinet Pharmacodyn* 2021;48:321–38.
25 Sukumaran S, Almon RR, DuBois DC, *et al*. Circadian rhythms in gene expression: Relationship to physiology, disease, drug disposition and drug action. *Adv Drug Deliv Rev* 2010;62:904–17.
26 Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. *Ann Clin Biochem* 2006;43:344–53.
27 Matsunaga N, Nakamura N, Yoneda N, *et al*. Influence of feeding schedule on 24-h rhythm of hepatotoxicity induced by acetaminophen in mice. *J Pharmacol Exp Ther* 2004;311:594–600.
28 DeBruyne JP, Weaver DR, Dallmann R. The hepatic circadian clock modulates xenobiotic metabolism in mice. *J Biol Rhythms* 2014;29:277–87.
29 Takiguchi T, Tomita M, Matsunaga N, *et al*. Molecular basis for rhythmic expression of CYP3A4 in serum-shocked HepG2 cells. *Pharmacogenet Genomics* 2007;17:1047–56.
30 Hamdan AM, Koyanagi S, Wada E, *et al*. Intestinal expression of mouse Abcg2/breast cancer resistance protein (BCRP) gene is under control of circadian clock-activating transcription factor-4 pathway. *J Biol Chem* 2012;287:17224–31.
31 Bruguerolle B, Valli M, Bouyard L, *et al*. Effect of the hour of administration on the pharmacokinetics of lidocaine in the rat. *Eur J Drug Metab Pharmacokinet* 1983;8:233–8.
32 Klotz U, Antonin KH, Bieck PR. Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. *J Pharmacol Exp Ther* 1976;199:67–73.
33 Thiessen JJ, Sellers EM, Denbeigh P, *et al*. Plasma protein binding of diazepam and tolbutamide in chronic alcoholics. *J Clin Pharmacol* 1976;16:345–51.
34 Abel JG, Sellers EM, Naranjo CA, *et al*. Inter- and intrasubject variation in diazepam free fraction. *Clin Pharmacol Ther* 1979;26:247–55.
35 Nakano S, Watanabe H, Nagai K, *et al*. Circadian stage-dependent changes in diazepam kinetics. *Clin Pharmacol Ther* 1984;36:271–7.
36 Christian CA, Herbert AG, Holt RL, *et al*. Endogenous positive allosteric modulation of GABA(A) receptors by diazepam binding inhibitor. *Neuron* 2013;78:1063–74.
37 Agosto J, Choi JC, Parisky KM, *et al*. Modulation of GABAA receptor desensitization uncouples sleep onset and maintenance in Drosophila. *Nat Neurosci* 2008;11:354–9.
38 Saliba RS, Michels G, Jacob TC, *et al*. Activity-dependent ubiquitination of GABA(A) receptors regulates their accumulation at synaptic sites. *J Neurosci* 2007;27:13341–51.
39 Li Q, Li Y, Wang X, *et al*. Fbxl4 Serves as a Clock Output Molecule that Regulates Sleep through Promotion of Rhythmic Degradation of the $GABA_A$ Receptor. *Curr Biol* 2017;27:3616–25.
40 Yanielli PC, Kanterewicz BI, Cardinali DP. Circadian Changes in Anxiolysis-Related Behavior of Syrian Hamsters. Correlation with Hypothalamic GABA Release. *Biol Rhythm Res* 1996;27:365–73.
41 Desai D, Momin A, Hirpara P, *et al*. Exploring the Role of Circadian Rhythms in Sleep and Recovery: A Review Article. *Cureus* 2024;16:e61568.
42 Foster RG. Sleep, circadian rhythms and health. *Interface Focus* 2020;10:20190098.
43 Borbély A. The two-process model of sleep regulation: Beginnings and outlook. *J Sleep Res* 2022;31:e13598.
44 Kasper S, Wehr TA, Bartko JJ, *et al*. Epidemiological findings of seasonal changes in mood and behavior. A telephone survey of Montgomery County, Maryland. *Arch Gen Psychiatry* 1989;46:823–33.
45 Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 2012;62:63–77.
46 Spurny-Dworak B, Reed MB, Handschuh P, *et al*. The influence of season on glutamate and GABA levels in the healthy human brain investigated by magnetic resonance spectroscopy imaging. *Hum Brain Mapp* 2023;44:2654–63.
47 Klotz U, Ziegler G. Physiologic and temporal variation in hepatic elimination of midazolam. *Clin Pharmacol Ther* 1982;32:107–12.