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REVIEW ARTICLE

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Remimazolam – current status, opportunities and challenges

J. Robert Sneyd[1*]

Abstract

The short acting benzodiazepine remimazolam has been well characterised for use during procedural sedation. Onset of hypnotic effect is swifter than midazolam and recovery is faster with a period of antegrade amnesia. Haemodynamic changes associated with remimazolam sedation are modest and there is no pain on injection. General anaesthesia may be induced and maintained by infusion of remimazolam in combination with a suitable opioid. Hypotension is less frequent than when propofol is used. In addition, remimazolam may be a suitable alternative to propofol or etomidate for inducing anaesthesia in haemodynamically compromised patients prior to maintenance with a volatile agent.
A small proportion of patients are slow to recover consciousness after total intravenous anaesthesia (TIVA) with remimazolam/opioid combinations. Preliminary experience suggests that flumazenil may be useful in this group however studies are required to define the appropriate dosage and timing for flumazenil administration. Future developments may include sedation and anaesthesia for infants and children as well as intensive care sedation for all age groups. These indications require demonstration in well designed clinical trials.

Keywords Sedation, Remimazolam, Midazolam, Propofol

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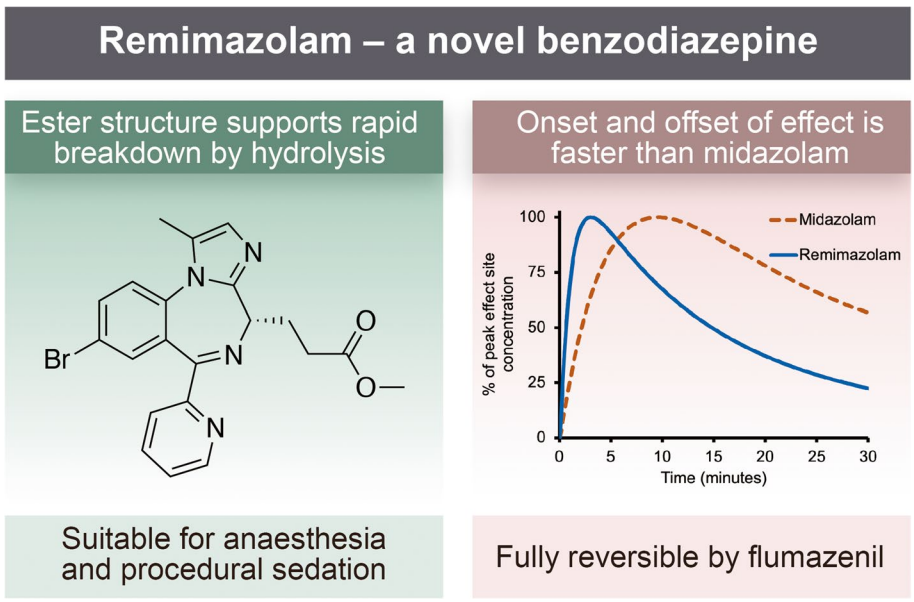
Graphical Abstract



1 Main text

Remimazolam is a short acting benzodiazepine whose effects are terminated by ester hydrolysis Fig. 1. This review briefly summarises remimazolam's profile in procedural sedation whilst addressing in more detail future opportunities in induction and maintenance of general anaesthesia. Future possibilities including intensive care sedation and paediatrics are considered.

1.1 Early development programme and regulatory approvals

Clinical development of remimazolam has been slow with a sparse programme of volunteer studies [3] and clinical trials [4, 5] leading eventually to regulatory approvals. Remimazolam is licensed for procedural sedation in Europe, the UK and the USA. Approval for induction and maintenance of anaesthesia has been granted in China, Korea and Japan and is imminent in Europe. The indications requested in applications to regulatory authorities and the wording of subsequent approvals are influenced by precedents, medical culture and commercial considerations. In China, Korea and Japan the concept of procedural sedation is not clearly distinguished from general anaesthesia, hence the broader approval within which procedural sedation is regarded as a subset of anaesthesia. In other territories, procedural sedation is well established as a specific indication requiring a bespoke regulatory application and approval.

1.2 Onset and offset of hypnotic effect

Volunteer studies and clinical trials in procedural sedation have established that remimazolam possesses pharmacokinetic characteristics intermediate between propofol and midazolam whilst enjoying a pharmacodynamic profile

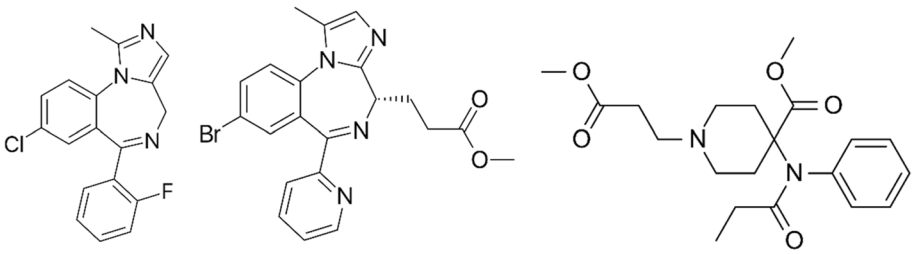


Fig. 1 Midazolam, remimazolam and remifentanil. In remimazolam and remifentanil, the introduction of an ester side group allows rapid hydrolysis [1]. Reproduced with permission from: Sneyd JR, Rigby-Jones AE. Remimazolam for anaesthesia or sedation. Curr Opin Anaesthesiol 2020; 33: 506–11 [2]

similar to that of midazolam [2]. Specifically, following remimazolam administration the onset of hypnotic effect is substantially swifter than that of midazolam and possibly similar to that seen with propofol, depending on the chosen dose and rate of administration [6]. Like midazolam, remimazolam causes antegrade amnesia—variously described as equivalent [4] to or less than [7] that produced by midazolam. When compared to midazolam in users of central nervous system (CNS) depressants, remimazolam was considered to have less abuse potential than midazolam [7]. Nasal administration of remimazolam powder is effective as an hypnotic but unacceptably painful [8].

1.3 Recovery from sedation and anaesthesia

Recovery of consciousness and normalisation of psychometric testing after remimazolam sedation is markedly faster than when midazolam is used [4] Fig. 2. Limited data describe recovery from remimazolam based general anaesthesia however preliminary reports suggested that it may be substantially delayed in a small number of "outliers" to whom the administration of flumazenil may be considered [9, 10].

1.4 Pharmaceutical presentation

Remimazolam is presented as a powder for dilution immediately before use. This reflects its ester formulation and the possibility of drug breakdown. However, subject to preparation using suitable aseptic techniques, storage for up to 24 h is acceptable. As an acid salt, Remimazolam solutions are unlikely to support bacterial growth. This contrasts with European formulations of propofol which have a neutral pH, a high lipid content and no added antiseptic. Remimazolam is a chiral molecule presented as the S-enantiomer which is prepared by stereoselective synthesis [18].

Precipitation has been reported when remimazolam besylate has been co-administered with certain electrolyte solutions based on sodium acetate or sodium lactate [19–21]. Consequently, mixing of remimazolam with compound sodium lactate solution for infusion is not recommended. Given the widespread perioperative use of various Ringer's solutions, this restriction may constrain remimazolam use for induction and maintenance of general anaesthesia.

Although primarily tested and licensed as remimazolam besylate, a salt of benzenesulfonic acid, an alternative salt remimazolam tosylate has been developed and licensed in China. Although no head-to-head comparisons have been reported, the two formulations appear to be functionally equivalent.

1.5 Issues of cost and volume

As is typically the case with new medicines, remimazolam is considerably more expensive than its generic

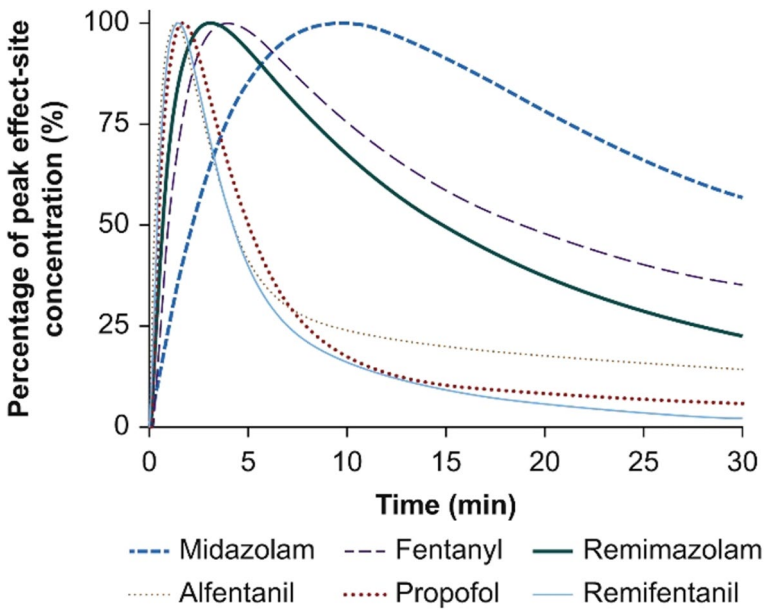


Fig. 2 Effect-site opioid and hypnotic concentrations over time as a proportion of the peak effect-site concentration. Midazolam [11] (heavy blue dashes), fentanyl [12] (thin purple dashes), remimazolam [13] (heavy green line), alfentanil [14] (thin brown dotted line), propofol [15] (large red dots), and remifentanil [16] (thin blue line). Onset and offset of remimazolam are intermediate between propofol and fentanyl, and faster than midazolam. Simulated using STANPUMP. STANPUMP is freely available from the author at opentci.org/code/stanpump. Reproduced with permission from: Sneyd JR, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and the case for remimazolam: a narrative review. Br J Anaesth 2021;127: 41–55 [17]

competitors (propofol and midazolam). An inevitable consequence of its short duration of action is a requirement to administer (relatively) large amounts of drug to maintain sedation or anaesthesia for extended periods.

Although clinical trial registries show several studies of remimazolam based intensive care sedation either underway or completed, few data have been published. One investigation using simulations recommended remimazolam 0.25 mg/kg/hr in combination with remifentanil for patients requiring sedation after surgery [13]. Were such a scheme to be applied to a 70 kg adult then in excess of 20 ampoules of remifentanil 20 mg would be required to cover a 24 h period of sedation.

In pricing terms, assuming a consistent cost per milligram of drug, this makes for one of two scenarios. Either, if the drug is priced to be commercially viable for single dose administration then its use for extended procedures becomes expensive. Alternatively, if the pricing is reduced to make maintenance attractive then single doses become something of a bargain. The same consideration afflicted remifentanil and this is one of several reasons why remifentanil is unattractive as a component of intensive care sedation.

1.6 Environmental impact

The environmental impact of volatile anaesthetic agents together with the carbon footprint of the entire process of drug production, distribution, administration and (where necessary) destruction is of great contemporary interest [22]. In this regard, clinicians may reasonably ask manufacturers to provide relevant data positioning their products against competitors. Such data is currently not generally available for remimazolam. In the case of intravenous products such as remimazolam the footprint includes the relevant syringes, tubing, needles, cannulae and bottles necessary for its use.

1.7 Practical issues and drug administration

1.7.1 Tolerance and tachyphylaxis

Tolerance and tachyphylaxis are two important concepts to consider when administering benzodiazepines, a class of drugs commonly used for their anxiolytic, hypnotic, anticonvulsant, and muscle-relaxant effects. Tolerance refers to a decrease in the effectiveness of a drug over time, requiring the individual to take progressively larger doses to achieve the same therapeutic effect. Tachyphylaxis, refers to a rapid decrease in the effectiveness of a drug following repeated administration, even with stable dosing. This is a specific form of tolerance that can occur rapidly, within hours or days, and is thought to be related to changes in the receptors targeted by benzodiazepines. When mini-pigs were sedated with remimazolam or midazolam for up to 28 days, remimazolam dose requirements escalated (as did the midazolam requirements of control animals) [23]. Since mini-pigs are a reasonable physiological and pharmacological analogue for humans, these data suggest that remimazolam tolerance will develop in humans receiving prolonged infusions of remimazolam.

Both tolerance and tachyphylaxis can have important implications for the use of benzodiazepines, as they can limit their efficacy and potentially increase the risk of adverse effects, such as dependence, overdose, and withdrawal symptoms. Reduced effect following remimazolam administration has been described in patients receiving long-term benzodiazepine administration [24, 25].

1.7.2 Anaphylaxis

A small number of cases of apparent anaphylaxis have been reported following administration of remimazolam [26–28]. Remimazolam injection contains dextran, a known allergen. Therefore, when evaluating these case reports it is important that alternative explanations including allergy to dextran, other perioperative drugs, latex and chlorhexidine be carefully considered. Nevertheless, careful investigations including skin testing and measurement of tryptase concentrations have confirmed at least a proportion of reported cases. The incidence of remimazolam anaphylaxis is probably low but clarification is required concerning possible cross reaction with midazolam and the relevance of previous exposures to remimazolam. Anaphylactic reactions to remimazolam have been consistently severe and therefore deserve to be taken seriously. Fortunately, affected patients respond to standard symptomatic resuscitation. Continued vigilance and improved testing methodology are recommended in order that the true incidence and genesis of these anaphylactic events is more clearly understood [29].

1.8 Future developments

1.8.1 Further characterisation of remimazolam for induction and maintenance of anaesthesia

To date, studies of remimazolam anaesthesia focused on demonstrating it to be safe and effective thereby supporting regulatory submissions. Thus the major European multi-centre comparison of remimazolam and propofol use as an endpoint non-inferiority to propofol for hypnotic effect [30]. This is important in itself—were a purported new hypnotic inferior in hypnotic effect then it would scarcely be worth further attention. However, non-inferiority is not a reason to adopt a new drug. Currently there is considerable clinician focus on intra-operative hypotension and also on episodes of hypotension during the immediate post-operative period [31]. Since anaesthetic induced hypotension is both harmful and remediable then it makes sense to identify and adopt strategies

for its mitigation [32]. Induction of anaesthesia is an especially critical phase of an anaesthetic when a patient may experience drug induced hypotension and/or intense sympathetic stimulation. Although careful evaluation of individual patients co-variates, [33] possibly by using machine-learning, [34] may identify patients at increased risk, it nevertheless make sense to prefer hypnotics with minimum circulatory impact. Etomidate [35–37] (which causes adrenocortical depression) and ketamine [38] (which causes hallucinations) both enjoy some clinician support as induction agents in haemodynamically compromised or 'at risk' patients [39]. A recent systematic review identified eight studies involving 738 patients in which remimazolam was compared to propofol for general anaesthesia. Post-induction hypotension was less frequent in patients receiving remimazolam whilst the times to post-operative recovery endpoints were similar [40].

Arterial blood pressure is not the only characteristic of anaesthesia induction which merits attention. Propofol appears uniquely suited to subsequent insertion of a supraglottic airway device. Although remimazolam anaesthesia can be used in this circumstance, especially with a concomitant opioid, inadequate relaxation and patient movement are relatively common [41].

Benzodiazepines have long been identified as effective induction agents [42–44] however slow onset of hypnotic effect and delayed recovery of consciousness have prevented general deployment. The favourable pharmacokinetics of remimazolam invite revisiting of benzodiazepine anaesthesia—especially for 'high-risk' patients [17]. Doi and co-workers used remimazolam to induce and maintain anaesthesia in surgical patients of American Society of Anesthesiologists physical status (ASA grade) of I or II [10] and also ASA III [9]. In both studies, induction of anaesthesia was achieved by remimazolam infusion 6–12 mg/kg/hr. Subsequently, remimazolam tosilate has been effective for induction of anaesthesia in cardiac surgery patients whilst maintaining stable haemodynamic characteristics and incurring fewer adverse events that patients randomised to receive etomidate [45]. These data suggest that remimazolam infusion may be a suitable induction agent for general application to compromised and at-risk patients and arguably makes the continued use of etomidate hard to justify.

Comparing the haemodynamic characteristics of hypnotics is fraught with methodological difficulties. During induction of anaesthesia, differences in drug distribution (pharmacokinetics) and effect site equilibration ($t_{1/2}k_{e0}$) give characteristic onset profiles. Whilst investigators may make every effort towards equivalence, comparing individual hypnotics during induction is often like comparing an apple and an orange. Although widened access to electronic brain monitoring may appear to offer an objective measure of "anaesthetic depth", we cannot be sure that an individual monitor of effect (for example the bispectral index (BIS) monitor) is affected in the same way and to the same degree by hypnotics with entirely different mechanisms of action. Thus barbiturates and propofol cause frontal lobe electroencephalogram (EEG) beta activation [46], whereas ketamine has other (different) effects [47]. There is also no compelling evidence that equivalent values of the Bispectral Index produced by different hypnotics are necessarily equivalent. Whilst hypotension during induction of anaesthesia is immediate and sometimes dramatic, organ injury appears to be driven by cumulated hypotension i.e. Area Under the Curve [32, 48]. Consequently, when comparing hypnotics for propensity towards hypotension we must consider maintenance as well as induction of anaesthesia. In the case of propofol, decreasing the rate of drug administration is effective at moderating hypotension during induction [49]. Similar results were found with thiopental, etomidate and methohexital [50]. However, during maintenance of anaesthesia, hypotension is more likely with propofol than with remimazolam [30]. Now we await outcome data to demonstrate that improved intra-operative blood pressure control translates into reductions of mortality or complications or improved patient satisfaction or days alive at home [51, 52].

1.9 Paediatrics

Clinical trials in children are at least as expensive as adult studies and the potential clientele smaller both in terms of number of patients and mass of drug required. Accordingly, paediatric development of a new drug typically lags behind equivalent indications in adults. This hiatus is recognised by the US Food and Drug Administration (FDA) who, through the Best Pharmaceuticals for Children Act (BPCA) are able to extend by six months the period of marketing exclusivity for sponsors that voluntarily complete appropriate paediatric studies—even if they do not ultimately provide sufficient evidence to justify a paediatric product licence.

Currently, paediatric experience with remimazolam is limited. A handful of case reports describe its use in children, typically in complex cases or unusual circumstances [53–60]. Clinical trial registry listings suggest that some early clinical trials are planned, underway or recently completed however none are yet published.

1.10 Intensive care sedation

Extending remimazolam use into the intensive care unit requires substantial additional data. Firstly, the hypnotic effect must resist tachyphylaxis and tolerance in

order that excessive dose escalation may be avoided. Next, the pharmacokinetics in intensive care unit (ICU) patients cannot be assumed to mirror that of a more general population. Finally, we need to consider the mass of drug administered (often considerable), the potential for accumulation of metabolites and issues of cost and volume. Starting with relevant basic science, remimazolam metabolism was investigated in a 3-D bioreactor filled with human liver cells. Remimazolam metabolism was stable over a five-day period and there was no evidence of harmful drug effects on the hepatocytes [61]. In contrast, during a 49 patient pilot study of remimazolam ICU sedation, seven patients developed unexpectedly high remimazolam concentrations after 24 h of sedation [13]. However, further details of the patients are not available since the study has not been published.

Patients admitted to ICU following major elective surgery often require a period of mechanical ventilation. This group are attractive for research and provide a valid study population however their comorbidities (particularly sepsis) and multi-organ dysfunction make extrapolating data gained in this group to a more general ICU population problematic.

Establishing the appropriate dosing scheme for remimazolam ICU sedation is an important research objective. A single-centre study of 23 patients requiring mechanical ventilation after surgery found that a loading dose of 0.02–0.05 mg/kg remimazolam followed by 0.2–0.35 mg/kg/hr provided satisfactory sedation whilst avoiding cardiorespiratory compromise [62].

A reasonable starting point in the general ICU population is to gain experience with a new drug administered to critically ill patients for short periods. In a pilot study, Zhao and colleagues compared remimazolam with midazolam and propofol in ICU patients requiring gastrointestinal endoscopy [63]. Remimazolam was noninferior to the old drugs. Whilst by no means addressing all the questions above, this provides useful starting point in the ICU development. Unfortunately, the retrospective design and the mixing of propofol and midazolam patients in the control group limits our confidence in the conclusions and prospective randomised controlled trials are required.

In a small but better designed study, Tang and colleagues randomised adults who required mechanical ventilation for more than 24 h to receive remimazolam or propofol [64]. Performance of the two sedation schemes was broadly similar.

Larger, and properly powered studies are required to establish the impact, if any, of remimazolam ICU sedation on mortality and morbidity. In addition, the widespread perception that benzodiazepines are associated with confusional states in ICU patients requires detailed exploration with regard to remimazolam. When remimazolam was used to induce and maintain general anaesthesia in orthopaedic patients the incidence of postoperative delirium was 15.6% in the remimazolam group and 4.4% in the propofol group [65]. Whilst this was not statistically significant it may mean that the study was underpowered. Certainly, continued vigilance and further research in this area are essential.

1.11 Target Controlled Infusion (TCI) of remimazolam

A broad range of hypnotics and opioids are potentially suitable for administration by Target Controlled Infusion (TCI). However, TCI is most widely used for propofol, typically accompanied by remifentanil (either TCI or manually controlled). This limited deployment of TCI is in part due to pharmacokinetics and pharmacodynamics. As an example, consider infusion of epinephrine. Turning the infusion rate up or down produces an almost immediate pressure response, TCI has nothing to add. In practice, a pharmacokinetic (PK)/pharmacodynamic (PD) "sweet spot" exists for compounds whose onset and offset are relatively swift but not sufficiently so to allow titration by simply increasing and decreasing infusion rate. In this regard, remifentanil is a borderline case suitable for either manual control or TCI. Remimazolam has pharmacokinetics intermediate between propofol and midazolam and appears suitable for TCI. Currently no TCI models for remimazolam have been published however, appropriate development work is underway.

Current prescribing information (based in large part upon the clinical trial program) continues to recommend repeated bolus injections rather than continuous infusion for patients requiring procedural sedation. This could usefully be revisited especially when a proven TCI model becomes available.

A further consideration is dilution. Dilution to 2.5 mg/mL is recommended however this seems bizarre and 2 mg/mL might be a better choice.

1.12 Characterising and exploiting PK/PD advantages

1.12.1 Reversal with flumazenil and re-sedation

Reversibility of hypnotic effect by the application of flumazenil is a core characteristic of benzodiazepines. Remimazolam shares this characteristic with midazolam and diazepam. Initial experiences of flumazenil reversal at the end of total intravenous anaesthesia with alfentanil and midazolam led Raeder to comment "We conclude that total intravenous anaesthesia with alfentanil and midazolam with flumazenil reversal is a promising technique for short outpatient anaesthetic procedures" [66]. Unfortunately, subsequent experiences have been less

satisfactory with a minority of patients becoming markedly re-sedated [67, 68] and the technique has subsequently been abandoned. The much shorter off-transient of remimazolam effect invites revisiting of flumazenil reversal. Currently few data exist to characterise this interaction. In clinical trials where individual patients (outliers) recovered slowly, a minority went on to receive flumazenil. In Doi and colleagues dose-finding comparison of propofol and remimazolam anaesthesia [10] the protocol allowed flumazenil ministration at 30 min after the remimazolam infusion had been discontinued. Flumazenil was administered to 9% of patients following which awakening was rapid. Similar findings were reported with high risk surgical patients (ASA III) [9]. Whilst these findings are cautiously optimistic they do not offer a sound basis for elective practice. The receptor mechanics and underpinning theory are complex but relevant. Simulations provide a sound basis for illustrating the genesis of re-sedation [69]. We need to see formal evaluation including dose finding with different doses of flumazenil given to patients not awake at (say) five or 10 min after the end of remimazolam administration. These should be supported by detailed psychometric assessment for at least an hour. It is possible that, subject to proper confirmatory studies, "routine" flumazenil may be an important adjunct to remimazolam anaesthesia and sedation. Currently the practice cannot be recommended in the absence of adequate supporting studies. A recent report of seizures after flumazenil reversal of remimazolam serves as a warning that the safety of this approach requires thorough evaluation before general adoption can be recommended [70].

1.12.2 Driving after sedation? Can we prove a negative?

Clinical practice is conservative and patients receiving procedural sedation are typically advised to avoid driving, operating machinery and making important decisions for 24 h (or "overnight") often with considerable ambiguity about precise timings. This advice is typically inconsistent and may be driven more by clinician anxiety than pharmacokinetics, pharmacodynamics or neuro psychometric research. British patients who have received nitrous oxide sedation are permitted to drive home after uncomplicated colonoscopy [71]. However, this bold innovation has not yet been followed with equivalent liberal practice after intravenous sedation.

Neuro-psychometric testing of bronchoscopy patients following sedation with remimazolam and fentanyl demonstrated a rapid return of cognitive function to baseline (pre-sedation) levels [5]. This suggests that a more liberal approach to post procedural activities may be defensible. Certainly, these results support more detailed investigations to provide a robust evidence base for future liberalisation. Use of a driving simulator for this type of research may be a more effective method of assessing fitness to drive than abstract psychometric measurements.

1.12.3 Special characteristics

In addition to "standard" clinical trials leading towards a product licence application, remimazolam has also been the subject of some special interest/speculative research initiatives. These initiatives are typically curiosity driven and whilst they suggest future lines of enquiry should not be taken as indicating how current patients should be treated. Investigators commonly assumed that any beneficial effect demonstrated by midazolam will automatically be duplicated when replaced by remimazolam. Given the general consistency of benzodiazepine pharmacology this is likely true, however, that consistency cannot be assumed in the absence of specific data for each circumstance.

Wigmore and colleagues demonstrated a substantial difference in outcomes between propofol and inhalational maintenance of anaesthesia amongst patients undergoing cancer surgery [72]. However, the data were collected retrospectively. Subsequent studies have been equivocal and current recommendations are not to change practice [73]. Against this background of uncertainty, we should note with interest that midazolam appears to affect cancer cell biology [74–76]. however, the underpinning pathways are complex and the association between a benzodiazepine and favourable indications (or outcomes) may be epiphenomena rather than indicating a causal relationship.

Remimazolam is also associated with potentially beneficial effects in models of sepsis, [77] liver injury [78] and cerebral ischaemia [79].

1.12.4 What are the prospects for remimazolam?

A recent review focused on remimazolam's cost effectiveness concluded that the areas of potential advantage included: lack of pain on injection, availability of flumazenil reversal, reduced cardiorespiratory depression, esterase metabolism and suitability for administration bynon-anaesthesiologist healthcare providers [80]. However, these advantages come at a significant cost premium over midazolam. In today's financially constrained healthcare environment it is likely that the drug's acquisition cost will provide a substantial obstruction to widespread deployment. Use of remimazolam by non-anaesthesiologists in circumstances where sedation had previously been provided by specialists may prove cost-effective.

Abbreviations

ASA	American society of anesthesiologists
BIS	Bispectral index
BPCA	Best pharmaceuticals for children act
CNS	Central nervous system
EEG	Electroencephalogram
FDA	Food and drug administration
ICU	Intensive care unit
PD	Pharmacodynamic
PK	Pharmacokinetic
TCI	Target controlled infusion
TIVA	Total intravenous anaesthesia

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Clinical trial number and registry URL
Not applicable.

Authors' contributions
JRS did everything.

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Availability of data and materials
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Ethics approval and consent to participate
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Consent for publication
Not applicable.

Competing interests
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