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REVIEW

Recent advances in intravenous anesthesia and anesthetics [version 1; referees: 2 approved]

Mohamed Mahmoud[1], Keira P. Mason [iD] [2]

[1]Department of Anesthesiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, 3333 Burnet Avenue, Cincinnati, OH, 45229, USA
[2]Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA, 02115, USA

Abstract

Anesthesiology, as a field, has made promising advances in the discovery of novel, safe, effective, and efficient methods to deliver care. This review explores refinement in the technology of soft drug development, unique anesthetic delivery systems, and recent drug and device failures.

Keywords
Intravenous Anesthesia, Midazolam, Xenon, Propofol

Open Peer Review

Referee Status: ✔✔

	Invited Referees	
	1	**2**
version 1 published 17 Apr 2018	✔	✔

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Corresponding author: Mohamed Mahmoud (mohamed.mahmoud@cchmc.org)

Author roles: Mahmoud M: Writing – Original Draft Preparation, Writing – Review & Editing; **Mason KP**: Writing – Original Draft Preparation, Writing – Review & Editing

Introduction

The first generation of intravenous (IV) agents for anesthesia induction and maintenance, as an alternative to volatile agents, dates back to the introduction of thiopental in the 1930's. Since then, propofol, ketamine, etomidate, dexmedetomidine, and benzodiazepines represent some of the more significant contributions to IV anesthetic or sedative agents. Researchers continue to develop both new formulations of these existing agents and new chemical entities in strides to improve safety, predictability, efficacy, onset, and recovery profile and to minimize side effects. Novel drug development is challenging, costly (2.5 billion dollars on average), and risky[1]. Only 1 in 10 drugs in phase I development will go on to obtain Food and Drug Administration (FDA) approval[2], and some drugs are withdrawn from the market, even after approval, because of unanticipated limitations and drawbacks.

Since its introduction, target-controlled infusion (TCI) technology has evolved from a research tool into a now-routine part of anesthesia delivery in many countries (USA excluded) worldwide. Advancement in this technology has the potential to expand the precision, reliability, efficacy, and safety of IV anesthesia delivery.

This review of the literature will highlight the recent developments and failures in drug and device innovations and novel drug delivery systems.

New innovations in drug development

Recent and evolving drug innovations are primarily focused on modifying the chemical structures of existing drugs or drug classes with intent to improve their pharmacodynamic, pharmacokinetic, and side effect properties. The following section reviews remimazolam, etomidate, and propofol derivatives and alternatives which have been formulated to offer improvements on the parent compounds.

Remimazolam and ADV6209

Midazolam is a widely used sedative and anxiolytic administered as a popular sedation choice and is used for patient care in a variety of inpatient and outpatient settings. Some drawbacks to the use of midazolam include lack of analgesia and prolonged recovery times in patients with liver disease. Remimazolam is a new, short-acting, ester-based anesthetic agent that allows for rapid esterase-mediated metabolism independent of hepatic or renal enzymes and function[3,4]. It is currently in phase III clinical development for procedural sedation in the USA. As the name implies, remimazolam combines the properties of two unique drugs already established in anesthesia: midazolam and remifentanil. It acts on GABA receptors, as does midazolam, and exhibits pharmacokinetic properties common to the ester-based opioid remifentanil. The addition of a benzodiazepine to remifentanil targets a hopeful synergy between the two, with improved sedation and anxiolysis. In animal studies, remimazolam produced a more rapid onset and faster recovery than did midazolam[5]. Remimazolam is primarily cleared by tissue esterase enzymes, carboxylesterases (CESs). CESs participate in the decomposition and metabolism of endogenous and exogenous compounds, which can greatly affect the metabolism of esters, mainly including hCE-1 and hCE-2[6]. Accumulation should

not occur after infusion of remimazolam because it is primarily cleared by unique tissue esterase enzymes, which convert it into an inactive carboxylic acid metabolite (CNS7054)[7,8]. This novel anesthetic agent has a relatively short context-sensitive half-life of 7–8 minutes, even after a 2-hour infusion, and, as with midazolam, can be reversed with flumazenil.

While remimazolam was initially developed for use as a drug for procedural sedation, more studies are currently focused on utilizing this agent for the induction and maintenance of general anesthesia. A recent study examined the feasibility of delivering inhaled remimazolam alone or as an adjunct to remifentanil in rodents. Remimazolam significantly potentiated the analgesic effect of remifentanil, without lung irritation, bronchospasm, or other adverse pulmonary events[9].

In the USA, the initial development of remimazolam was intended for sedation for adult colonoscopy[10–12]. In the EU, it is undergoing development for general anesthesia in patients undergoing non-cardiac and cardiac surgery, including intensive care unit (ICU) sedation for up to 24 hours after the operation. In Japan, a clinical phase III program in anesthesia has also been conducted. Remimazolam doses of 0.075 to 0.2 mg/kg showed good effect in a phase I trial for safety and efficacy[8]. Dosages for bolus or infusion are awaited.

Remimazolam has potentially important clinical applications owing to its rapid offset of action and maintenance of stable hemodynamics. Most of the current trials involved infusions of bolus or duration infusions; thus, additional information is required to determine how metabolism is affected by prolonged infusions or repeat boluses. Additional studies are required to provide more data on diverse patient populations (weight, age range, and comorbidities, including renal and hepatic insufficiency). It has not been studied in pregnant patients or the pediatric population. Comprehensive pharmacokinetic and pharmacodynamic as well as safety studies are still required, and many questions remain to be answered before this drug can enter clinical practice.

ADV6209: new formulation of oral midazolam

A novel formulation of oral midazolam is currently under investigation, with phase I and II trials now started in both adults and children. This innovative 0.2% aqueous midazolam solution has been formulated by combining a sweetener (sucralose), an aroma (orange aroma), and y-cyclodextrin with a citric acid solution of midazolam[13]. This formulation also appears to improve the longevity of the oral formulation's shelf-life (slower degradation)[14]. Initial studies indicate that the pharmacokinetic and pharmacodynamic parameters are unaltered with a 0.2% midazolam formulation, although there are important advantages of increased palatability. A recent study examined the pharmacokinetic characteristics of the ADV6209 oral formulation in children from 6 months to 18 years old, showing that the measured pharmacokinetic parameters of ADV6029 were close to those reported in the literature with other midazolam formulations, such as extemporaneous oral solutions or syrups[15]. The future role of this drug may be important in offering anxiolysis and sedation with improved patient acceptance and tolerance.

Etomidate derivatives

Etomidate is a highly potent hypnotic agent which was introduced into clinical practice in 1972 and gained popularity largely because of its relatively benign cardiovascular and respiratory effects. Its side effects include pain at injection site, myoclonus, and nausea and vomiting. The most serious side effect of prolonged etomidate infusions is increased mortality in the critically ill, which is a consequence of the inhibition of 11β-hydroxylase activity and suppression of adrenocortical steroid synthesis. Subsequently, etomidate is no longer administered as a prolonged infusion and is limited to a single bolus, albeit even limited use is still controversial. Recent drug development goals are to retain etomidate's highly desirable properties while avoiding any suppression of adrenocortical function[16].

Methoxycarbonyl etomidate (MOC-etomidate) (Figure 1) was the first soft etomidate analogue to be studied. Similar to remifentanil, esmolol, and remimazolam, it contains a metabolically labile ester moiety that is rapidly hydrolyzed by esterases to form a carboxylic acid metabolite and does not produce prolonged adrenocortical suppression in rats after bolus administration[17]. The resulting carboxylic acid metabolite (MOC-ECA) has GABAA receptor, hypnotic, and adrenocortical inhibitory potencies which are approximately 300-fold lower than those of the parent compound, MOC-etomidate[18].

Carboetomidate is an etomidate analogue that does not inhibit steroid production. The reduced ability to suppress *in vitro* and *in vivo* steroid synthesis as compared to etomidate probably reflects carboetomidate's lower binding affinity to 11β-hydroxylase and its inability to form a coordination bond with the heme iron at the enzyme's active site[19,20]. MOC-carboetomidate is meant to combine the rapid metabolism of MOC-etomidate and the minimal adrenal suppression of carboetomidate[21]. Similar to carboetomidate, MOC-carboetomidate is poorly soluble in water and has a slower onset of action (1.3-minute *in vitro* metabolic half-life) as compared to MOC-etomidate (0.35 minutes).

Cyclopropyl-methoxycarbonyl metomidate (CPMM, also known as ABP-700) (Figure 1) is a second-generation etomidate. It is a novel, potent, positive allosteric modulator of the GABAA receptor that possesses promising pharmacodynamic and pharmacokinetic profiles in animal studies: it exhibits high potency and hypnosis that reverses within several minutes of stopping continuous infusions of up to 2 hours[22]. A recent study showed that CPMM (as opposed to MOC-etomidate) infusion is context insensitive because its metabolite fails to reach concentrations in either the blood or the cerebrospinal fluid which are sufficient to have a hypnotic effect[16]. In August 2017, the Medicines Company announced that it has discontinued the development of MDCO 700 because findings from completed animal studies did not support phase III development of the candidate.

New propofol derivatives and alternatives

Propofol has been a transformative anesthetic agent since its introduction 40 years ago and is still considered to be a near-ideal anesthetic agent. Its success in the clinical setting is a result of its rapid onset, short duration of action, and minimal side effects. However,

propofol is associated with a number of important disadvantages: its oil emulsion adds a risk of bacterial contamination and hyperlipidemia. There may be significant pain upon IV injection and a potentially fatal risk of propofol infusion syndrome (PIS). With these challenges, attention has now shifted to the development of new formulations and alternatives to improve the pharmacologic profile and overcome some of the disadvantages. In this section, we provide an update on the new propofol formulations and alternatives that have been developed to improve on the drawbacks.

New propofol formulation. Currently, there are many anesthetics undergoing clinical development that have been modified to overcome the shortcomings of propofol. However, the ideal drug that is entirely satisfactory does not exist. 2,6-Disubstituted alkylphenols (Haisco HSK3486) are the result of a new propofol modification and seem to possess promising anesthetic properties[23]. The sedation evaluation of this new formulation demonstrated its better potency as well as faster onset and recovery compared to propofol[23].

Propofol alternatives. AZD-3043 (AstraZeneca US, Wilmington, DE, USA) is a water-insoluble drug formulated in an oil emulsion that is similar to propofol. When given IV to rats, AZD-3043 produced rapid-onset hypnosis and rapid recovery within 3 minutes of discontinuing infusions ranging from 20 minutes to 5 hours[24]. Recent human studies showed that it has fast clearance and a relatively low volume of distribution, consistent with the rapid onset and offset profile[25,26]. Metabolism occurs because of the action of plasma and tissue esterase to an inactive metabolite with minimal hypnotic effect. In contrast to propofol, pain with this injection has not been reported[26]. However, this drug appears to have a number of drawbacks: erythema, chest discomfort, dyspnea, and episodes of involuntary movements[27,28].
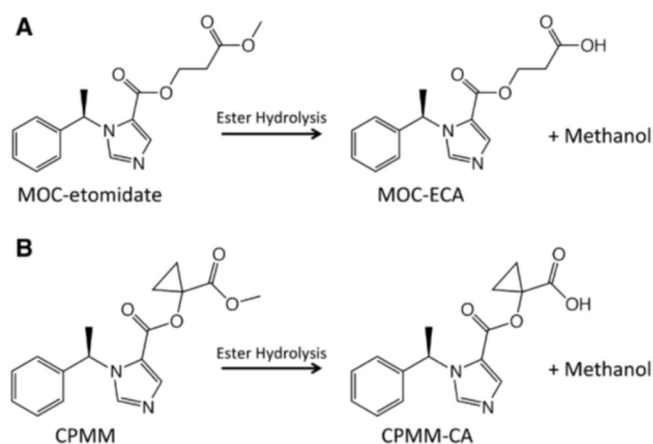

Figure 1. Structures of parent hypnotics and their carboxylic acid metabolites. A) Methoxycarbonyl etomidate (MOC-etomidate) and MOC-etomidate's carboxylic acid metabolite (MOC-ECA). B) Cyclopropyl-methoxycarbonyl metomidate (CPMM) and CPMM's carboxylic acid metabolite (CPMM-CA). Permission was obtained for the reproduction of this figure.

Phaxan™ (PHAX, Chemic Labs, Canton, MA) comprises 10 mg/mL alphaxalone and 13% 7-sulfobutylether β-cyclodextrin (betadex) in an aqueous solution. It is a fast onset-offset IV anesthetic like propofol but causes less cardiovascular depression[29]. Animal studies showed that it has a greater therapeutic index than propofol[29]. The first human study compared it to an equivalent dose of propofol and demonstrated that, as with propofol, it has fast-onset, short-duration anesthesia and comparatively rapid cognitive recovery but with less cardiovascular depression and airway obstruction. There was no pain on injection[30].

Modifications of propofol emulsion. Pain during injection of propofol is not a new problem (incidence 30–90%)[31]. Some patients recall the induction of anesthesia as the most painful part of the perioperative period[32]. It has been reported that pain from injection is ranked third among the 33 most common anesthesia problems in outpatient procedures[33]. The exact mechanism of pain on injection is not known. Factors that appear to influence the incidence and the severity of pain include menstrual cycle, temperature, injection rate, infusion equipment, concentration of propofol, patient age, venous occlusion, and pretreatment medications[34].

Modifications to the emulsion formulation have been attempted to overcome pain on injection and infection risk. Microemulsions of propofol are thermodynamically stable and easier to produce; however, their injection causes further pain. Recently, a novel micro to macro (M2M) approach of destabilizing a microemulsion immediately prior to injection was developed[35]. This novel approach could potentially improve stability and reduce pain on injection.

Another modification of propofol is to increase the proportion of medium-chain triglycerides (MCTs) in the emulsion. MCTs are more polar than long-chain triglycerides (LCTs) and are more rapidly metabolized. Propofol-Lipuro® is a mixed MCT–LCT propofol formulation that has an oil phase that allows a larger proportion of propofol to be dissolved in it and, thereby, reduces pain[36]. The emulsion did not affect the pharmacokinetics or pharmacodynamics of propofol, caused less pain upon injection, and increased the speed of triglyceride elimination[37]. This agent has been available outside of the USA since 1999.

Xenon
Xenon was first administered to humans in 1951[38]. It offers the advantages of having the lowest blood gas partition coefficient of any anesthetic, being non-flammable, being a non-teratogen with a minimal effect on the cardiovascular system, and having no deleterious effects on neurocognition in non-human models[39–41]. It was approved for adult use in the EU in 2007, and the minimum alveolar concentration of xenon in adults is 63%[42]. The future role of xenon as a neuroprotective agent remains to be determined[43]. A recent meta-analysis indicates that, in adults, xenon offers advantages of greater hemodynamic stability and a faster emergence from both inhalational and propofol anesthesia[44]. A study is currently underway to examine the role of xenon as an adjuvant to inhalational anesthesia in the pediatric population undergoing interventional procedures of cardiac catheterization[45]. The future

implications for the application of xenon for sedation have yet to be explored.

New innovations in drug delivery
Target-controlled infusion
Innovations in computer technology, pharmacokinetic modeling, and IV infusion delivery devices have fostered the development of TCIs. TCI represents an innovative method to deliver IV drugs via computer models, with goals of achieving a defined ("target") drug concentration at a specific body compartment or organ (brain)[46]. TCI is used to administer propofol and opioids for sedation and general anesthesia to millions of patients every year. TCI was first described in the 1980s for clinical pharmacology research[47]. The first-generation delivery pumps designed to specifically administer propofol were first approved in 1996, and the second generation provided the user with the ability to administer a selection of drugs (e.g. propofol and remifentanil) using different pharmacokinetic models.

Every anesthetic agent accumulates in the tissue during drug delivery. This accumulation confounds the relationship between the infusion rate set by the provider and the drug concentration in the patient. TCI devices are designed to account for the accumulation of drug in tissues and to adjust the infusion rate in order to achieve and maintain a steady-state drug concentration in the plasma or effect site[48,49]. When using pharmacokinetic-derived models specific to a particular drug, a TCI system incorporates patient characteristics (weight, height, age, sex, and additional biomarkers) to achieve a targeted serum-level concentration[49,50]. This technology constantly estimates the concentration of a drug at the target and in the plasma, allowing the clinician to make changes based on clinical or physiological (bispectral index monitoring) indicators.

The TCI systems are identified as open- and closed-loop systems. In the open-loop systems, the providers select a specific drug and a specific pharmacokinetic or pharmacodynamic model from the drug library incorporated in the device[49]. Published models have been embedded in the pumps for propofol, remifentanil, sufentanil, and alfentanil[46]. A limitation of this delivery technique is that it lacks real-time feedback from the patient to the TCI delivery system. Thus, continuous clinical assessment of the patient and refining of the target is often required.

A closed-loop system is a system wherein the measured output(s) is used by a controller to determine a new input to the system (Figure 2). The controller which closes the loop can be manual or automated. A single closed-loop controller in anesthesia has been used for hypnosis[51], neuromuscular blockade[52], analgesia[51], arterial blood pressure control[53], and fluid optimization[54].

Currently, most TCI technology is based on plasma concentrations rather than effect-site concentrations. A recent pharmacokinetic–pharmacodynamic model used effect-site rather than plasma concentration to demonstrate that the rousability associated with dexmedetomidine reflects a response to repeated auditory stimulation[55]. In comparison to the open-loop system, the closed-loop
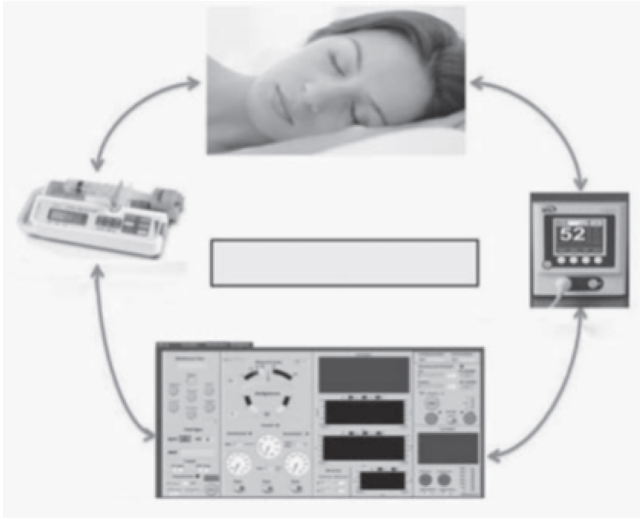
Figure 2. Closed-loop system for hypnosis. There are three elements in every closed-loop system: a central operating software (brain of the system), one or more target-control variables (hypnosis monitor), and one or more drug delivery systems (infusion pump). Permission was obtained for the reproduction of this figure.

system may offer the advantages of more precise dosing, decrease in some workload functions, improved and standardized control of the depth of sedation and anesthesia, decreased consumption of drug, improved hemodynamic stability, faster postoperative recovery, and minimized individual operator variability in titration of the sedative agent[56].

Failure of new innovations
Some technological innovations initially offered promise. However, as with any new innovation, some devices and drugs disappointed. The lack of success of these agents and devices could be related to safety, quality of anesthesia delivery, or financial reasons. In this section, we will discuss the recent failure of Sedasys, the computer-assisted personalized sedation system (CAPS), and fospropofol, both of which designed to improve the delivery and side effect profile of propofol.

Computer-assisted personalized sedation system
Initially, there was optimism that Sedasys could revolutionize the field of non-operating room sedation by integrating continuous physiologic monitoring with patient feedback (response to auditory stimuli) to control the depth of sedation. The physiologic monitoring includes non-invasive arterial blood pressure, pulse oximetry, capnography, and electrocardiogram, all consistent with the American Society of Anesthesiologists (ASA) Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists and ASA Standards for Basic Anesthetic Monitoring[57,58]. This closed-loop system was intended to maintain sedation and minimize the risks of respiratory depression, cardiovascular instability, and loss of responsiveness. The first-to-market product (FDA approval 2013) in the CAPS category is the SEDASYS®

Computer-Assisted Personalized Sedation System (SEDASYS® System, Ethicon Endo-Surgery, Johnson and Johnson). This technology was intended to administer mild to moderate propofol sedation only to healthy adult patients of ASA 1 and 2 for gastrointestinal (GI) endoscopic procedures.

Although SEDASYS provided a higher degree of patient and clinician satisfaction and fewer adverse events compared to any other standard-of-care delivery regimens (fentanyl and versed)[59], Ethicon, Inc., announced in March 2016 that it would no longer market Sedasys. Sedasys failed to gain popularity and adoption for the following reasons: 1) the device was programmed to only decrease the sedation depth (propofol dose) but not to increase it, 2) the dosing schedule was not efficient for the fast pace and turnover of most diagnostic upper GI endoscopic procedures, and 3) the device failed to satisfy both patients and providers, limited by the FDA approval for no more than moderate sedation[60].

Although future CAPS devices may aim for deep sedation, clinical observation skills must be utilized in conjunction with continuously and vigilantly following the patient's respiratory, cardiovascular, and neurologic status.

Fospropofol
Fospropofol (Lusedra Eisai Inc., Woodcliff Lake, NJ, USA) is a water-soluble phosphate ester prodrug of propofol that was FDA approved in December 2008 for monitored anesthesia care. Upon administration, fospropofol is hydrolyzed by endothelial cells and completely metabolized by alkaline phosphatase to yield propofol, phosphate, and formaldehyde[61]. Pain on injection is observed less frequently with fospropofol than with propofol. Without lipids, egg products, or preservatives, fospropofol eliminates the allergic responses, bacterial infections, and hyperlipidemic concerns associated with propofol. Fospropofol was recently discontinued in the USA; the likely reasons include 1) its delayed onset of effect (peak effect is in 8 minutes with clinical effect in 4–13 minutes)[62] and slower recovery compared to propofol and 2) its significant associated perineal paresthesia and pruritus.

Conclusion
New innovations in drug development and delivery contribute to continued improvement in anesthesia. Large clinical trials are needed to provide the greatest level of evidence and safety prior to widespread clinical implementation.

References

1. DiMasi JA, Grabowski HG, Hansen RW: **Innovation in the pharmaceutical industry: New estimates of R&D costs.** *J Health Econ.* 2016; **47**: 20–33.
PubMed Abstract | **Publisher Full Text**

2. **F** Hay M, Thomas DW, Craighead JL, *et al.*: **Clinical development success rates for investigational drugs.** *Nat Biotechnol.* 2014; **32**(1): 40–51.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

3. Rogers WK, McDowell TS: **Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures.** *IDrugs.* 2010; **13**(12): 929–37.
PubMed Abstract

4. **F** Kilpatrick GJ, McIntyre MS, Cox RF, *et al.*: **CNS 7056: a novel ultra-short-acting Benzodiazepine.** *Anesthesiology.* 2007; **107**(1): 60–6.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

5. Upton RN, Somogyi AA, Martinez AM, *et al.*: **Pharmacokinetics and pharmacodynamics of the short-acting sedative CNS 7056 in sheep.** *Br J Anaesth.* 2010; **105**(6): 798–809.
PubMed Abstract | **Publisher Full Text**

6. Ross MK, Crow JA: **Human carboxylesterases and their role in xenobiotic and endobiotic metabolism.** *J Biochem Mol Toxicol.* 2007; **21**(4): 187–96.
PubMed Abstract | **Publisher Full Text**

7. **F** Wiltshire HR, Kilpatrick GJ, Tilbrook GS, *et al.*: **A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation.** *Anesth Analg.* 2012; **115**(2): 284–96.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

8. **F** Antonik LJ, Goldwater DR, Kilpatrick GJ, *et al.*: **A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics.** *Anesth Analg.* 2012; **115**(2): 274–83.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

9. **F** Bevans T, Deering-Rice C, Stockmann C, *et al.*: **Inhaled Remimazolam Potentiates Inhaled Remifentanil in Rodents.** *Anesth Analg.* 2017; **124**(5): 1484–90.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

10. Borkett KM, Riff DS, Schwartz HI, *et al.*: **A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy.** *Anesth Analg.* 2015; **120**(4): 771–80.
PubMed Abstract | **Publisher Full Text**

11. **F** Pambianco DJ, Borkett KM, Riff DS, *et al.*: **A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy.** *Gastrointest Endosc.* 2016; **83**(5): 984–92.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

12. Worthington MT, Antonik LJ, Goldwater DR, *et al.*: **A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy.** *Anesth Analg.* 2013; **117**(5): 1093–100.
PubMed Abstract | **Publisher Full Text**

13. Marçon F, Mathiron D, Pilard S, *et al.*: **Development and formulation of a 0.2% oral solution of midazolam containing gamma-cyclodextrin.** *Int J Pharm.* 2009; **379**(2): 244–50.
PubMed Abstract | **Publisher Full Text**

14. Mathiron D, Marçon F, Dubaele JM, *et al.*: **Benefits of methylated cyclodextrins in the development of midazolam pharmaceutical formulations.** *J Pharm Sci.* 2013; **102**(7): 2102–11.
PubMed Abstract | **Publisher Full Text**

15. **F** Marçon F, Guittet C, Manso MA, *et al.*: **Population pharmacokinetic evaluation of ADV6209, an innovative oral solution of midazolam containing cyclodextrin.** *Eur J Pharm Sci.* 2018; **114**: 46–54.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

16. **F** Pejo E, Liu J, Lin X, *et al.*: **Distinct Hypnotic Recoveries After Infusions of Methoxycarbonyl Etomidate and Cyclopropyl Methoxycarbonyl Metomidate: The Role of the Metabolite.** *Anesth Analg.* 2016; **122**(4): 1008–14.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

17. **F** Cotten JF, Husain SS, Forman SA, *et al.*: **Methoxycarbonyl-etomidate: a novel rapidly metabolized and ultra-short-acting etomidate analogue that does not produce prolonged adrenocortical suppression.** *Anesthesiology.* 2009; **111**(2): 240–9.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

18. Ge RL, Pejo E, Haburcak M, *et al.*: **Pharmacological studies of methoxycarbonyl etomidate's carboxylic acid metabolite.** *Anesth Analg.* 2012; **115**(2): 305–8.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Pejo E, Feng Y, Chao W, *et al.*: **Differential effects of etomidate and its pyrrole analogue carboetomidate on the adrenocortical and cytokine responses to endotoxemia.** *Crit Care Med.* 2012; **40**(1): 187–92.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Shanmugasundararaj S, Zhou X, Neunzig J, *et al.*: **Carboetomidate: an analog of etomidate that interacts weakly with 11β-hydroxylase.** *Anesth Analg.* 2013; **116**(6): 1249–56.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

21. Pejo E, Cotten JF, Kelly EW, *et al.*: ***In vivo*** and ***in vitro*** **pharmacological studies of methoxycarbonyl-carboetomidate.** *Anesth Analg.* 2012; **115**(2): 297–304.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

22. Campagna JA, Pojasek K, Grayzel D, *et al.*: **Advancing novel anesthetics: pharmacodynamic and pharmacokinetic studies of cyclopropyl-methoxycarbonyl metomidate in dogs.** *Anesthesiology.* 2014; **121**(6): 1203–16.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

23. **F** Qin L, Ren L, Wan S, *et al.*: **Design, Synthesis, and Evaluation of Novel 2,6-Disubstituted Phenol Derivatives as General Anesthetics.** *J Med Chem.* 2017; **60**(9): 3606–17.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

24. **F** Egan TD, Obara S, Jenkins TE, *et al.*: **AZD-3043: a novel, metabolically labile sedative–hypnotic agent with rapid and predictable emergence from hypnosis.** *Anesthesiology.* 2012; **116**(6): 1267–77.
PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

25. Björnsson MA, Norberg Å, Kalman S, *et al.*: **A Recirculatory Model for Pharmacokinetics and the Effects on Bispectral Index After Intravenous Infusion of the Sedative and Anesthetic AZD3043 in Healthy Volunteers.** *Anesth Analg.* 2015; **121**(4): 904–13.
PubMed Abstract | **Publisher Full Text**

26. Norberg Å, Koch P, Kanes SJ, *et al.*: **A Bolus and Bolus Followed by Infusion Study of AZD3043, an Investigational Intravenous Drug for Sedation and Anesthesia: Safety and Pharmacodynamics in Healthy Male and Female Volunteers.** *Anesth Analg.* 2015; **121**(4): 894–903.
PubMed Abstract | **Publisher Full Text**

27. Kalman S, Koch P, Ahlén K, *et al.*: **First Human Study of the Investigational Sedative and Anesthetic Drug AZD3043: A Dose-Escalation Trial to Assess the Safety, Pharmacokinetics, and Efficacy of a 30-Minute Infusion in Healthy Male Volunteers.** *Anesth Analg.* 2015; **121**(4): 885–93.
PubMed Abstract | **Publisher Full Text**

28. Sear JW, Egan TD: **David (Propofol Wannabes) Versus Goliath (Propofol): AZD-3043 Goes Up Against the Giant!** *Anesth Analg.* 2015; **121**(4): 849–51.
PubMed Abstract | **Publisher Full Text**

29. **F** Goodchild CS, Serrao JM, Kolosov A, *et al.*: **Alphaxalone Reformulated: A Water-Soluble Intravenous Anesthetic Preparation in Sulfobutyl-Ether-β-Cyclodextrin.** *Anesth Analg.* 2015; **120**(5): 1025–31.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

30. Monagle J, Siu L, Worrell J, *et al.*: **A Phase 1c Trial Comparing the Efficacy and Safety of a New Aqueous Formulation of Alphaxalone with Propofol.** *Anesth Analg.* 2015; **121**(4): 914–24.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

31. Picard P, Tramèr MR: **Prevention of pain on injection with propofol: a quantitative systematic review.** *Anesth Analg.* 2000; **90**(4): 963–9.
PubMed Abstract | **Publisher Full Text**

32. Jalota L, Kalira V, George E, *et al.*: **Prevention of pain on injection of propofol: systematic review and meta-analysis.** *BMJ.* 2011; **342**: d1110.
PubMed Abstract | **Publisher Full Text**

33. Wu Q, Zhang N, Shen Y, *et al.*: **Influence of polyvinyl chloride infusion extension tube on propofol injection pain: a randomised controlled study.** *Eur J Anaesthesiol.* 2014; **31**(12): 663–8.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

34. **F** Wang W, Zhou L, Wu LX, *et al.*: **5-HT$_3$ Receptor Antagonists for Propofol Injection Pain: A Meta-Analysis of Randomized Controlled Trials.** *Clin Drug Investig.* 2016; **36**(4): 243–53.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

35. Damitz R, Chauhan A: **"Micro to macro (M2M)"--A novel approach for intravenous delivery of propofol.** *Int J Pharm.* 2015; **494**(1): 218–26.
PubMed Abstract | **Publisher Full Text**

36. Sun NC, Wong AY, Irwin MG: **A comparison of pain on intravenous injection between two preparations of propofol.** *Anesth Analg.* 2005; **101**(3): 675–8. table of contents.
PubMed Abstract | **Publisher Full Text**

37. Larsen R, Beerhalter U, Erdkönig R, *et al.*: **Injektionsschmerz durch Propofol-MCT/LCT bei Kindern. Ein Vergleich mit Propofol-LCT.** *Anaesthesist.* 2001; **50**(9): 676–8.
Publisher Full Text

38. Cullen SC, Gross EG: **The anesthetic properties of xenon in animals and human beings, with additional observations on krypton.** *Science.* 1951; **113**(2942): 580–2.
PubMed Abstract | **Publisher Full Text**

39. Derwall M, Timper A, Kottmann K, *et al.*: **Neuroprotective effects of the inhalational anesthetics isoflurane and xenon after cardiac arrest in pigs.** *Crit*

Care Med. 2008; **36**(11 Suppl): S492–5.
PubMed Abstract | **Publisher Full Text**

40. Hobbs C, Thoresen M, Tucker A, *et al*.: **Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia.** *Stroke.* 2008; **39**(4): 1307–13.
PubMed Abstract | **Publisher Full Text**

41. Chakkarapani E, Thoresen M, Liu X, *et al*.: **Xenon offers stable haemodynamics independent of induced hypothermia after hypoxia-ischaemia in newborn pigs.** *Intensive Care Med.* 2012; **38**(2): 316–23.
PubMed Abstract | **Publisher Full Text**

42. Nakata Y, Goto T, Ishiguro Y, *et al*.: **Minimum alveolar concentration (MAC) of xenon with sevoflurane in humans.** *Anesthesiology.* 2001; **94**(4): 611–4.
PubMed Abstract | **Publisher Full Text**

43. F Alam A, Suen KC, Hana Z, *et al*.: **Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon.** *Neurotoxicol Teratol.* 2017; **60**: 102–16.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

44. F Law LS, Lo EA, Gan TJ: **Xenon Anesthesia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.** *Anesth Analg.* 2016; **122**(3): 678–97.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

45. Devroe S, Lemiere J, van de Velde M, *et al*.: **Safety and feasibility of xenon as an adjuvant to sevoflurane anaesthesia in children undergoing interventional or diagnostic cardiac catheterization: study protocol for a randomised controlled trial.** *Trials.* 2015; **16**: 74.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

46. F Absalom AR, Glen JI, Zwart GJ, *et al*.: **Target-Controlled Infusion: A Mature Technology.** *Anesth Analg.* 2016; **122**(1): 70–8.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

47. Schüttler J, Schwilden H, Stoekel H: **Pharmacokinetics as applied to total intravenous anaesthesia. Practical implications.** *Anaesthesia.* 1983; **38 Suppl**: 53–6.
PubMed Abstract | **Publisher Full Text**

48. White PF: **Intravenous anesthesia and analgesia: what is the role of target-controlled infusion?** *J Clin Anesth.* 1996; **8**(3 Suppl): 26S–28S.
PubMed Abstract | **Publisher Full Text**

49. F Struys MM, De Smet T, Glen JI, *et al*.: **The History of Target-Controlled Infusion.** *Anesth Analg.* 2016; **122**(1): 56–69.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

50. F Hannivoort LN, Eleveld DJ, Proost JH, *et al*.: **Development of an Optimized Pharmacokinetic Model of Dexmedetomidine Using Target-controlled Infusion in Healthy Volunteers.** *Anesthesiology.* 2015; **123**(2): 357–67.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

51. F Hemmerling TM, Arbeid E, Wehbe M, *et al*.: **Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized

controlled trial.** *Br J Anaesth.* 2013; **110**(6): 1031–9.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

52. Kansanaho M, Hynynen M, Olkkola KT: **Model-driven closed-loop feedback infusion of atracurium and vecuronium during hypothermic cardiopulmonary bypass.** *J Cardiothorac Vasc Anesth.* 1997; **11**(1): 58–61.
PubMed Abstract | **Publisher Full Text**

53. Sia AT, Tan HS, Sng BL: **Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study.** *Anaesthesia.* 2012; **67**(12): 1348–55.
PubMed Abstract | **Publisher Full Text**

54. Rinehart J, Chung E, Canales C, *et al*.: **Intraoperative stroke volume optimization using stroke volume, arterial pressure, and heart rate: closed-loop (learning intravenous resuscitator) versus anesthesiologists.** *J Cardiothorac Vasc Anesth.* 2012; **26**(5): 933–9.
PubMed Abstract | **Publisher Full Text**

55. F Colin PJ, Hannivoort LN, Eleveld DJ, *et al*.: **Dexmedetomidine pharmacokinetic-pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation.** *Br J Anaesth.* 2017; **119**(2): 200–10.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

56. F Liu N, Chazot T, Genty A, *et al*.: **Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop *versus* manual control: a prospective, randomized, multicenter study.** *Anesthesiology.* 2006; **104**(4): 686–95.
PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

57. Anesthesiologists ASo: **Statement on Nonoperating Room Anesthetizing Locations.** 2013. Accessed 2/12/2015.
Reference Source

58. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists: **Practice guidelines for sedation and analgesia by non-anesthesiologists.** *Anesthesiology.* 2002; **96**(4): 1004–17.
PubMed Abstract | **Publisher Full Text**

59. Pambianco DJ, Vargo JJ, Pruitt RE, *et al*.: **Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study.** *Gastrointest Endosc.* 2011; **73**(4): 765–72.
PubMed Abstract | **Publisher Full Text**

60. Goudra B, Singh PM: **Failure of Sedasys: Destiny or Poor Design?** *Anesth Analg.* 2017; **124**: 686–8.
PubMed Abstract | **Publisher Full Text**

61. Lang B, Yang J, Wang Y, *et al*.: **An improved design of water-soluble propofol prodrugs characterized by rapid onset of action.** *Anesth Analg.* 2014; **118**(4): 745–54.
PubMed Abstract | **Publisher Full Text**

62. Garnock-Jones KP, Scott LJ: **Fospropofol.** *Drugs.* 2010; **70**(4): 469–77.
PubMed Abstract | **Publisher Full Text**

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The referees who approved this article are:

Version 1

1 **Wensheng Zhang** Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
   Competing Interests: No competing interests were disclosed.

1 **Anuj Chauhan** Department of Chemical Engineering, University of Florida, Gainesville, FL, USA
   Competing Interests: No competing interests were disclosed.