# New Hypnotic Drug Development and Pharmacologic Considerations for Clinical Anesthesia

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**KEYWORDS**

• Hypnotics • Propofol analogues • Etomidate derivatives • Remimazolam
• Ketamine derivatives • Barbiturates

**KEY POINTS**

- Since the public demonstration of ether as a novel, viable anesthetic for surgery in 1846, the field of anesthesia has continually sought the ideal anesthetic—rapid onset, potent sedation-hypnosis with a high therapeutic ratio of toxic dose to minimally effective dose, predictable clearance to inactive metabolites, and minimal side effects.
- In the quest to provide the safest anesthetic to surgical patients, modern anesthesiologists have used a variety of induction agents, including volatile gases, phenols, imidazoles, benzodiazepines, phencyclidines, and barbiturates.
- Many of these agents have been used virtually unchanged since their emergence on the pharmaceutical market, but there has been remarkable progress in the arena of both new drug development and creation of "soft drug" analogues of existing compounds.
- We review current progress of novel hypnotic agent development and provide an update on the most promising drugs poised to enter clinical practice. In addition, we describe trends in novel agent development, implications for health care costs, and implications for perioperative care.

## INTRODUCTION

Since the public demonstration of ether as a novel, viable anesthetic for surgery in 1846, the field of anesthesia has continually sought the ideal anesthetic—rapid onset, potent sedation-hypnosis with a high therapeutic ratio of toxic dose to minimally effective

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dose, predictable clearance to inactive metabolites, and minimal side effects. In the quest to provide the safest anesthetic to surgical patients, modern anesthesiologists have used a variety of induction agents, including volatile gases, phenols, imidazoles, benzodiazepines, phencyclidines, and barbiturates. Many of these agents have been used virtually unchanged since their emergence on the pharmaceutical market, such as propofol and sevoflurane several decades ago, but there has been remarkable progress in the arena of both new drug development and creation of "soft drug" analogues of existing compounds (Table 1). As described in prior literature, soft drugs are those compounds created by fusing a known sedative-hypnotic with a metabolically labile moiety (most commonly an ester) with the hopes of facilitating predictable, rapid enzymatic metabolism, increasing hemodynamic stability and decreasing adverse effects related to the parent compound.[1] This approach to development has also been described as a subclass of "retrometabolic drug design."[2] Novel compounds, in contrast, are largely discovered via rational design (which historically has had minimal success) or most recently via high throughput screening.[3] This article aims to review current progress of novel induction agent development and provide an update on the most promising drugs poised to enter clinical practice. In addition, the authors describe trends in novel agent development, implications for health care costs, and implications for perioperative care.

## NOVEL AGENTS

### *Phenols*

#### *PF0713*

As a propofol analogue with 2 sec-butyl groups in the place of 2 isopropyl groups, PF0713 ((R, R)-2,6-di-sec-butylphenol) likewise acts as a $GABA_A$ receptor modulator

**Table 1**
**Drug classes and novel derivatives of common hypnotics**

| Drug Class | Example Agent | Primary Mechanism of Action | Novel Agent |
|---|---|---|---|
| Phenols | Propofol | $GABA_A$ receptor modulator | • PF0713<br>• Fospropofol |
| Imidazoles | Etomidate | $GABA_A$ receptor modulator, agonist at higher doses | • Methoxycarbonyl etomidate<br>• Cyclopropyl MOC etomidate<br>• Carboetomidate<br>• Methoxycarbonyl carboetomidate |
| Benzodiazepines | Midazolam | $GABA_A$ agonist | • Remimazolam |
| Benzodiazepine-like agents | None | $GABA_A$ agonist | • JM-1232 |
| Phencyclidines | Ketamine | NDMA antagonist | • Norketamine ester analogues, R1-R5<br>• MXE<br>• Fluoroketamine |
| Halogenated ethers | Isoflurane<br>Sevoflurane | Unknown<br>Unknown | • Emulsified isoflurane, IV<br>• Emulsified sevoflurane, IV |
| Barbiturates | Thiopental | $GABA_A$ receptor modulator, agonist at higher doses | • Ultra-short-acting barbituric and thiobarbituric acid derivatives |
| Nucleosides | Uridine | Uridine receptor | • N3-phenacyluridine |
| Phenylacetates | Propanidid | $GABA_A$ receptor modulator | • AZD3043 |