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EDITORIAL

# Neurotoxicity of sedative drugs: a matter of concern in adults?

Giovanni Landoni[1,2*], Yuki Kotani[3] and Vladimir Lomivorotov[4]



Over 5 million patients are admitted to intensive care units (ICUs) annually in the United States (with a population of approximately 340 million), while Australia and New Zealand (with a combined population of approximately 32 million) report more than 200,000 adult ICU admissions each year [1, 2]. Cardiovascular deterioration, respiratory failure, and neurological conditions are among the most common reasons for ICU admission in adults. Sedation is widely used in critically ill patients to improve ventilator synchrony, alleviate anxiety and discomfort, and reduce oxygen consumption [3].

The sedative agents used in the ICU include intravenous drugs (e.g., propofol, benzodiazepines, dexmedetomidine, clonidine, ketamine, and opioids) and inhalational anesthetics. Sedative choice takes into account comorbidities, hemodynamic status, and the side effects of each agent. Most anesthetics exert neuroprotective effects by reducing cerebral oxygen consumption and neurotransmitter release. Through suppression of neuronal activity, these drugs are also used to interrupt seizures [3]. Ketamine remains a controversial agent regarding neuroprotection, as it increases cerebral metabolism and cerebral blood flow but may provide neuroprotection by blocking N-methyl-D-aspartate (NMDA) glutamate receptors.

On the other hand, ICU sedation causes neurotoxicity, an adverse effect on the structure or function of the nervous system. Elderly patients represent a vulnerable population, being at high risk of anesthetic-induced neurotoxicity (e.g., long-term cognitive decline, post-traumatic stress disorder) due to age-related brain changes, pre-existing neurodegeneration, amyloid-beta accumulation, and neuroinflammation, which may be exacerbated by sedatives [4]. Clinicians should also bear in mind that other common drugs (e.g., antibiotics) can induce neurotoxicity and that timely management of the underlying condition minimizes the risk of confusion and delirium [4].

Concerns on the harmful effects of anesthetics on the brain were first raised in the early 2000s in animal studies involving developing brains. Several hours of an NMDA receptor blockade administration during early neonatal life triggered apoptotic neurodegeneration in a rat developing brain and common anesthetics also induced neurodegeneration [5]. The precise mechanisms of anesthetic-induced neurotoxicity remain unclear, but the primary culprit is the potentiation of gamma-aminobutyric acid type A receptor activity with disruption of brain connectivity [5]. Oxidative stress and mitochondrial dysfunction are implicated in propofol-induced neurotoxicity [6]. Preliminary evidence in mice suggests that inhalational anesthetics, only when used at a high dose, may promote nuclear factor-kappa B pathway [7], being partly responsible for Alzheimer's disease development. However, data of these pathways in humans are lacking. Ethical constraints preclude the feasibility of conducting similar mechanistic studies in humans.

ICU sedation requires balancing patient comfort while minimizing distress and avoiding deleterious effects of under- and over-sedation. It also reflects the interplay between evidence-based medicine and clinical intuition. In critically ill patients, variability in pharmacokinetics and pharmacodynamics—drug interactions, organ dysfunction, inconsistent absorption, altered protein binding, hemodynamic instability, and drug accumulation—can contribute to adverse events [3].

Historically, benzodiazepines were the gold standard for ICU sedation due to their anxiolytic, amnestic, and hypnotic properties. However, evidence indicates

*Correspondence: landoni.giovanni@hsr.it
[1] Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
Full author information is available at the end of the article

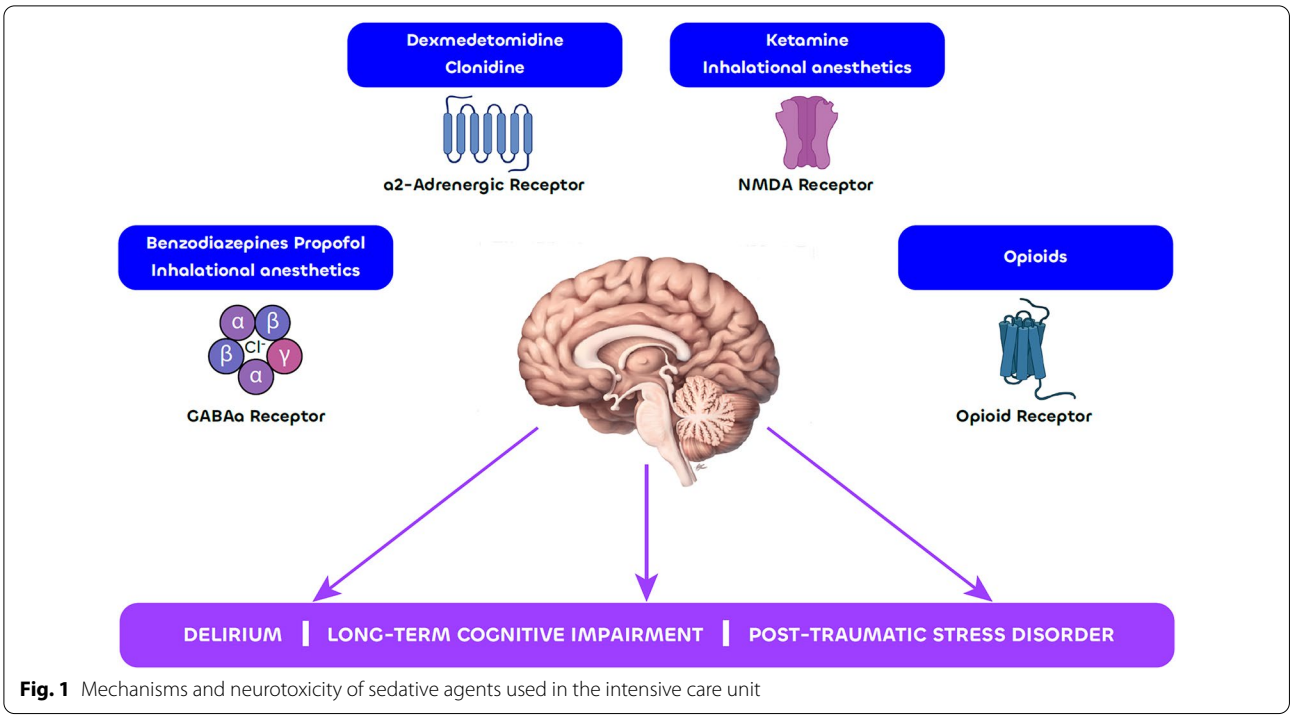


**Fig. 1** Mechanisms and neurotoxicity of sedative agents used in the intensive care unit

that benzodiazepines are associated with high rates of delirium, cognitive decline, and prolonged mechanical ventilation [3]. Current guidelines discourage using benzodiazepine due to their delirium risk, particularly in older patients [3]. Consequently, their use is limited to specific scenarios such as refractory seizures and alcohol withdrawal. Remimazolam, a relatively new benzodiazepine approved in 2020 for procedural sedation, is gaining popularity, though its long-term neurological effects remain undefined [8].

Propofol is the most commonly used hypnotic agent in perioperative and ICU settings due to its favorable pharmacokinetics. However, propofol may impair the organ-protective effects of other interventions, potentially leading to worse clinical outcomes [6].

Dexmedetomidine, an α2 adrenergic agonist, is one of the most extensively studied sedatives in perioperative and ICU settings. While it may reduce delirium after elective surgery, its clinical efficacy in critically ill patients remains uncertain [9]. Clonidine, another α2 agonist, has recently gained attention but may increase agitation and bradycardia [9].

Ketamine may improve mood in ICU patients with depression and is used at low dose for adjunctive analgesia, but is associated with increased risk of hallucination [10].

A recent trial showed that among patients with acute respiratory distress syndrome, inhaled sevoflurane sedation resulted in lower 90-day survival compared to propofol sedation [11]. Opioids may induce delirium and hyperalgesia [12]. Neurotoxic effects of sedative agents commonly used in the ICU are summarized in Supplementary Table 1.

It is important to note that almost all sedatives cause systemic vasodilation, which can exacerbate neuronal injury. Mechanisms and neurotoxicity of these sedatives are summarized in Fig. 1.

Sun Tzu, in *The Art of War*, stated, "The supreme art of war is to subdue the enemy without fighting." While sedatives are indispensable in critically ill patients, several strategies can help minimize their adverse effects and improve outcomes, including light sedation, daily sedation interruptions, objective sedation monitoring (e.g., bispectral index), and analgosedation using opioids and regional anesthesia techniques [13]. Protocolized sedation may be a safe and effective approach by shortening the duration of sedation exposure [13].

Avoiding sedation and invasive mechanical ventilation during extracorporeal membrane oxygenation (ECMO)—a practice known as "awake ECMO"—is gaining popularity due to its potential benefits, including reduced delirium rates, shortened mechanical ventilation durations, and facilitated rehabilitation [14].

Sedation stewardship is a relatively new concept in the management of critically ill patients aimed at optimizing sedation to improve patient outcomes. The key aspects of this concept include individualized sedation plans based on the patient's condition, comorbidities, and

responsiveness to treatment, lighter sedation, the use of alternative sedative strategies, and interdisciplinary collaboration. The presence of a dedicated pharmacist in the ICU may accelerate its implementation through expert pharmacovigilance [15].

While sedation continues to be a cornerstone of critical care, the precise mechanisms underlying sedative-induced neurotoxicity remain elusive and should be addressed in future mechanistic studies. Knowledge gaps persist regarding which patients may benefit from sedation, which patients may have poor responses, and whether different sedatives are associated with different patient-relevant outcomes. Hopefully, ongoing randomized trials (NCT04341350, NCT06251375, and NCT06767358) will shed light on patient-relevant outcomes of sedative-induced neurotoxicity in critically ill patients.

**Supplementary Information**
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**Author details**
[1] Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy. [2] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy. [3] Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Japan. [4] Department of Anesthesiology and Perioperative Medicine, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, USA.

**Declarations**

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None.

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