generation in both rodent and primate models.[3,4] What is unclear is the relevance of these models to humans. To quote an occasionally used phrase, "rats are funny people," and a prolonged exposure of 10-day-old rat pups to isoflurane, while mimicking the gestational age of a 36-week premature infant, may not be applicable to the relatively brief exposure of humans to volatile agents in a typical operating room setting. Prolonged use in the intensive care unit (ICU), however, is far different and comes closer to the exposure duration of the animal models.[3,4] Even Sackey *et al.* mention reversible symptoms of ataxia, tremor, and clonus in children in whom volatile anesthetics have been used for sedation.[1] Although the potential harm to patients exhibiting these symptoms is unclear, their presence is unlikely to beneficial. Similarly, the aging brain may be vulnerable to yet-to-be elucidated neurotoxic effects of volatile anesthetics. Postoperative cognitive dysfunction in the elderly is a well-known phenomenon whose precise etiology is elusive, but again, animal studies suggest a possible correlation with expressions of Alzheimer-like pathology in rodents after volatile anesthetic exposure.[5] As is the case in studies of the developing brain, the relevance of animal models to human clinical care is unclear, but the prolonged exposure to volatile anesthetics in a scenario of ICU sedation approaches experimental conditions in animal studies. Finally, the mutagenic effects of volatile anesthetic exposure continue to be debated in the literature with some evidence to support acceleration of cancers after anesthesia.[6]

The use of benzodiazepines, narcotics, and intravenous hypnotic agents such as propofol for ICU sedation is well established with an acceptable safety profile. As with any pharmaceutical therapy, there are side effects and challenges associated with their long-term administration, especially when relying on clinical guidance for management when muscle relaxants are used and without Bispectral Index or other monitors of depth of anesthesia. In the report by Sackey *et al.*, it is likely that the same therapeutic goals could have been accomplished with better titration of intravenous agents and use of Bispectral Index or similar technology and without the use of volatile anesthetics. It is increasingly clear that prolonged exposure to volatile anesthetics, especially in the immature, elderly, and compromised brain (the patients most likely to be in an ICU), may be associated with significant risk that is not justified by the clinical benefit of their use for ICU sedation. Until more definitive studies are done, I believe the use of volatile anesthetics for prolonged sedation should be approached with great caution, if at all.

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*In Reply:*

We appreciate Dr. Mychaskiw's cautioning words regarding possible negative effects of volatile anesthetics for intensive care unit (ICU) sedation. Perhaps they reflect the apprehension that many anesthetists/intensivists feel regarding the growing body of evidence revealing possible injurious effects of sedatives and anesthetics on the central nervous system. Because these medications are indispensable in modern medicine, we seem to be "damned if we do, damned if we don't." This may be particularly true in our most vulnerable patients: the very young and very old. We hope to further the discussion with some additional reflections here.

The main purpose of our article was to highlight the clinical impact of sedation strategies on patient outcomes.[1] This specific case using isoflurane illustrates that volatile anesthetics may be a therapeutic option for deep sedation of intubated ICU patients. Although we grant that isoflurane is relatively unproven for this indication, we would tend not to agree with the assertion that "the use of benzodiazepines, narcotics and intravenous hypnotics, like propofol, for ICU sedation is well-established with an acceptable safety profile." The cited and worrisome recent findings of neurodegenerative and apoptotic effects have been found to apply as well to barbiturates, ketamine, benzodiazepines, and propofol.[2–4] To our knowledge, only the $\alpha$-2-agonists have not been found to cause these changes. Dr. Mychaskiw rightly wonders what significance these animal findings bear on clinical medicine, but at least in the pediatric setting Wilder *et al.* have revealed in a large cohort that relatively modest exposure to general anesthesia before the age of 4 yr was related to increased risk of learning disability later in life.[5] Unfortunately, at our current level of knowledge there is nothing to say that risk is lessened by using one class of drug over another or that inhaled anesthetics are more harmful than intravenous.

In fact, increasing evidence points toward additional clinically relevant problems with commonly used sedative drugs. Benzodiazepines, among the most common drugs in our arsenal, contribute to the development of delirium after ICU sedation.[6] Delirium is associated with increased hospital length of stay and with increased mortality.[7] Propofol, common in adult ICUs despite the above mentioned concerns, is not recommended for long-term sedation in children or in higher infusion rates for adults because of the risk of propofol infusion syndrome.[8] Moreover, long-term use of propofol may contribute to withdrawal.[9]

Several studies of volatile anesthetics for sedation purposes in humans—with clinically relevant endpoints—have shown promising results. Rapid pulmonary excretion and limited metabolism of all the modern agents are intrinsically attractive characteristics. Wake-up times are shorter and more predictable than with intravenous sedatives, as is time to cooperation.[10,11] There may be beneficial cardiac effects of volatile anesthetic sedation.[12] The memory panorama from the ICU stay, an important patient-related outcome,[13] also appears to be favorable compared with that of midazolam.[14]

Simply put, we need more evidence and knowledge about the advantages and risks of the sedative drugs that we use, be they benzodiazepines and propofol or volatile anesthetics. We advocate for additional evaluation of volatile anesthetics as a promising option for long-term sedation in ventilator-dependent ICU patients. In any case, we can not afford to idly administer routine cocktails of sedatives unaware of the risks we may be taking. Every patient deserves a carefully considered sedation strategy.

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# Incomplete Validation of Risk Stratification Indices

*To the Editor:*

Using 2001–2006 Medicare hospital data (Medicare Provider Analysis and Review [MEDPAR]) in approximately 17 million patients aged 65 yr and older, Sessler and colleagues[1] have proposed four risk stratification indices (RSIs) for mortality and duration of hospital stay. With a complex, stepwise hierarchical-selection algorithm, the authors[1] chose a parsimonious set of statistically significant predictors from the approximately 20,500 International Classification of Diseases, Ninth Revision, diagnostic and procedure codes. For example, in-hospital mortality was modeled on 184 predictor codes with odds ratios varying from 0.131 to 57.821. Using a split sample design, these RSIs were internally validated on MEDPAR data for another 17 million patients and were externally validated on 100,000 patient records from the Cleveland Clinic (Ohio; Perioperative Health Documentation System). Working in the parameter space ($\beta$ coefficients), validation of the RSIs was demonstrated on the development, validation, and external datasets by the c (concordance) statistic,[2] which revealed very good discrimination in all datasets.

However, the performance of these RSIs has not been adequately justified. To do so requires calculation of the