The literature seems to confirm an important association between sleep duration and global cognitive decline, especially in individuals with insufficient (four hours a night) or excessive sleep (10 hours a night). A recent meta-analysis found that people with the most frequent sleep disorders in the general population (insomnia, sleep apnea, excessive daytime sleepiness, sleep-related movement disorder, and circadian rhythm disorder) may be vulnerable to all-cause dementia, Alzheimer’s disease and vascular dementia.

In recent years, laboratory studies have revealed the pathophysiological mechanisms involved in this relationship. A recent gold-standard real-time iontophoretic method for exploring and quantifying the extracellular space of the living brain has shown that deep sleep (natural or induced) increases interstitial fluid by 60%, resulting in a remarkable increase in the convective exchange between cerebrospinal fluid and interstitial fluid, which substantially increases the rate of β-amyloid protein clearance during sleep. This new hypothesis about the pathophysiology of neurodegenerative diseases opens the way for future research on the neuroprotective role of drugs that promote healthier sleep patterns. Furthermore, data restricted to pre-clinical and animal models suggest that some hypnotic drugs may act as neuroprotective agents. For example, a study of trazodone in rats found important neuroprotection at clinically relevant doses over an extended period, without systemic toxicity. But is this also the case for benzodiazepines, anticonvulsants, melatonin, and others?

Although hypnotics with different mechanisms of action appeared in the last decade (especially on the international market), long-term clinical studies supporting their use in patients with chronic insomnia are lacking. Even benzodiazepine receptor agonists (also called Z-drugs), frequently prescribed for older adults, have short- and long-term risks. Studies not sponsored by the pharmaceutical industry, and therefore less prone to conflicts of interest, confirmed the clinical suspicion that such drugs increase the risk of adverse outcomes among older adults, including delirium, cognitive decline, dementia, falls, fractures, hospitalizations, and mortality. Hence, the available evidence suggests that these drugs may be inappropriate for use in older adults for any length of time.

Furthermore, little is known about the impact of older drugs, including antidepressants, on the quality and structure of sleep. A recent Cochrane Collaboration review concluded that short-term, only low-dose doxepin and trazodone had a modest effect on sleep quality compared to placebo. However, the studies included in this review involved small samples and short-term follow-up, among other methodological limitations. Thus, there is no consistent scientific support for using antidepressants (such as amitriptyline, agomelatine, mirtazapine and even trazodone) as hypnotics in the Brazilian clinical practice. The loss of patent protection is certainly one reason these drugs continue to be poorly investigated regarding sleep properties and risks in populations susceptible to long-term adverse effects, such as older adults.

According to the National Controlled Products Management System (SNGPC), approximately 2.3 million zolpidem tablets (all available doses) and 950 000 trazodone
Considering that these doses of trazodone are generally used to treat insomnia, this antidepressant prescription represents 40% of the global market of drugs for insomnia. Additionally, despite the lack of evidence, the prescription of zolpidem in clinical practice continues to be a routine.

The lack of scientific evidence on the use of these drugs for the treatment of sleep disorders gives rise to misleading information about their indication, which limits the therapeutic arsenal of geriatricians. The risk of adverse events in older adults using drugs for insomnia is substantially higher. For instance, according to the UpToDate® clinical database, trazodone can have unwanted consequences in older adults, such as postural hypotension, and a higher risk of falls and, as a consequence, fractures, although this conclusion was based on a single uncontrolled retrospective database-based study.

Another critical controversy is the safety of the long-term use of hypnotics. Even though many instruction leaflets state these medications should not be used for prolonged periods (zolpidem leaflet states that use “should not exceed four weeks”), chronic hypnotic use tends to be the rule in the daily prescription of general physicians and specialists. However, the lack of scientific evidence to support the long-term safety (or even effectiveness) of these drugs and the increasing reports of accidents, neuropsychiatric effects and abuse of hypnotics support the deprescription of these drugs.

Unfortunately, public (i.e., regulatory bodies) or private (i.e., the pharmaceutical industry) actions to clarify these dilemmas have been insufficient. In addition to new pharmacological therapies, we need to reexamine the most commonly prescribed drugs for insomnia in clinical practice using robust research methodologies to provide insightful evidence about the effects of long-term use of medications on cognitive risks and accidents (such as falls) in older adults. Obviously, in Brazil, such studies are expected to be financed by the government and its funding agencies rather than commercial interests. Restricting the use of hypnotics in medical practice due to a lack of evidence also limits access to effective treatment for an older population already suffering from multiple comorbidities, including the high prevalence of sleep complaints.

CONFLICTS OF INTEREST
The authors have no conflict of interest to declare.

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AUTHOR CONTRIBUTIONS
EFC: Conceptualization, investigation, methodology, visualization, writing – original draft, writing – review & editing.
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