

EDITORIAL

# Off-label use of midazolam in older inpatients: analysis of prescribing practices in a French hospital (MIDnight study)

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This editorial refers to the article 'Off-label use of midazolam in older inpatients: analysis of prescribing practices in a French hospital (MIDnight study)' by Hugues Michelon et al. published in this issue of *Fundamental and Clinical Pharmacology*.

The MIDnight study carried out in a geriatric hospital confirms the hypothesis of gaps between recommendations and off-label use of drugs, like midazolam. Such gaps expose patients to risks and prescribers to legal issues. However, withdrawing midazolam would be an additional risk since it would deprive patients of an unequalled drug. The authors of the article [1] chose to deal with this dilemma in a multi-phase evaluation program aimed at analyzing practices, understanding use factors, and producing recommendations to make prescriptions and their use in the elderly safer.

Attributing the gap to geriatricians' carelessness would mean ignoring that their prescriptions involve clinical situations without authorized therapeutic solutions.

The story of midazolam traces the discovery of three dosages serving a continuum of use from birth [2] to death:

1/ High doses were used before the molecule was marketed [3]. Such doses allowed anesthesiologists to induce sleep in seconds. In palliative care units (PCUs), anesthesiologists used these high doses intentionally to alleviate anxiety about death. Consequently, the term Continuous Deep Sedation Maintenance (CSMP) was created.

Mobile PCUs transferred this practice to geriatrics where CSMP appears to be less common than in other adult PCUs. Indeed, toward the end of life, elderly people may choose to wait for death while enjoying the remaining time with maximum well-being.

2/ Low doses were used intentionally in burn victims [4]. Opioids and nitrous oxide may be contraindicated or insufficient to overcome fear of pain. In this case, titration makes it possible to reach the lowest dose allowing for a triad of effects: anxiolysis, well-being, amnesia of fear and of its associated psychological trauma. Such low doses have been used for brief and anxiogenic care: wound and pressure sore care, dental

care, and premedication before endoscopy. Low doses in scans and MRI scans have led to extraordinary relief from anxiety due to claustrophobia without associated drowsiness. In geriatrics, this effect soothes feelings of asphyxia, without asphyxiation by desaturation.

3/ Intermediate doses put an end to psychomotor agitation, a use discovered by resuscitator anesthetists practicing in medical ambulances. When faced with extreme agitation and wrath, they were unable to find venous routes. They tried the nasal route which induced cessation of agitation without drowsiness. Emergency departments shared this experience with psychiatrists and geriatricians. This led to a new use to treat behavioral and psychological disorders of dementia (BPSD).

Evaluation with NPI-ES, or PGI-DSS [5], showed that a low dose of midazolam combined with a low dose of antipsychotic was more effective than benzodiazepine or antipsychotic alone [6]. In BPSD, in nonconvulsive epileptic states, nasal midazolam can be used as a diagnostic test [7]. The nasal route which appears simple [4] is, however, difficult to use because the face must be approached, which is felt as an intrusion aggravated by the pain of an acid. A complementary drug would be low-dose valproate. Its anti-conflict activities in animals [8] could match anxiolytic effects in humans [9,10] in addition to the sedative effects of manic agitation.

The lipophilicity of all benzodiazepines explains fat accumulation (the ratio of which increases with age), long elimination half-life and the risk of associated complications: falls, fractures, chokes, pneumopathies, incontinence, sleep apnea, and memory disorders. These complications have led to the deprescription of molecules with long half-life. Midazolam reassured with its short half-life. Since it was also the only water-soluble benzodiazepine, it was the least inappropriate in geriatrics [11]: The rapid peak allows patients to be

treated without delay; the rapid disappearance of the peak and the water solubility reduce complications due to accumulation. Water solubility makes the use of the subcutaneous route possible, which is particularly interesting in pediatrics and geriatrics.

Multiple use of those three dosages of midazolam benefits from the history of its twin of 1982, triazolam, whose peak features let insomniacs experience, from the first dose, unspeakable well-being followed by a hypnotic grip on sleep [12], with no residual effect on waking. Such benefits are to be contrasted with unpredictable effects (inter-individual variations [2], metabolism by cytochrome P-450, interactions). Pharmacovigilance revealed the risks of the peak: (i) at the peak: hallucinations [13], homicides, suicides, automatic behavior with amnesia [14] and facilitation of psychological control; (ii) on the descent: withdrawal syndrome, anxiety rebound from the first dose [15] and addiction with the need to increase doses. These risks led to the withdrawal of triazolam.

As for midazolam, German hospitals have withdrawn it from premedication in the elderly [16].

Covid-19 caused midazolam stock shortage in intensive care units. PCUs and geriatrics were asked to spare midazolam, and to replace it with clonazepam or diazepam by parenteral, nasal, or oral transmucosal route.

Beyond the focus on midazolam, the merit of MIDnight is to highlight the value of the clinical pharmacy activity and the collaborative work involving pharmacists, physicians, nurses, and users.

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