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COMMENTARY

Author's Reply to Kotlinska-Lemieszek: "Should Midazolam Drug–Drug Interactions Be of Concern to Palliative Care Physicians?"

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We thank Dr. Kotlinska-Lemieszek for her interest and comment [1] on our article *Drug Interactions in Dying Patients* [2]. She suggests that more attention should be drawn to the risk of drug–drug interactions (DDIs) with the benzodiazepine midazolam, in opposition to our estimation of a low DDI potential in our study.

Indeed, alterations in the activity of cytochrome P450 (CYP) 3A are the most frequent cause of pharmacokinetic DDIs and have serious clinical implications. The reason is the pivotal role of CYP3A in human drug metabolism. As the principal P450 enzyme in both the liver and the gut wall, accounting for 35 and 80 % of the total CYP abundance at these sites [3], CYP3A is involved in the metabolism of more than 50 % of the drugs currently on the market [4]; and numerous inhibitors and inducers have been shown to substantially alter, clinically significantly, the exposure and, subsequently the pharmacodynamics, of various substrates [5, 6].

Apart from negligible direct glucuronidation via UDP-glucuronosyltransferase 1A4 [7], midazolam is almost exclusively metabolised via CYP3A to its hydroxy metabolites and is consequently prone to be involved in many DDIs. Due to the extensive intestinal metabolism of oral midazolam (average intestinal availability $\sim$50 % [3]), the risk of DDIs must be considered even higher for oral perpetrators coadministered with oral midazolam. As a result of this and the impressive findings in the clinical DDI studies pointed out by Kotlinska-Lemieszek, midazolam even plays an outstanding role as a probe CYP3A substrate in various quantitative DDI prediction models, such as in vitro–in vivo extrapolation simulation models [8–12] or fully in vivo-based models [13]. Therefore, in this context, we totally agree with Kotlinska-Lemieszek to consider in general a very high potential risk of DDIs for midazolam in clinical settings.

However, in our study [2] we evaluated the potential for DDIs in a very specific clinical setting by only assessing dying patients in hospice care. The drugs prescribed during the last days of life were classified into three categories (low, moderate and high DDI potential) according to a flag score, which was dependent on the frequency of prescriptions of a certain drug and the frequency of potential DDIs of this drug in the observed patient group. Thus, we assessed the low potential for DDIs of midazolam for our specific population of dying patients in the context of typical drug combinations prescribed in this situation. This finding must be seen in the special therapeutic setting of end-of-life care, where pharmacotherapy should be symptom-oriented, and drugs for the prevention or modification of primary or secondary diseases should usually be discontinued [14]. Consequently, due to very rare prescription rates or even a complete absence of the typical CYP3A inhibitors (e.g. only four prescriptions of fluconazole as the only azole antifungal in 364 patients, no macrolides, etc.) or inducers (except the interaction between carbamazepine and midazolam, which is specifically discussed in our article) compared with a relatively high prescription rate of midazolam (16 %), a general lower risk for CYP3A-mediated DDIs was found. In accordance with the assessment of potential DDIs on a palliative care unit in a previous study [15], this also explains the general low risk of other

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benzodiazepines. For example, in the absence of strong CYP2C19 inhibitors (e.g. fluvoxamine, fluconazole, voriconazole, moclobemide), diazepam also showed a low potential in the palliative care setting. Nevertheless, we would like to stress that one has to consider the limitations of our scoring instrument [2], and that the results should not imply an uncritical use without taking into account each patient's particular therapeutic situation, but rather serve as a general road map for physicians in this specific clinical setting. Clearly, our results were not intended to be extrapolated to other clinical settings; using the same screening approach for DDIs, for example in patients in an intensive care unit, one would probably obtain completely different findings, possibly predicting a high potential for midazolam to be involved in DDIs.

Finally, referring to the comment by Kotlinska-Lemieszek regarding the important role of midazolam in end-of-life care as a frequently used drug for palliative sedation, we also would like to underline the beneficial and safe use of midazolam to adequately relieve various refractory symptoms in terminal patients [16]. As Kotlinska-Lemieszek already mentioned, midazolam emerges as an attractive candidate due to the possibility of administration by the preferred subcutaneous route in these patients owing to its high subcutaneous bioavailability [17]. Correspondingly, midazolam has recently been suggested as one of the four essential drugs needed for quality care of dying patients [18]. By carefully titrating midazolam to the desired clinical effect (facilitated by its short half-life) and monitoring the patient through inspection, we consider the overall risk for DDIs of midazolam to be minimal in this clinical setting, particularly in light of our comments above.

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Conflicts of interest Sebastian Frechen and Jan Gaertner have no conflicts of interest that are directly relevant to the content of this comment.

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