Zolpidem pharmacokinetics and pharmacodynamics in metabolic interactions involving CYP3A: sex as a differentiating factor

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To the editor:

We read with interest the recent paper by Polasek et al. on the evaluation of zolpidem as a mechanism-based inactivator of human CYP3A *in vitro* that was accompanied by the assessment of its metabolic interaction potential with CYP3A drugs [1]. The article clearly points out the mechanism of inactivation of human CYP3A *in vitro* and describes the implications of this mechanism for the *in vivo* metabolic interactions involving CYP3A. Given the prescription rate of zolpidem, this issue is of vital importance in terms of the drug's efficacy and patients' safety.

However, one issue that was not addressed in the discussion of this interesting paper is that of the association between the patient's sex and the endocrine specificity of zolpidem—as if zolpidem pharmacokinetics is a gender-independent factor. Based on current knowledge, the pharmacokinetics of zolpidem seems to be related to endocrine factors associated with CYP3A4 metabolism. As such, low plasma concentrations of free testosterone may contribute to lower CYP3A activity, with women achieving up to 50% higher zolpidem plasma levels, while exposure to testosterone activates the biotransformation via CYP3A [2]. This effect is conspicuous in the relative higher

incidence of adverse drug reactions with zolpidem in women [3].

The conclusions of the study reported in the paper are valid for the model study on male subjects. It would have been interesting, however, if the discussion were to have included the exciting element of endocrine-related differences in zolpidem action.

Conflict of interest statement The authors declare that they have no conflict of interest.

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