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Letter to the Editor

Zolpidem abuse, dependence and withdrawal syndrome: sex as susceptibility factor for adverse effects

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We read with interest the *British Journal of Clinical Pharmacology*'s Spring 2007 special issue, addressing the issue of adverse drug reactions (ADR), suggesting how reactions can be prevented or minimized, generating hypotheses for further study, and proposing ways forward for future research. The issue tackled the susceptibility factors for ADR associated with age, polypharmacy, ethnic factors and the problems associated with prenatal exposure to drugs. However, our impression was that it left unaddressed the important issue of a patient's sex as a susceptibility factor for ADRs.

Patient's sex influences both pharmacodynamics and pharmacokinetics, seemingly related to the endocrine factors that are the most prominent in drugs metabolized via CYP3A4, probably due to the action of sex hormones. The lower plasma concentrations of free testosterone, for example, may contribute to lower CYP3A activity, and exposure to testosterone activates the biotransformation of a number of CYP3A substrates [1].

Sex as a susceptibility factor for adverse effects seems to be well illustrated by cases of zolpidem abuse, dependence and withdrawal syndrome. As zolpidem dependence and withdrawal syndrome have been seen in subjects taking 160–2000 mg d^{-1} [2, 3], the pharmacodynamics is of vital interest. A number of such cases have been described [4] and the core hypothesis on the phenomena described in those case reports is that zolpidem at high doses might lose its selectivity on GABA-A receptor and exhibit the same pharmacological effects as classical benzodiazepines [2]. Zolpidem metabolism is mediated by human cytochromes P450 (CYP), with a dominant role of CYP3A4 and a contributory role of CYP2C9, 1A2, 2D6 and 2C19 in decreasing order of importance, but not of 2A6, 2E1 or 2C8 [1, 5]. Thus the pharmacokinetic interactions may occur in patients receiving a number of concomitant treatments, including analgesics, antiarrythmics, antibiotics, antiepileptics, antihistamines, antineoplasm, antiparkinsonian drugs, antiprogestorone agents, antirejection drugs, β-blockers, calcium-channel blockers, HMG-CoA reductase inhibitors, non-nulceoside reverse transcriptase inhibitors, protease inhibitors, proton pump inhibitors, steroids and triptans [6]. *In vitro* studies have indicated that the rate of transformation of zolpidem to its major hydroxylate metabolite in human liver microsomes is increased by an average of 70% by coincubation with equimolar amounts of testosterone [1]. Also, in the presence of renal insufficiency and/or hepatic impairment, plasma protein binding of zolpidem is decreased [7, 8]. However, most zolpidem-related disorders involve women. This may be associated with the fact that insomnia is more prevalent in women (1.5 : 1 female : male ratio). On the other hand, women achieve up to 50% higher zolpidem plasma concentrations [9] and sex-related differences in zolpidem clearance are significant [1, 10]. In contrast, zolpidem clearance is higher and half-life shorter in women using oral contraceptives, which may contribute to the observed increased incidence of ADRs in women [7].

Thus, in many cases pharmacokinetics and pharmacodynamics contribute to the ADRs observed with zolpidem. However, sex should also be considered as a susceptibility factor for zolpidem ADRs and consideration of a patient's sex can significantly improve zolpidem pharmacotherapy with regard to efficacy and safety.

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