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LETTER TO THE EDITORS

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Lorazepam should no longer be used as a prototypical benzodiazepine

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Jackson et al. reported in the last issue of Psychopharmacology (2003) that lorazepam (2 mg) cross generalizes with the alcohol stimulus in humans, a result that was interpreted as indicating cross-species generality of the $GABA_A$ component of the alcohol discriminative stimulus. We would like to draw attention to the fact that the selection of lorazepam as the drug to prove their point is somewhat unfortunate, because there is a considerable body of data suggesting that this drug is an atypical benzodiazepine (BZ). Firstly, it has been reported that animals (baboons and rats) trained to discriminate lorazepam show a unique generalization profile when compared to those trained to discriminate other BZs (Ator and Griffiths 1997, 1999): they are more likely to generalize only to compounds that are full agonists of BZ receptors and do not reliably generalize to compounds that enhance GABA, such as barbiturates, and classic anticonvulsants and sedative/hypnotics, including ethanol, chloral hydrate, and valproic acid. Hence, it seems unwise to consider that generalization from alcohol to lorazepam in fact indicates the cross-species generality of the $GABA_A$ component of the alcohol discriminative stimulus, as claimed by Jackson et al., because lorazepam does not produce equivalent discriminative effects to those of most $GABA_A$ ligands.

Lorazepam also leads to acute cognitive effects in humans that are by no means equivalent to those observed after the ingestion of other BZ: it leads to almost no acute tolerance and to qualitatively different effects, as verified by the use of detailed brain mapping technology (Itil et al. 1989). Other atypical effects include the widely publicised disruption of performance in measures of many types of perceptual priming, as well as of visual information processing (see Pompéia et al. 2003).

Unfortunately, most of the above-mentioned studies did not follow specific methodologies for selecting equipotent doses of lorazepam and the BZ with which it was being compared. If non-equipotent doses are used, what seems to characterize qualitative differences between drugs may in fact consist of quantitative differences, a fact that would imply that all BZ act in a similar manner. However, a recent within-subject comparison of visual and auditory event-related potential (ERP) effects of acute doses of lorazepam and flunitrazepam, a BZ with standard effects, revealed that lorazepam does in fact induce an atypical disruption of visual ERPs even when the doses of both drugs are equated following strict criteria (Pompéia et al. 2003).

As detailed by Pompéia et al. (2003), priming and visual disruption brought about by lorazepam are thought to be mediated through BZ binding sites at $GABA_A$ receptors, but scant attention has been given to the fact that similar effects are not observed for other BZ agonists, which all supposedly act at the same binding sites. Lorazepam's pharmacokinetics cannot account for these atypical effects, as this drug is no different from other BZs in terms of liposolubility, plasma-protein binding characteristics, absorption and elimination half-life parameters or receptor affinity. There are only two indications of specific pharmacological characteristics of lorazepam that may determine its atypical effects. Firstly, lorazepam's association/dissociation rate constants to central BZ receptors differ from those of certain BZ compounds. An example of the importance of this pharmacological characteristic, although not related to GABAergic ligands, is that fast dissociation rate constants from D_2 receptors can determine why atypical antipsychotics have a different profile from typical compounds (Kapur and Seeman 2001).

Secondly, binding studies show that lorazepam is most potent in the cerebellum, while most BZs are not differentially potent across brain regions (Sanger and Benavides 1993), even though there is no indication that lorazepam binds differently to BZ_1- and BZ_2-type receptors when compared to other full agonists. Considering that it has been suggested that drugs that have qualitatively different effects from others in their class may display binding profiles to as yet uncharacterised recep-

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tors (e.g. Sanger et al. 1999), it may well be that there are specific receptors for lorazepam.

In short, lorazepam displays an atypical profile when compared to other benzodiazepines, for reasons still unknown. Therefore, this drug should no longer be used as a reference/prototypical BZ, as is so often done throughout the literature.

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