

# Psychological Medicine

MONOGRAPH SUPPLEMENT 13

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The natural history of  
tolerance to the  
benzodiazepines by A. Higgitt,  
P. Fonagy and M. Lader

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Cambridge University Press

## The natural history of tolerance to the benzodiazepines

Benzodiazepine dependence is *the* iatrogenic disorder of the 1980s. Although the legal fall-out is only in its early stages, the issue of possible pharmaceutical or medical negligence in the prescription of these drugs is at the fore-front of public as well as scientific debate. A cornerstone of the argument is the development of physical dependence on this group of drugs. The close relationship of the development of tolerance and dependence makes the careful laboratory scrutiny of the reaction over time of previously unmedicated human volunteers to a range of benzodiazepines a focal point of the debate.

The study reported here looked at tolerance to three benzodiazepines of short, medium and long elimination half-lives. Tolerance was seen within the first two weeks to all the drugs on a wide range of measures including endocrinological and psychophysiological indicators. The presence of permanent changes in the central nervous system following long-term benzodiazepine administration is implicated by a separate study, also reported here, where patients previously successfully withdrawn from long-term benzodiazepine ingestion were exposed to diazepam and were found to manifest reduced responsiveness compared to controls.

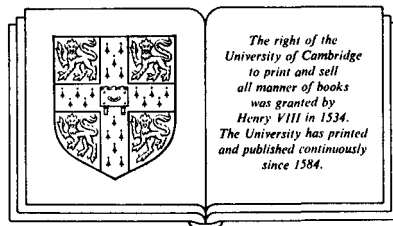
Close examination of the data revealed that no simple model based solely upon central nervous system changes at the receptor level can adequately account for the pattern of different responses to drugs varying only in elimination half-life. A model which also takes into account the likely psychological reactions of patients to the effects of these drugs proposed in the final chapter provides a better fit with the data.

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A. Higgitt, P. Fonagy and M. Lader

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