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462 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Epidemiological research has linked benzodiazepine prescribing to serious medical conditions including dementia, infections and cancer.38–41 However, a causal relationship has not been established and evidence is conflicting.39,41 All studies in this area are confounded by the failure to include illicit use of benzodiazepines. Respiratory depression is rare with oral therapy but is possible when parenteral routes are used.25 Buccal and intranasal administration may also cause respiratory depression.42,43 The use of the specific benzodiazepine antagonist flumazenil is effective in reversing respiratory25 depression but is not without risk (e.g. convulsions and arrhythmia, particularly in mixed overdoses with TCAs) so selective use is recommended.44 Flumazenil has a much shorter half-life than many benzodiazepines, making close observation of the patient essential for several hours after administration. Intravenous injections of benzodiazepine can be painful and can lead to thrombophlebitis because of the low water solubility of benzodiazepines, so it is necessary to use solvents in the preparation of injectable forms. Diazepam is available in emulsion form (Diazemuls® in the UK) to overcome these problems. Drug interactions Benzodiazepines do not induce microsomal enzymes and so do not frequently precipitate pharmacokinetic interactions with any other drugs. Most benzodiazepines are metabolised by CYP3A4, which is inhibited by erythromycin, several SSRIs and ketoconazole. It is theoretically possible that co-administration of these drugs will result in higher serum levels of benzodiazepines. Pharmacodynamic interactions (usually increased sedation) can occur. Benzodiazepines are associated with an important interaction with methadone (see Chapter 5) and should be used with caution in patients prescribed clozapine (increased risk of cardiopulmonary depression) and not at all with intramuscular olanzapine. References

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