18 - Chapter 13 Psychotropic drugs in special condition

01 - Psychotropics in overdose

Psychotropics in overdose

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 13 Psychotropics in overdose Suicide attempts and suicidal gestures are frequently encountered in psychiatric and general practice, and psychotropic drugs are often taken in overdose (Table 13.1). This section gives brief details of the toxicity in overdose of commonly used psychotropics. It is intended to help guide drug choice in those thought to be at risk of suicide, to give some indication of safe quantities to prescribe and to help identify symptoms of overdose. This section gives no information on the treatment of psychotropic overdose and readers are directed to specialist poisons centres. In all cases of suspected overdose, urgent referral to acute medical facilities is, of course, strongly advised. Psychotropic drugs in special conditions Table 13.1 Psychotropic drugs in overdose. Drug or drug group Toxicity in overdose* Smallest dose likely to cause death Signs and symptoms of overdose Antidepressants Agomelatine1,2 Low No deaths reported. In early trials, 800mg was maximum tolerated dose. EU SPC reports no serious effects from 2.45g overdose. A mixed overdose of 7.5g caused only drowsiness and mild tachycardia. Sedation, agitation, stomach pains, dizziness Brexanolone3 Not known No deaths reported. Two cases of accidental overdose due to pump malfunction. Sudden loss of consciousness (Continued)

914 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 13 Table 13.1 (Continued) Drug or drug group Toxicity in overdose* Smallest dose likely to cause death Signs and symptoms of overdose Bupropion4–7 Moderate Around 4.5g, although largest overdose of 15g was not fatal.3,8 Tachycardia, seizures, QRS prolongation, QT prolongation, arrhythmia. Agitation and toxic psychosis also reported. Fatal serotonin syndrome may occur if taken with venlafaxine.9 Dextromethorphan and bupropion3 Probably moderate Unclear. Bupropion inhibits metabolism of the dextromethorphan which may result in more severe/persistent overdose. Bupropion: as above Dextromethorphan: nausea, vomiting, stupor, coma, respiratory depression, seizures, tachycardia, hyperexcitability, toxic psychosis Duloxetine10–13 Low Unclear – no deaths from single overdose reported but involved in numerous mixed overdose deaths. Drowsiness, bradycardia, hypotension May be asymptomatic Esketamine14 Not known Unclear. No deaths reported. Predicted to mirror ketamine overdose including sedation, hypertension, tachycardia, respiratory depression.15 Ketamine16 Moderate Iatrogenic overdoses of up to 50mg/kg IV are not usually fatal if prompt treatment is given. Mechanical ventilation may be required. Illicit overdose is rarely fatal unless other drugs present.15 Sedation, respiratory depression, hypertension, tachycardia

Lofepramine17,18 Low Unclear. Fatality unlikely if lofepramine taken alone. Sedation, coma, tachycardia, hypotension MAOIs17,19–21 (not moclobemide) High Phenelzine – 400mg Tranylcypromine – 200mg Tremor, weakness, confusion, sweating, tachycardia, hypertension Mianserin22–24 Low Unclear but probably more than 1000mg. Fatality unlikely if mianserin taken alone. Sedation, coma, hypotension, hypertension, tachycardia, possible QT prolongation Mirtazapine4,25–28 Low Fatality unlikely in overdose of mirtazapine alone. One death reported following overdose with 990mg.29 Sedation. Even large overdose may be asymptomatic. Tachycardia/ hypertension sometimes seen. Agitation. Moclobemide30,31 Low Unclear, but probably more than 8g. Fatality unlikely if moclobemide taken alone. Vomiting, sedation, disorientation Reboxetine4,32 Low Not known. Fatality unlikely in overdose of reboxetine alone. Sweating, tachycardia, changes in blood pressure SSRIs18,33–36 Low Unclear. Probably above 1–2g. Fatality unlikely if SSRI taken alone. Vomiting, tremor, drowsiness, tachycardia, ST depression. Seizures and QT prolongation possible. Citalopram most toxic of SSRIs in overdose28,37 (coma, seizures, arrhythmia); escitalopram is less toxic.38,39

Psychotropic drugs in special conditions CHAPTER 13 Table 13.1 (Continued) Drug or drug group Toxicity in overdose* Smallest dose likely to cause death Signs and symptoms of overdose Trazodone11,40–43 Low Unclear but probably more than 10g. Fatality unlikely in overdose of trazodone alone. Mortality rate about 1 in 10,000 overdose exposures.28 Drowsiness, nausea, hypotension, dizziness. Rarely QT prolongation, arrhythmia. Tricyclics17,19,20,44 (not lofepramine) High Around 500mg. Doses over 50mg/kg usually fatal. Sedation, coma, tachycardia, arrhythmia (QRS, QT prolongation), hypotension, seizures Venlafaxine4,45–48 (desvenlafaxine causes similar effects but may be less toxic49) Moderate Probably above 5g, but seizures may occur after ingestion of 1g Vomiting, sedation, tachycardia, hypertension, seizures, acidosis, hypoglycaemia. Rarely QT prolongation, arrhythmia, rhabdomyolysis. Very rarely cardiac arrest/MI, heart failure. Vilazodone50,51 Low Doses below 300mg are not fatal. No fatalities recorded in 714 overdose exposures.28 Drowsiness, agitation, vomiting, seizures Vortioxetine52 Low Unclear. An overdose of 250mg caused no symptoms. Nausea, somnolence, diarrhoea, pruritis Antipsychotics Amisulpride53–55 Moderate Around 16g QT prolongation, arrhythmia, cardiac arrest Aripiprazole56–58 Low Unclear. Fatality unlikely when taken alone. Sedation, lethargy, GI disturbance, drooling Asenapine59 Probably low Unclear. No deaths from overdose reported. Oral absorption very limited. Sedation, confusion, facial dystonia, benign ECG changes Brexpiprazole3 Probably low No information available Presumably agitation and nausea Butyrophenones60–62 (e.g. haloperidol) Moderate Haloperidol – probably above 500mg. Arrhythmia may occur at 300mg. Sedation, coma, dystonia, NMS, QT prolongation, arrhythmia Cariprazine63 Low EU SPC reports one (non-fatal) overdose of 48mg Sedation, low blood pressure Clozapine64,65 Moderate Around 2g, but very much lower in those not tolerant to its effects66 Lethargy, coma, tachycardia, hypotension, hypersalivation, pneumonia, seizures Iloperidone67–69 Probably moderate Unclear but probably more than 500mg. Potent effect on QT interval. Sedation, tachycardia, respiratory depression, hypotension likely Lumateperone70 Probably low No overdoses reported Presumably sedation and dizziness (Continued)

916 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 13 Table 13.1 (Continued) Drug or drug group Toxicity in overdose* Smallest dose likely to cause death Signs and symptoms of overdose Lurasidone71 Low Unclear. An overdose of 1360mg was not fatal.72 One study reported no deaths in 821 overdose exposures.28 Very limited information. Minimal effect on QT interval.

Olanzapine64,73–76 Moderate Unclear. Fatal outcomes have been reported for acute overdoses as low as 450mg. Lethargy, confusion, myoclonus, myopathy, hypotension, tachycardia, delirium. Possibly QT prolongation. Olanzapine and samidorphan3 Moderate Unclear. An overdose of 110mg/110mg was not fatal. Possible altered risk of fatality in opioid overdose due to opioid blockade. As for olanzapine Phenothiazines60,77–79 (e.g. chlorpromazine, fluphenazine) Moderate Chlorpromazine 5–10g Sedation, coma, tachycardia, arrhythmia, pulmonary oedema, hypotension, QT prolongation, seizures, dystonia, NMS Pimavanserin80 Not known No overdoses reported but pimavanserin prolongs QT interval in clinical doses. Probably QT prolongation and arrhythmia. ?Nausea, vomiting, confusion.81 Quetiapine28,64,82,83 Moderate Unclear. Probably more than 5g. Fatalities can occur in single substance overdose. Lethargy, delirium, tachycardia, QT prolongation, respiratory depression, hypotension, rhabdomyolysis, NMS Risperidone64,84,85 (assume the same for paliperidone) Low Unclear. Fatality rare in those taking risperidone or paliperidone alone. Lethargy, dystonia, tachycardia, changes in blood pressure, QT prolongation. Renal failure with paliperidone. Ziprasidone86–91 Low Around 10g. Fatality unlikely when taken alone. Drowsiness, lethargy, QT prolongation, Torsades de pointes Mood stabilisers Carbamazepine92–94 Moderate Around 20g, but seizures may occur at around 5g; an overdose of 44g was not fatal. Somnolence, coma, respiratory depression, ataxia, seizures, tachycardia, arrhythmia, electrolyte disturbance Lamotrigine95,96 Low At least 4g. Two deaths reported – one after 4g, the other after 7.5g, but overdoses of >40g have not proved fatal. Drowsiness, vomiting, ataxia, seizures, tachycardia, dyskinesia, QT prolongation Lithium97–99 Moderate Chronic toxicity probably more dangerous but single overdose is occasionally fatal. Six acute overdose deaths recorded in UK 2005–2012.100 Nausea, diarrhoea, tremor, confusion, weakness, lethargy, seizures, coma, cardiovascular collapse, bradycardia, arrhythmia, heart block, renal failure Valproate101–105 Moderate Unclear but probably more than 20g. Doses over 400mg/kg cause severe toxicity. Somnolence, coma, cerebral oedema, respiratory depression, blood dyscrasia, hypotension, hypothermia, seizures, electrolyte disturbance (hyperammonaemia)

Psychotropic drugs in special conditions CHAPTER 13 Table 13.1 (Continued) Drug or drug group Toxicity in overdose* Smallest dose likely to cause death Signs and symptoms of overdose Others Benzodiazepines106–108 Low Probably more than 100mg diazepam equivalents. Often involved in fatal mixed overdose but can be fatal when taken alone. Alprazolam is most toxic. Drowsiness, ataxia, nystagmus, respiratory dysarthria, depression, coma Buspirone28 Low Limited data. Deaths not reported. Not known Daridorexant3 Not known No overdoses reported. In trials, 200mg was maximum dose. Not known. Likely increased somnolence, muscle weakness, cataplexy-like symptoms, headache. Lemborexant3 Not known No overdoses reported. In trials, 75mg was maximum dose. Not known. Likely increased somnolence. Methadone109–111 High 20–50mg may be fatal in non-users. Co-ingestion of benzodiazepines increases toxicity. Drowsiness, nausea, hypotension, respiratory depression, coma, pulmonary oedema, constricted pupils, rhabdomyolysis Modafinil112–114 Low Unclear, but no fatalities reported. Overdoses of >6g have not caused death. Tachycardia, insomnia, agitation, anxiety, nausea, hypertension, dystonia Pitolisant115 Not known No overdoses reported. In trials, 216mg was maximum dose. Probably QT prolongation, headache, insomnia, irritability, nausea, abdominal pain Pregabalin116–118 Low Often involved in fatal mixed overdose (e.g. with opiates) but can be fatal when taken alone. One overdose of 8.4g caused unconsciousness and coma. May be asymptomatic. Sedation and coma may occur Solriamfetol3 Not known No overdoses reported. In trials, 1200mg was maximum dose. Probably hypertension, tachycardia, QT prolongation Suvorexant114,119 Low Unclear. No deaths reported.

An overdose of 100mg caused enhanced sedation. Sedation, vomiting Zolpidem120–122 Low Unclear. Probably >200mg, but an overdose of 9g was not fatal. Fatality rare in those taking zolpidem alone. Drowsiness, agitation, respiratory depression, tachycardia, coma, absent brainstem reflexes Zopiclone106,123,124 Low Unclear. Probably >100mg. Fatality rare in those taking zopiclone alone. Ataxia, nausea, diplopia, drowsiness, coma * High = less than 1 week’s supply likely to cause serious toxicity or death. Moderate = 1–4 weeks’ supply likely to cause serious toxicity or death. Low = death or serious toxicity unlikely even if more than 1 month’s supply taken. GI, gastrointestinal; IV, intravenous; MAOIs, monoamine oxidase inhibitors; MI, myocardial infarction; NMS, neuroleptic malignant syndrome; SPC, summary of product characteristics.

02 - References

References

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mirtazapine (Remeron) supratherapeutic ingestions. J Emerg Med 2008; 34:77–78. 27. Berling I, et al. Mirtazapine overdose is unlikely to cause major toxicity. Clin Toxicol (Phila) 2014; 52:20–24. 28. Nelson JC, et al. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. Poison Control Centers, 2000–2014. Am J Psychiatry 2017; 174:438–450. 29. Vignali C, et al. Mirtazapine fatal poisoning. Forensic Sci Int 2017; 276:e8–e12. 30. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. Psychopharmacology (Berl) 1992; 106 Suppl:S127–S129. 31. Myrenfors PG, et al. Moclobemide overdose. J Intern Med 1993; 233:113–115. 32. Baldwin DS, et al. Tolerability and safety of reboxetine. Rev Contemp Pharmacother 2000; 11:321–330. 33. Cheeta S, et al. Antidepressant--related deaths and antidepressant prescriptions in England and Wales, 1998–2000. Br J Psychiatry 2004; 184:41–47. 34. Barbey JT, et al. SSRI safety in overdose. J Clin Psychiatry 1998; 59 Suppl 15:42–48. 35. Jimmink A, et al. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit 2008; 30:365–371. 36. Tarabar AF, et al. Citalopram overdose: late presentation of torsades de pointes (TdP) with cardiac arrest. J Med Toxicol 2008; 4:101–105. 37. Kraai EP, et al. Citalopram overdose: a fatal case. J Med Toxicol 2015; 11:232–236. 38. Yilmaz Z, et al. Escitalopram causes fewer seizures in human overdose than citalopram. Clin Toxicol (Phila) 2010; 48:207–212. 39. van Gorp F, et al. Clinical and ECG effects of escitalopram overdose. Ann Emerg Med 2009; 54:404–408. 40. Gamble DE, et al. Trazodone overdose: four years of experience from voluntary reports. J Clin Psychiatry 1986; 47:544–546. 41. Martinez MA, et al. Investigation of a fatality due to trazodone poisoning: case report and literature review. J Anal Toxicol 2005; 29:262–268. 42. Dattilo PB, et al. Prolonged QT associated with an overdose of trazodone. J Clin Psychiatry 2007; 68:1309–1310. 43. Service JA, et al. QT prolongation and delayed atrioventricular conduction caused by acute ingestion of trazodone. Clin Toxicol (Phila) 2008; 46:71–73. 44. Caksen H, et al. Acute amitriptyline intoxication: an analysis of 44 children. Hum Exp Toxicol 2006; 25:107–110. 45. Howell C, et al. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. Br J Clin Pharmacol 2007; 64:192–197. 46. Hojer J, et al. Fatal cardiotoxicity induced by venlafaxine overdosage. Clin Toxicol (Phila) 2008; 46:336–337. 47. Taylor D. Venlafaxine and cardiovascular toxicity. BMJ 2010; 340:327.

 48. Bekka E, et al. Dose-related hypoglycemia in venlafaxine poisoning: a retrospective cohort study. Clin Toxicol (Phila) 2022; 60:1336–1344. 49. Cooper JM, et al. Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects. Clin Toxicol (Phila) 2017; 55:18–24. 50. Russell JL, et al. Pediatric ingestion of vilazodone compared to other selective serotonin reuptake inhibitor medications. Clin Toxicol (Phila) 2017; 55:352–356. 51. Allergan USA Inc. Highlights of prescribing information: VIIBRYD (vilazodone hydrochloride) tablets for oral use. 2023; https://www.allergan.com/assets/pdf/viibryd_pi. 52. Mazza MG, et al. Vortioxetine overdose in a suicidal attempt: a case report. Medicine (Baltimore) 2018; 97:e10788. 53. Isbister GK, et al. Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. Med J Aust 2006; 184:354–356. 54. Ward DI. Two cases of amisulpride overdose: a cause for prolonged QT syndrome. Emerg Med Australas 2005; 17:274–276. 55. Isbister GK, et al. Amisulpride overdose is frequently associated with QT prolongation and torsades de pointes. J Clin Psychopharmacol 2010; 30:391–395. 56. Lofton AL, et al. Atypical experience: a case series of pediatric aripiprazole exposures. Clin Toxicol (Phila) 2005; 43:151–153. 57. Carstairs SD, et al. Overdose of aripiprazole, a new type of antipsychotic. J Emerg Med 2005; 28:311–313. 58.

Forrester MB. Aripiprazole exposures reported to Texas poison control centers during 2002–2004. J Toxicol Environ Health A 2006; 69:1719–1726. 59. Taylor JE, et al. A case of intentional asenapine overdose. Prim Care Companion CNS Disord 2013; 15:PCC.13l01547. 60. Haddad PM, et al. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002; 62:1649–1671. 61. Levine BS, et al. Two fatalities involving haloperidol. J Anal Toxicol 1991; 15:282–284. 62. Henderson RA, et al. Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. Hum Exp Toxicol 1991; 10:59–62. 63. Recordati Pharmaceuticals Limited. Summary of product characteristics. Reagila (cariprazine) 1.5mg, 3mg, 4.5mg and 6mg hard capsules. 2024 (last accessed August 2024); https://www.medicines.org.uk/emc/product/9401/smpc. 64. Trenton A, et al. Fatalities associated with therapeutic use and overdose of atypical antipsychotics. CNS Drugs 2003; 17:307–324. 65. Flanagan RJ, et al. Suspected clozapine poisoning in the UK/Eire, 1992–2003. Forensic Sci Int 2005; 155:91–99. 66. Shigeev SV, et al. [Clozapine intoxication: theoretical aspects and forensic-medical examination]. Sud Med Ekspert 2013; 56:41–46. 67. Vigneault P, et al. Iloperidone (Fanapt®), a novel atypical antipsychotic, is a potent HERG blocker and delays cardiac ventricular repolarization at clinically relevant concentration. Pharmacol Res 2012; 66:60–65. 68. Vanda Pharmaceuticals Inc. Highlights of prescribing information: FANAPT® (iloperidone) tablets. 2021; https://www.fanapt.com/product/ pi/pdf/fanapt.pdf. 69. Amon J, et al. A case of iloperidone overdose in a 27-year-old man with cocaine abuse. SAGE Open Med Case Rep 2016; 4:2050313x16660485. 70. Vyas P, et al. An evaluation of lumateperone tosylate for the treatment of schizophrenia. Expert Opin Pharmacother 2020; 21:139–145. 71. CNX Therapeutics Ltd (formerly Sunovion Pharmaceuticals Europe). Summary of product characteristics. Latuda 18.5mg, 37mg and 74mg film-coated tablets. 2022 (last accessed December 2023); https://www.medicines.org.uk/emc/product/3299/smpc. 72. Molnar GP, et al. Acute lurasidone overdose. J Clin Psychopharmacol 2014; 34:768–770. 73. Chue P, et al. A review of olanzapine--associated toxicity and fatality in overdose. J Psychiatry Neurosci 2003; 28:253–261. 74. Waring WS, et al. Olanzapine overdose is associated with acute muscle toxicity. Hum Exp Toxicol 2006; 25:735–740. 75. Morissette P, et al. Olanzapine prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. J Psychopharmacol 2007; 21:735–741. 76. Krka UK Ltd. Summary of product characteristics. Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 20mg tablets. 2023 (last accessed August 2024); https://www.medicines.org.uk/emc/product/14727/smpc. 77. Buckley NA, et al. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. J Toxicol Clin Toxicol 1995; 33:199–204. 78. Li C, et al. Acute pulmonary edema induced by overdosage of phenothiazines. Chest 1992; 101:102–104. 79. Flanagan RJ. Fatal toxicity of drugs used in psychiatry. Hum Psychopharmacol 2008; 23 Suppl 1:43–51. 80. Sahli ZT, et al. Pimavanserin: novel pharmacotherapy for Parkinson’s disease psychosis. Exp Opin Drug Discov 2018; 13:103–110. 81. Vanover KE, et al. Pharmacokinetics, tolerability, and safety of ACP-103 following single or multiple oral dose administration in healthy volunteers. J Clin Pharmacol 2007; 47:704–714. 82. Ngo A, et al. Acute quetiapine overdose in adults: a 5-year retrospective case series. Ann Emerg Med 2008; 52:541–547. 83. Bertol E, et al. Overdose of quetiapine – a case report with QT prolongation. Toxics 2021; 9:339. 84. Liang CS, et al. Acute renal failure after paliperidone overdose: a case report. J Clin Psychopharmacol 2012; 32:128. 85. Lapid MI, et al. Acute dystonia associated with paliperidone overdose. Psychosomatics 2011; 52:291–294. 86. Gomez-Criado MS, et al. Ziprasidone overdose: cases recorded in the database of Pfizer-Spain and literature review. Pharmacotherapy 2005; 25:1660–1665. 87. Arbuck DM. 12,800-mg ziprasidone overdose without significant ECG

changes. Gen Hosp Psychiatry 2005; 27:222–223. 88. Insa Gomez FJ, et al. Ziprasidone overdose: cardiac safety. Actas Esp Psiquiatr 2005; 33:398–400. 89. Klein-Schwartz W, et al. Prospective observational multi-poison center study of ziprasidone exposures. Clin Toxicol (Phila) 2007; 45:782–786. 90. Tan HH, et al. A systematic review of cardiovascular effects after atypical antipsychotic medication overdose. Am J Emerg Med 2009; 27:607–616. 91. Alipour A, et al. Torsade de pointes after ziprasidone overdose with coingestants. J Clin Psychopharmacol 2010; 30:76–77.

 92. Spiller HA. Management of carbamazepine overdose. Pediatr Emerg Care 2001; 17:452–456. 93. Schmidt S, et al. Signs and symptoms of carbamazepine overdose. J Neurol 1995; 242:169–173. 94. Pap C, et al. Severe carbamazepine overdose associated with shock, repeated seizures and extreme high serum concentrations treated by extended intermittent hemodiafiltration. 42nd International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 24–27 May 2022, Tallinn, Estonia. Clin Toxicol 2022; 60:abstract 145. 95. Alabi A, et al. Safety profile of lamotrigine in overdose. Ther Adv Psychopharmacol 2016; 6:369–381. 96. Alyahya B, et al. Acute lamotrigine overdose: a systematic review of published adult and pediatric cases. Clin Toxicol (Phila) 2018; 56:81–89. 97. Tuohy K, et al. Acute lithium intoxication. Dial Transplant 2003; 32:478–481. 98. Chen KP, et al. Implication of serum concentration monitoring in patients with lithium intoxication. Psychiatry Clin Neurosci 2004; 58:25–29. 99. Offerman SR, et al. Hospitalized lithium overdose cases reported to the California Poison Control System. Clin Toxicol (Phila) 2010; 48:443–448. 100. Ferrey AE, et al. Relative toxicity of mood stabilisers and antipsychotics: case fatality and fatal toxicity associated with self-poisoning. BMC Psychiatry 2018; 18:399. 101. Isbister GK, et al. Valproate overdose: a comparative cohort study of self poisonings. Br J Clin Pharmacol 2003; 55:398–404. 102. Spiller HA, et al. Multicenter case series of valproic acid ingestion: serum concentrations and toxicity. J Toxicol Clin Toxicol 2000; 38:755–760. 103. Sztajnkrycer MD. Valproic acid toxicity: overview and management. J Toxicol Clin Toxicol 2002; 40:789–801. 104. Eyer F, et al. Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. J Clin Psychopharmacol 2005; 25:376–380. 105. Robinson P, et al. Severe hypothermia in association with sodium valproate overdose. NZ Med J 2005; 118:U1681. 106. Reith DM, et al. Comparison of the fatal toxicity index of zopiclone with benzodiazepines. J Toxicol Clin Toxicol 2003; 41:975–980. 107. Isbister GK, et al. Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol 2004; 58:88–95. 108. Kleinman RA, et al. Benzodiazepine-involved overdose deaths in the USA: 2000–2019. J Gen Intern Med 2022; 37:2103–2109. 109. Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction 2004; 99:686–696. 110. Caplehorn JR, et al. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. Aust NZ J Public Health 2002; 26:358–362. 111. Martindale Pharma an Ethypharm Group Company. Summary of product characteristics. Methadone 5mg tablets. 2023; (last accessed August 2024) https://www.medicines.org.uk/emc/product/11838/smpc. 112. Spiller HA, et al. Toxicity from modafinil ingestion. Clin Toxicol (Phila) 2009; 47:153–156. 113. Carstairs SD, et al. A retrospective review of supratherapeutic modafinil exposures. J Med Toxicol 2010; 6:307–310. 114. Russell J, et al. Retrospective assessment of toxicity following exposure to Orexin pathway modulators modafinil and suvorexant. Toxicol Commun 2019; 3:33–36. 115. Bioprojet UK Limited. Summary of product characteristics. Wakix 18 mg film-coated tablets (pitolisant). 2023; https://www.medicines.org. uk/emc/product/14454/smpc. 116. Miljevic C, et al. A case of pregabalin

intoxication. Psychiatriki 2012; 23:162–165. 117. Wood DM, et al. Significant pregabalin toxicity managed with supportive care alone. J Med Toxicol 2010; 6:435–437. 118. Kriikku P, et al. Pregabalin and gabapentin in non-opioid poisoning deaths. Forensic Sci Int 2021; 324:110830. 119. Trautman W, et al. Orexin antagonist overdose should not keep you up at night: mild toxicity in a large suvorexant overdose. Clinical Toxicology 2023; 61 Suppl 2: abstract 205. http://doi.org/10.1080/15563650.2023.2233835. 120. Gock SB, et al. Acute zolpidem overdose – report of two cases. J Anal Toxicol 1999; 23:559–562. 121. Garnier R, et al. Acute zolpidem poisoning – analysis of 344 cases. J Toxicol Clin Toxicol 1994; 32:391–404. 122. De Donatis D, et al. Extremely high-dosage zolpidem poisoning with favorable outcome. J Clin Psychopharmacol 2021; 41:222–223. 123. Pounder D, et al. Zopiclone poisoning. J Anal Toxicol 1996; 20:273–274. 124. Bramness JG, et al. Fatal overdose of zopiclone in an elderly woman with bronchogenic carcinoma. J Forensic Sci 2001; 46:1247–1249.

03 - Driving and psychotropic medicines

Driving and psychotropic medicines

04 - Effects of mental illness

Effects of mental illness

05 - Psychiatric medicines, driving and UK law

Psychiatric medicines, driving and UK law

Psychotropic drugs in special conditions CHAPTER 13 Driving and psychotropic medicines Everyone has a legal duty to drive safely and in almost all countries drivers are legally responsible for accidents they cause, whether or not they are under the influence of drugs or alcohol.1 Many factors have been shown to affect driving performance. These include age, gender, personality, physical and mental state and being under the influence of alcohol, prescribed medicines, street drugs or over-the-counter medicines.2,3 Studying the effects of any of these individual factors in isolation is extremely difficult. Some studies have attempted to categorise medicinal drugs according to how they affect driving performance,4 and some have assessed the effect of medication on tests such as response time and attention,5 but these tests do not directly measure ability to drive. As many as 10% of people killed or injured in road traffic accidents (RTAs) are taking psychotropic medication (Table 13.2).5 Patients with personality disorders and alcoholism have the highest rates of motoring offences and are more likely to be involved in accidents.5 In most countries, people whose driving ability may be impaired through their illness or prescribed medication are required to inform their motor insurer. Failure to do so is considered to be ‘withholding a material fact’ and may render the insurance policy void. Effects of mental illness In the UK, severe mental disorder is a so-called ‘prescribed disability’ for the purposes of the Road Traffic Act 1988.6 Regulations define mental disorder as including mental illness, arrested or incomplete development of the mind, psychopathic disorder or severe impairment of intelligence or social functioning. There is an assessing fitness to drive guide.7 Among physical conditions commonly seen in mental illness, licence restrictions may also apply to people with diabetes, particularly if treated with insulin or if there are established micro- or macrovascular complications. In the USA, regulations related to driving and mental health disorders vary somewhat from state to state (see US Department of Motor Vehicles website [www.dmvusa.com] for each state). Many people with early dementia are capable of driving safely.8,9 In the UK, all drivers with new diagnoses of Alzheimer’s disease and other dementias must notify the Driver and Vehicle Licensing Agency (DVLA).8 The doctor may need to make an immediate decision on safety to drive and ensure that the DVLA is notified.10 There are no data to support ongoing driving assessments as a way of maintaining driving ability or improving road safety of drivers with dementia.11,12 In the USA, some states mandate that doctors report a diagnosis of dementia but in others the issue may

only arise on licence renewal. Interestingly, states in which reporting is mandatory have a relatively lower rate of dementia diagnosis.13 Psychiatric medicines, driving and UK law Most countries prohibit the use of a range of illicit substances when driving. In the UK drug–driving law gives threshold blood concentration for eight drugs associated with illicit use (with a zero tolerance approach – the threshold is set to reveal any recent use) and eight medicinal drugs.14 For the latter group, Table 13.3 gives the legal limit and expected plasma concentrations in clinical use.

922 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 13 Table 13.2 Psychotropics and driving. Drug group Effect Alcohol Alcohol causes sedation and impaired co-ordination, vision, attention and information processing. Alcohol-dependent drivers are twice as likely to be involved in RTAs and offences than licensed drivers as a whole,5 and a third of all fatal RTAs involve alcohol-dependent drivers.5 Young drivers who use alcohol in combination with illicit drugs are particularly high risk.15,16 Antiseizure medications Initial, dose-related adverse effects may affect driving ability (e.g. diplopia, ataxia and sedation). In most countries there are strict rules regarding epilepsy and driving that over-ride considerations of medication effects. Carbamazepine has minor adverse effects on driving.17,18 Lamotrigine may have limited effects on driving ability.19 Valproate may not increase the risk of RTAs.20 Antidepressants People who are prescribed an antidepressant have an increased risk of being involved in an RTA.21 SSRIs may have some advantages over TCAs but driving ability is still diminished compared with healthy individuals,22 suggesting that depression itself may make a major contribution.23,24 SSRIs tend not to impair driving in healthy volunteers.25–27 In remitted patients on SSRIs, driving performance may likewise not be impaired.28 Initiation effects caused by mirtazapine diminish to an extent when it is given as a single dose at night but many people experience substantial hangover which can impair driving.29 Effects may disappear in chronic treatment.30 Trazodone also appears to impair driving ability31 – a review of 27 studies suggested that only trazodone among antidepressants afforded an increased risk of RTAs.32 Agomelatine and venlafaxine may actually improve driving performance.33 Vortioxetine has no effect.30 Intranasal esketamine seems to have no effect on driving ability 8 hours post-dose34 or the day after.35 Antipsychotics Sedation and EPSEs can impair co-ordination and response time.2 A high proportion of patients treated with antipsychotics may have an impaired ability to drive.36,37 One study found patients with schizophrenia taking atypical antipsychotics or clozapine performed better in tests of skills related to car driving ability than patients with schizophrenia taking FGAs,38 but 25% of all patients were severely impaired with respect to driving skills. SGAs seem to cause less impairment than FGAs39 and are preferred. Hypnotics and anxiolytics Benzodiazepines cause sedation and impairment of attention, information processing, memory and motor co-ordination, and along with opiates are the medicines most frequently implicated in RTAs.32,40 When used as anxiolytics and hypnotics, benzodiazepines, zopiclone and zolpidem are associated with an increased risk of RTAs.40 There is some gender variation in the pharmacokinetics of zolpidem with females having higher drug plasma concentrations than males for any given dose; the driving ability of females may therefore be particularly impaired.3 Zolpidem may additionally be associated with automatism and ‘sleep driving’.41 Zaleplon and the newer hypnotics acting at melatonin or serotonin receptors have not been found to have any negative residual effects on driving ability.42,43 Orexin receptor antagonists (suvorexant and lemborexant), available in some countries, appear not to impair driving the day after being taken.44,45 There is some evidence that daridorexant impairs driving ability during the first few days of use.46 Lithium Lithium may impair visual adaptation to the dark2 but the implications for driving safety are unknown. Many patients treated with lithium can be

shown to be unfit to drive19 although the exact contribution of lithium is difficult to determine. Elderly people who take lithium may be at increased risk of being involved in an injurious RTA.47 Lithium causes a greater degree of driving impairment than lamotrigine.39 Methylphenidate Some studies have demonstrated that reaction time is longer in patients with ADHD, which may in turn be associated with increased driving risks.48 Other studies have found that methylphenidate improved driving performance in adults with ADHD,49 again suggesting that illness may make a bigger contribution to fitness to drive than the specific pharmacology of the treatment.49 Opioids Opioids have major adverse effect on the risk of RTAs.50 Buprenorphine and methadone reduce driving ability at low doses in non-addicts.51 EPSEs, extrapyramidal side effects; RTAs, road traffic accidents; TCAs, tricyclic antidepressants.

06 - Other medicines

Other medicines

07 - UK DVLA

UK DVLA

Psychotropic drugs in special conditions CHAPTER 13 In regards to methadone, doses of up to 80mg a day generally give plasma levels below the UK legal limit.61 The legal limits listed here apply only to those who are lawfully prescribed the drug in question – the driver may be subject to prosecution if it can be proved the drugs were taken illicitly. Other medicines Many psychotropics can impair alertness, concentration and driving performance. Medicines that block H1, α1--adrenergic or cholinergic receptors may be particularly problematic. Sedative antihistamines used in mental health conditions (promethazine, diphenhydramine) very probably impair driving ability.62 Effects are particularly marked at the start of treatment and after increasing the dose. Drivers must be made aware of any potential for impairment and are advised to evaluate their driving performance at these times. They must stop driving if adversely affected.63 The use of alcohol will further increase any impairment. Some antipsychotics and antidepressants lower the seizure threshold. In the UK, the DVLA advises this is taken into consideration when prescribing for a driver. Medication-induced sedation Many psychotropics are sedating. The more sedating a medicine is, the more likely it is to impair driving ability. Other medicines, either prescribed or bought over the counter, may also be sedative and/or affect driving ability (e.g. antihistamines5). One study found that 89% of patients taking other psychotropics in addition to antidepressants failed a battery of ‘fitness to drive’ tests.64 Since the degree of sedation any individual will experience is very difficult to predict, patients prescribed sedating medicines should be advised not to drive if they feel sedated. In the UK it is the responsibility of the driver to ensure they are fit to drive. UK DVLA Duty of the driver In the UK it is the legal responsibility of the licence holder or applicant to notify the DVLA of any medical condition that may affect safe driving. A list of relevant medical conditions can be found in the DVLA assessing fitness to drive guide.65 Table 13.3 Benzodiazepines concentration in normal dosing and the UK legal limit. Drug/daily dose Range of concentrations reported Legal limit Clonazepam 0.5–6.0mg52,53 5–80mcg/L 50mcg/L Diazepam 5–30mg54 50–1000mcg/L 550mcg/L Flunitrazepam 0.5–2.0mg55,56 10–20mcg/L 300mcg/L Lorazepam 1–4mg57,58 10–70mcg/L 100mcg/L Oxazepam 15–30mg59 250–600mcg/L 300mcg/L Temazepam 10–20mg60 200–900mcg/L 1000mcg/L

08 - UK General Medical Council guidelines for pre

UK General Medical Council guidelines for prescribers66

09 - References

References

924 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 13 Duty of the prescriber Make sure the patient understands that their condition may impair their ability to drive. If the patient is incapable of understanding, notify the DVLA immediately. Explain to the patient that they have a legal duty to inform the DVLA. Note that the DVLA guidance specifies that patients under Section 17 of the 1983 Mental Health Act must be able to satisfy the standards of fitness for their respective conditions and be free from any effects of medication that would affect driving adversely, before resuming driving. Very few patients will fulfil these criteria. UK General Medical Council guidelines for prescribers66 ■ ■Patients who disagree with the diagnosis or the effect of the condition on their ability to drive should seek a second opinion and refrain from driving until this has been obtained. ■ ■If the patient continues to drive while unfit, you should make every reasonable effort to persuade them to stop. This may include telling their next of kin if they agree you may do so. ■ ■If they continue to drive, inform the DVLA. Tell the patient you are going to do this and write to the patient to confirm you have done so. Document the advice given clearly in the patient’s notes. References

1. Annas GJ. Doctors, drugs, and driving – tort liability for patient-caused accidents. N Engl J Med 2008; 359:521–525.
2. Metzner JL, et al. Impairment in driving and psychiatric illness. J Neuropsychiatry Clin Neurosci 1993; 5:211–220.
3. Farkas RH, et al. Zolpidem and driving impairment – identifying persons at risk. N Engl J Med 2013; 369:689–691.
4. Ravera S, et al. A European approach to categorizing medicines for fitness to drive: outcomes of the DRUID project. Br J Clin Pharmacol 2012; 74:920–931.
5. Noyes R, Jr. Motor vehicle accidents related to psychiatric impairment. Psychosomatics 1985; 26:569–580.
6. The National Archives. Road Traffic Act 1991. 1991; http://www.legislation.gov.uk/ukpga/1991/40/contents.
7. Driver and Vehicle Licensing Agency. Guidance: assessing fitness to drive: a guide for medical professionals. 2016 (last updated February 2024, last checked May 2024); https://www.gov.uk/government/publications/assessing-fitness-to-drive-a-guide-for--medical-professionals.
8. Driver and Vehicle Licensing Agency. Assessing fitness to drive – a guide for medical professionals. 2016 (last updated 2018, last accessed May 2024). https://www.gov.uk/dvla/fitnesstodrive.
9. Piersma D, et al. Prediction of fitness to drive in patients with Alzheimer’s dementia. PLoS One 2016; 11:e0149566.

10. Breen DA, et al. Driving and dementia. BMJ 2007; 334:1365–1369.
11. Martin AJ, et al. Driving assessment for maintaining mobility and safety in drivers with dementia. Cochrane Database Syst Rev 2013; 8:CD006222.
12. Toups R, et al. Driving performance in older adults: current measures, findings, and implications for roadway safety. Innov Aging 2022; 6:igab051.
13. Jun H, et al. State Department of Motor Vehicles reporting mandates of dementia diagnoses and dementia underdiagnosis. JAMA Network Open 2024; 7:e248889.
14. Department for Transport. Changes to drug driving law. 2013 (last updated August 2017, last accessed May 2024); https://www.gov.uk/ government/collections/drug-driving.
15. Biecheler MB, et al. SAM survey on 'drugs and fatal accidents': search of substances consumed and comparison between drivers involved under the influence of alcohol or cannabis. Traffic Inj Prev 2008; 9:11–21.
16. Oyefeso A, et al. Fatal injuries while under the influence of psychoactive drugs: a cross--sectional exploratory study in England. BMC Public Health 2006; 6:148.
17. Kaussner Y, et al. Effects of oxcarbazepine and carbamazepine on driving ability: a double-blind, randomized crossover trial with healthy volunteers. Psychopharmacology (Berl) 2010; 210:53–63.
18. Ramaekers G, et al. A comparative study of the effects of carbamazepine and the NMDA receptor antagonist remacemide on road tracking and car-following performance in actual traffic. Psychopharmacology (Berl) 2002; 159:203–210.
19. Segmiller FM, et al. Driving ability according to German guidelines in stabilized bipolar I and II outpatients receiving lithium or lamotrigine. J Clin Pharmacol 2013; 53:459–462.

Psychotropic drugs in special conditions CHAPTER 13 20. Bramness JG, et al. An increased risk of road traffic accidents after prescriptions of lithium or valproate? Pharmacoepidemiol Drug Saf 2009; 18:492–496. 21. Olesen AV, et al. Use of psychotropic medication and risk of road traffic crashes: a registry-based case–control study in Denmark, 1996–2018. Psychopharmacology (Berl) 2022; 239:2537–2546. 22. Brunnauer A, et al. The effects of most commonly prescribed second generation antidepressants on driving ability: a systematic review: 70th birthday Prof. Riederer. J Neural Transm 2013; 120:225–232. 23. Bramness JG, et al. Minor increase in risk of road traffic accidents after prescriptions of antidepressants: a study of population registry data in Norway. J Clin Psychiatry 2008; 69:1099–1103. 24. Verster JC, et al. Psychoactive medication and traffic safety. Int J Environ Res Public Health 2009; 6:1041–1054. 25. Iwamoto K, et al. The effects of acute treatment with paroxetine, amitriptyline, and placebo on driving performance and cognitive function in healthy Japanese subjects: a double-blind crossover trial. Hum Psychopharmacol 2008; 23:399–407. 26. Ridout F, et al. A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance. Hum Psychopharmacol 2003; 18:261–269. 27. Wingen M, et al. Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: a crossover trial. J Clin Psychiatry 2005; 66:436–443. 28. Miyata A, et al. Driving performance of stable outpatients with depression undergoing real-world treatment. Psychiatry Clin Neurosci 2018; 72:399–408. 29. Verster JC, et al. Mirtazapine as positive control drug in studies examining the effects of antidepressants on driving ability. Eur J Pharmacol 2015; 753:252–256. 30. Theunissen EL, et al. A randomized trial on the acute and steady-state effects of a new antidepressant, vortioxetine (Lu AA21004), on actual driving and cognition. Clin Pharmacol Ther 2013; 93:493–501. 31. Ip EJ, et al. The effect of trazodone on standardized field sobriety tests. Pharmacotherapy 2013;

33:369–374. 32. Rudisill TM, et al. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. Accid Anal Prev 2016; 96:255–270. 33. Brunnauer A, et al. Driving performance and psychomotor function in depressed patients treated with agomelatine or venlafaxine. Pharmacopsychiatry 2015; 48:65–71. 34. Van de Loo A, et al. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double- blind, placebo-controlled study. Psychopharmacology (Berl) 2017; 234:3175–3183. 35. Dijkstra FM, et al. The effects of intranasal esketamine on on-road driving performance in patients with major depressive disorder or persistent depressive disorder. J Psychopharmacol 2022; 36:614–625. 36. Grabe HJ, et al. The influence of clozapine and typical neuroleptics on information processing of the central nervous system under clinical conditions in schizophrenic disorders: implications for fitness to drive. Neuropsychobiology 1999; 40:196–201. 37. Wylie KR, et al. Effects of depot neuroleptics on driving performance in chronic schizophrenic patients. J Neurol Neurosurg Psychiatry 1993; 56:910–913. 38. Brunnauer A, et al. The impact of antipsychotics on psychomotor performance with regards to car driving skills. J Clin Psychopharmacol 2004; 24:155–160. 39. Brunnauer A, et al. Driving performance under treatment of most frequently prescribed drugs for mental disorders: a systematic review of patient studies. Int J Neuropsychopharmacol 2021; 24:679–693. 40. Dassanayake T, et al. Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf 2011; 34:125–156. 41. Poceta JS. Zolpidem ingestion, automatisms, and sleep driving: a clinical and legal case series. J Clin Sleep Med 2011; 7:632–638. 42. Verster JC, et al. Hypnotics and driving safety: meta-analyses of randomized controlled trials applying the on-the-road driving test. Curr Drug Saf 2006; 1:63–71. 43. Torres R, et al. Simulated driving performance in healthy adults after night-time administration of 20 mg tasimelteon. J Sleep Res 2022; 31:e13430. 44. Vermeeren A, et al. On-the-road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers. Sleep 2019; 42:zsy260. 45. Vermeeren A, et al. On-the-road driving performance the morning after bedtime use of suvorexant 15 and 30 mg in healthy elderly. Psychopharmacology (Berl) 2016; 233:3341–3351. 46. Muehlan C, et al. Driving performance after bedtime administration of daridorexant, assessed in a sensitive simulator. Clin Pharmacol Ther 2022; 111:1334–1342. 47. Etminan M, et al. Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. BMJ 2004; 328:558–559. 48. Hashemian F, et al. A comparison of the effects of reboxetine and placebo on reaction time in adults with attention deficit-hyperactivity disorder (ADHD). Daru 2011; 19:231–235. 49. Classen S, et al. Evidence-based review on interventions and determinants of driving performance in teens with attention deficit hyperactivity disorder or autism spectrum disorder. Traffic Inj Prev 2013; 14:188–193. 50. Hetland A, et al. Medications and impaired driving. Ann Pharmacother 2014; 48:494–506. 51. Strand MC, et al. Pharmacokinetics of single doses of methadone and buprenorphine in blood and oral fluid in healthy volunteers and correlation with effects on psychomotor and cognitive functions. J Clin Psychopharmacol 2019; 39:489–493. 52. Sjo O, et al. Pharmacokinetics and side-effects of clonazepam and its 7-amino-metabolite in man. Eur J Clin Pharmacol 1975; 8:249–254.

 53. Berlin A, et al. Pharmacokinetics of the anticonvulsant drug clonazepam evaluated from single oral and intravenous doses and by repeated oral administration. Eur J Clin Pharmacol 1975; 9:155–159. 54. Rutherford DM, et al. Plasma concentrations of diazepam and desmethyldiazepam during chronic diazepam therapy. Br J Clin Pharmacol 1978; 6:69–73. 55. Wickstrom E, et al. Pharmacokinetic and clinical observations on prolonged administration of flunitrazepam. Eur J Clin Pharmacol 1980;

17:189–196. 56. Mattila MA, et al. Flunitrazepam: a review of its pharmacological properties and therapeutic use. Drugs 1980; 20:353–374. 57. Greenblatt DJ, et al. Single- and multiple-dose kinetics of oral lorazepam in humans: the predictability of accumulation. J Pharmacokinet Biopharm 1979; 7:159–179. 58. Greenblatt DJ, et al. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci 1982; 71:248–252. 59. Smink BE, et al. The concentration of oxazepam and oxazepam glucuronide in oral fluid, blood and serum after controlled administration of 15 and 30 mg oxazepam. Br J Clin Pharmacol 2008; 66:556–560. 60. Greenblatt DJ, et al. Clinical pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet 1983; 8:233–252. 61. Ferrari A, et al. Methadone – metabolism, pharmacokinetics and interactions. Pharmacol Res 2004; 50:551–559. 62. European Monitoring Centre for Drugs and Drug Addiction. Drug use, impaired driving and traffic accidents. 2014 (last accessed May 2024); http://bookshop.europa.eu/uri?target=EUB:NOTICE:TDXD14016:EN:HTML. 63. Department of Transport. Medication and road safety: a scoping study. Road Safety Research Report No. 116. 2010 (last accessed May 2024); https://webarchive.nationalarchives.gov.uk/20101007211118/http://www.dft.gov.uk/pgr/roadsafety/research/rsrr/theme3/report16 findings.pdf. 64. Grabe HJ, et al. The influence of polypharmacological antidepressive treatment on central nervous information processing of depressed patients: implications for fitness to drive. Neuropsychobiology 1998; 37:200–204. 65. Driver and Vehicle Licensing Agency. At a glance guide to the current medical standards of fitness to drive. 2013 (last updated February 2024, last checked May 2024); https://www.gov.uk/government/publications/at-a-glance. 66. General Medical Council. Good practice in prescribing and managing medicines and devices. 2021 (last accessed May 2024); https://www. gmc-uk.org/guidance/ethical_guidance/14316.asp.