diazepam is ineffective or poorly tolerated include baclofen or sodium valproate but benefit may be less evident. There have been isolated anecdotal reports of improvement with vigabatrin, tiagabine, and gabapentin. Antiepileptics or baclofen may sometimes be combined with benzodiazepines. Cortico-steroids may be of benefit, although any response may take several weeks, and the chronic nature of the disorder and the high incidence of type 1 diabetes mellitus may make their use problematic. Other attempts at immunomodulation such as plasmapheresis have yielded variable results; there is some evidence of the efficacy of immunoglobulins.

References.

- 1. Toro C, et al. Stiff-man syndrome. Semin Neurol 1994; 14:
- 2. Gerhardt CL. Stiff-man syndrome revisited. South Med J 1995; 88: 805-808
- 3. Stayer C, Meinck H-M. Stiff-man syndrome: an overview. Neurologia 1998; 13: 83-8.
- 4. Levy LM, et al. The stiff-person syndrome an autoimmune disorder affecting neurotransmission of γ -aminobutyric acid. *Ann Intern Med* 1999; **131:** 522–30.
- 5. Meinck H-M. Stiff man syndrome. CNS Drugs 2001; 15:
- Dalakas MC, et al. High-dose intravenous immune globu stiff-person syndrome. N Engl J Med 2001; 345: 1870–6.
- Vasconcelos OM, Dalakas MC. Stiff-person syndrome. Curr Treat Options Neurol 2003; 5: 79–90.

Nausea and vomiting. Benzodiazepines, particularly lorazepam, are used as adjuncts in the management of nausea and vomiting induced by cancer chemotherapy (p.1700), particularly anticipatory emesis.

Premenstrual syndrome. For mention of the limited role of benzodiazepines in the management of premenstrual syndrome,

Schizophrenia. Benzodiazepines may be useful adjuncts to antipsychotics in the initial management of schizophrenia (p.955).

Sleep-associated movement disorders. Sleep-associated movement disorders (p.958) rarely require treatment other than the symptomatic treatment of sleep-related medical problems. A number of such conditions, including restless legs syndrome, sleepwalking, and night terrors, have been reported to respond to benzodiazepines. Although the muscle relaxant and anxiolytic action of a benzodiazepine can be helpful in bruxism (teeth grinding) it has been recommended that they should only be prescribed on a short-term basis during the acute phase.

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100**:

Substance dependence. The benzodiazepines are used in the management of symptoms of alcohol withdrawal (p.1626), of opioid withdrawal (p.101), and of cocaine withdrawal (p.1860).

Vertigo. Although intravenous diazepam has been used to abort acute attacks of vertigo of peripheral origin (p.565), it can prolong compensation and recovery from vestibular lesions.1

Rascol O, et al. Antivertigo medications and drug-induced vertigo: a pharmacological review. Drugs 1995; 50: 777–91.

Preparations

BP 2008: Diazepam Injection; Diazepam Oral Solution; Diazepam Rectal Diazepam Tablets:

USP 31: Diazepam Tablets, Diazepam Extended-release Capsules; Diazepam Injection; Diazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)

Arg.: Cuadel; Daiv, Dezepan; Diactal; Dipezona; Fabotranil; Glutasedan†; Lembrol; Pildan; Pildex T; Rupediz†; Saromet; Timab; Valium; Austral.: Antenex; Ducene; Valium; Valpam; Austral: Gewacalım; Psychopax; Stesolid; Umbrium; Valium; Valpam; Austral: Gewacalım; Psychopax; Stesolid; Umbrium; Valium; Valpam; Austral: Ansilive; Calmociteno; Compaz; Diazefast; Diazepan†; Dienpax; Kiatrium; Letansil; Menostress; Noan; Pazolini; Relapax; Somaplus; Uni Diazepax; Valium; Valiy; Vetansil; Canda: Diastat; Diazemuls; Novo-Dipam; Valium; Chille: Cardiosedantol; Elongal†; Pacinax; Cz.: Apaurin; Seduxen†; Stesolid; Denm: Apozepam; Hexalid; Stesolid; Valaxona; Valium; Fin.: Diapam; Medipam; Stesolid; Fin.: Novazam†; Valium; Ger.: Diazep; Faustan; Lamra; Stesolid; Tranquase†; Valiquid; Valium; Valocordin-Diazepam; Gr.: Apollonset; Atarviton; Stedon; Stesolid; Hong Kong; Diazemuls; Kratium; Stesolid; Valpam; Hung.: Seduxen; Stesolid; Hong Kong; Diazemuls; Stesolid; Valpam; Hung.: Seduxen; Stesolid; Ind.: Aniscialm; Diazemuls; Stesolid; Valium; Inde.: Assival; Diaz; Stesolid; Ital.: Aliseum; Ansiolin; Diazemuls; Stesolid; Valium; Mex.: Alboral; Arzepam; AT-V†; Benzyme; Diacepam†; Diapanl†; Diatex†; Freudal†; Ifa-Fonal; Laxyl; Onapan; Ortopsique; Prizem†; Relazepam; Tandial†; Valium; Zepan; Zepart†; Neth.: Diazemuls; Propam; Stesolid; Philipp: Nixtensyn; Trankli; Valium; Pol.: Relanium; Relsed; Port.: Bialzepam; Benzoni; Valium; Mex.: Alpaunin (Pena-Nywl); Relium (Pewywl); Seduxen (Ceyxcen); S.Afr.: Benzopin; Betapam; Calmpose; Doval; Pax, Tranjet; Valium; Singopore: Diapine; Diapo; Stesolid; Spalin: Aneuro; Aspaserine B6 Tranq†; Complutine; Gobanal; Pacinum; Sico Relax†; Stesolid; Valium; Singopore: Diapine; Diapo; Betapam; Calmpose; Doval; Pax, Tranjet; Valium; Singopore: Diapine; Diapo; Betapam; Diapine; Diapine; Diapo; Diapan; Diapine; Diapo; Stesolid; Spalin: Aneuro; Aspaserine B6 Tranq†; Complutine; Gobanal; Pacinum; Sico Relax†; Stesolid; Valium; Thal: Azepam; Diano;

Stesolid; Tensium; Valclair; **USA:** Diastat; Valium; **Venez.:** Talema; Telsomet; Valium;

etţ; vallumţ.

Multi-ingredient: Arg.: Arnol; Dafne; Dislembralţ; Faradil; Pasminox Somatico; Pildexţ; Tratobes; Austria: Betamed; Harmomed; Braz.: Dialudon; Dobesixţ; Moderine; Chile: Calmosedar; Diapam; Mesolonaţ; Multisedil; Promidar; Sedantol; Sedilit; Cz.: Seduxen RGţ; Fin.: Gastrodyn comp; Relapami; Vertipam; Gr.: Distedon; India: Depsonil-DZ; Dericip Plus; Indon: Analsik; Cetalgin; Danalgin; Hedis; Neurodial; Neurovai; Opineuron; Proneuron; Ital.: Gamibetal Plus; Spasen Somatico; Spasmeridan; Spasmomen Somatico; Valpinax; Valtrax; Mex.: Adepsique; Esbelaps; Numencial; Qual; Redotex; Port.: Gamibetal Compositumţ; Rus.: Reladom (Реладорм); Spain: Ansium; Tepazepam; Tropargal; Turk.: Spazmo-Valibini, USA: Emergent-Ez; Venez.: Tepazepamţ.

Dichloralphenazone (BAN)

Dicloralfenazona: Dikloraalifenatsoni: Dikloralfenazon.

 $C_{15}H_{18}CI_6N_2O_5 = 519.0.$ CAS — 480-30-8. ATC — N05CC04. ATC Vet — QN05CC04.

$$\begin{bmatrix} \mathrm{CCI_3-CH(OH)_2} \end{bmatrix}_2 \quad \begin{matrix} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ &$$

Pharmacopoeias. In US.

USP 31 (Dichloralphenazone). A white microcrystalline powder with a slight odour characteristic of cloral hydrate. Freely soluble in water, in alcohol, and in chloroform; soluble in dilute acids. It is decomposed by dilute alkalis liberating chloroform.

Dichloralphenazone dissociates when given, to form cloral hydrate and phenazone. It has the general properties of cloral hydrate (p.979), although it is less likely to cause gastric irritation after oral doses. Phenazone-induced skin eruptions may, however, occur (see p.116). Dichloralphenazone is used in some countries in combination preparations mainly for the treatment of tension and vascular headaches.

Porphyria. Dichloralphenazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric pa-

Preparations

USP 31: Isometheptene Mucate, Dichloralphenazone, and Acetami-

Proprietary Preparations (details are given in Part 3) Multi-ingredient: USA: Duradrin†; Midrin; Migratine†.

Difebarbamate (rINN)

Difébarbamate; Difebarbamato; Difebarbamatum. 1,3-Bis(3-butoxy-2-hydroxypropyl)-5-ethyl-5-phenylbarbituric acid dicarbamate ester.

Дифебарбамат $C_{28}H_{42}N_4O_9 = 578.7.$ CAS - 15687-09-9.

$$O = \begin{matrix} NH_2 \\ O \\ O \\ O \\ NH_2 \end{matrix} O CH_3$$

Difebarbamate is a barbiturate with general properties similar to those of amobarbital (p.961). Tetrabamate, a complex of difebarbamate, febarbamate, and phenobarbital, has been used in the management of anxiety disorders and alcohol withdrawal syndrome but was also associated with the development of hepatitis. Furthermore barbiturates are not considered appropriate in the management of these conditions.

Proprietary Preparations (details are given in Part 3) Multi-ingredient: Hung.: Atrium†.

Dixyrazine

Diksyratsiini; Dixirazina; Dixyrazin; Dixyrazinum; UCB-3412. 2-(2-{4-[2-Methyl-3-(phenothiazin-I0-yl)propyl]piperazin-Iyl}ethoxy)ethanol.

 $C_{24}H_{33}N_3O_2S = 427.6.$ CAS - 2470-73-7. ATC - N05AB01.ATC Vet - QN05AB01.

Profile

Dixyrazine is a phenothiazine with general properties similar to bisylazine is a phenomazine (p.969). It has a piperazine side-chain. It is given for its antipsychotic, antiemetic, and sedative properties in oral doses ranging from 20 to 75 mg daily. Dixyrazine has also been given by injection.

- 1. Larsson S, et al. Premedication with intramuscular dixyrazine (Esucos): a controlled double-blind comparison with morphine-scopolamine and placebo. Acta Anaesthesiol Scand 1988; 32: 131-4.
- 2. Karlsson E, et al. The effects of prophylactic dixyrazine on post-operative vomiting after two different anaesthetic methods for squint surgery in children. Acta Anaesthesiol Scand 1993; 37: 45-8.
- Oikkonen M, et al. Dixyrazine premedication for cataract surgery: a comparison with diazepam. Acta Anaesthesiol Scand 1994; 38: 214–17.
- 4. Feet PO, Götestam KG. Increased antipanic efficacy in combined treatment with clomipramine and dixyrazine. Acta Psychiatr Scand 1994; 89: 230-4.
- 5. Kokinsky E. et al. Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. *Acta Anaesthesiol Scand* 1999; **43:** 191–5.
- Glaser C, et al. Dixyrazine for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2004; 48: 1287-91.

Porphyria. Dixyrazine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals

Preparations

Proprietary Preparations (details are given in Part 3) Austria: Esucos; Fin.: Esucos; Ital.: Esucos; Norw.: Esucos; Swed.: Esucos.

Droperidol (BAN, USAN, HNN)

Dropéridol; Droperidoli; Droperidolis; Droperidolum; McN-JR-4749; R-4749. I-{I-[3-(4-Fluorobenzoyl)propyl]-I,2,3,6-tetrahydro-4-pyridyl}-benzimidazolin-2-one.

Дроперидол

 $C_{22}H_{22}FN_3O_2 = 379.4.$ CAS - 548-73-2. ATC - NOIAXOI; NO5AD08.ATC Vet - QN01AX01; QN05AD08.

Pharmacopoeias. In Eur. (see p.vii), Jpn, and US.

Ph. Eur. 6.2 (Droperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dimethylformamide. Protect from light.

USP 31 (Droperidol). A white to light tan amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 140 of alcohol, 1 in 4 of chloroform, and 1 in 500 of ether. Store under nitrogen in airtight containers at a temperature of 8° to 15°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. There is an increased risk of cardiotoxicity and prolongation of the QT interval (see p.970) with droperidol. Droperidol should not be used in patients with known or suspected QT prolongation; it should also be used with extreme caution in patients at risk of arrhythmias, including those

with impairment of cardiac function, hypokalaemia, or other electrolyte imbalance. It is recommended that a baseline ECG is performed in all patients before use of droperidol.

Uses and Administration

Droperidol is a butyrophenone with general properties similar to those of haloperidol (p.1001). The duration of action of droperidol has been reported to last about 2 to 4 hours although alteration of alertness may last for up to 12 hours.

One manufacturer of droperidol (Janssen-Cilag) voluntarily withdrew it from the market worldwide in March 2001 after reports of QT prolongation, serious ventricular arrhythmias, or sudden death in association with its use. However, in the USA, droperidol remained available from other manufacturers although its use was restricted to the management of nausea and vomiting after surgical or diagnostic procedures in patients who fail to show an adequate response to other treatments. It is also still available, in some other countries, for use as a premedicant, as an adjunct in anaesthesia, and for the control of agitated patients in acute psychoses and in mania. Droperidol has been used in the management of chemotherapy-induced nausea and vomiting. It has also been used with an opioid analgesic such as fentanyl citrate to maintain patients in a state of neuroleptanalgesia in which they are calm and indifferent to the surroundings and able to cooperate with the surgeon. The longer duration of action of droperidol must be kept in mind when using it with such opioid analgesics.

For the prevention of postoperative nausea and vomiting a maximum initial dose of 2.5 mg intramuscularly or intravenously has been given; additional doses of 1.25 mg may be given if necessary. Children aged 2 years and over have been given a maximum initial dose of 100 micrograms/kg intramuscularly or intravenously.

♦ References

 McKeage K, et al. Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. Drugs 2006: 66: 2123-47.

Preparations

BP 2008: Droperidol Injection; Droperidol Tablets; USP 31: Droperidol Injection.

Proprietary Preparations (details are given in Part 3) Austral.: Droleptan; Belg.: Dehydrobenzperidol; Braz.: Droperdal; Cz.: Dehydrobenzperidol; Fin.: Dehydrobenzperidol; Fin.: Dehydrobenzperidol; Fin.: Dehydrobenzperidol; Fin.: Dehydrobenzperidol; Fin.: Dehydrobenzperidol; Droleptan; India: Droperol; Ital.: Sintodian; Neth.: Dehydrobenzperidol; NZ: Droleptan; Port.: Dehidrobenzperidol; Xomolix; S.Afr.: Paxical; Spain: Dehidrobenzperidol; Swed.: Dridol; Thai.: Dehydrobenzperidol; USA: Inancine

Multi-ingredient: Arg.: Disifelit: Braz.: Nilperidol: Ital.: Leptofen.

Estazolam (USAN, rINN)

Abbott-47631; D-40TA; Estatsolaami; Estazolamum. 8-Chloro-6-phenyl-4H-1,2,4-triazolo[4,3-a]-1,4-benzodiazepine.

Эстазолам

 $C_{16}H_{11}CIN_4 = 294.7.$ CAS — 29975-16-4. ATC — N05CD04. ATC Vet - QN05CD04.

Pharmacopoeias. In Chin. and Jpn.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions As for Diazepam, p.987

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Peak plasma concentrations of estazolam are reached on average within 2 hours of oral doses. Estazolam is about 93% protein bound. Reported mean elimination half-lives have generally been in the range of 10 to 24 hours. Estazolam is extensively metabolised, mainly to 4-hydroxyestazolam and 1-oxoestazolam, which are considered inactive. These metabolites are excreted, either free or conjugated, in the urine with small amounts detected in the faeces. Only a small proportion of a dose is excreted as unchanged drug.

Uses and Administration

Estazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is given as a hypnotic in the short-term management of insomnia (p.957) in usual oral doses of 1 to 2 mg at night. Small or debilitated elderly patients may be given an initial dose of 0.5 mg.

Proprietary Preparations (details are given in Part 3)

Arg.: Somnatrol†; Braz.: Noctal; Denm.: Domnamid†; Fr.: Nuctalon; Indon.: Esilgan; Ital.: Esilgan; Ipn: Eurodin; Mex.: Tasedan; Philipp.: Esilgan; Port.: Kainever; USA: Prosom†.

Eszopiclone (USAN, rINN)

Eszopiclona; Eszopiclonum; (5)-Zopiclone; (+)-Zopiclone. (+)-(5S)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-I-carboxylate.

Эсзопикльон $C_{17}H_{17}CIN_6O_3 = 388.8.$ CAS — 138729-47-2.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of eszopiclone: Sleepeasy.

Profile

Eszopiclone is the (+)-isomer of zopiclone (p.1039) and is used similarly as a hypnotic in the short-term management of insom-

The usual oral dose is 2 mg immediately before bedtime; if appropriate, the dose may be started at or increased to 3 mg. In elderly patients who have difficulty falling asleep, the initial dose is 1 mg; this may be increased to 2 mg. For elderly patients who have difficulty staying asleep, the starting dose is 2 mg.

The starting dose should be reduced in patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4; a dose not exceeding 1 mg is recommended which may then be increased to 2 mg. For doses in patients with hepatic impairment, see below.

- ♦ Reviews.
- 1. Melton ST, et al. Eszopiclone for insomnia. Ann Pharmacother 2005: 39: 1659-66
- 2. Halas CJ. Eszopiclone. Am J Health-Syst Pharm 2006; 63: 41-8.

Administration in hepatic impairment. The starting oral dose of eszopiclone should be reduced to 1 mg at bedtime in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild to moderate impairment.

Preparations

Proprietary Preparations (details are given in Part 3) **Arg.:** Inductal; **USA:** Lunesta.

Ethchlorvynol (BAN. rINN)

β-Chlorovinyl Ethyl Ethynyl Carbinol; Etclorvinol; Éthchlorvynol; E-Ethchlorvynol; Ethchlorvynolum; Etkloorivinoli; Etklorvinol. I-Chloro-3-ethylpent-1-en-4-yn-3-ol.

Этхлорвинол $C_7H_9CIO = 144.6.$ CAS — 113-18-8. ATC — N05CM08. ATC Vet — QN05CM08.

Pharmacopoeias. In US.

USP 31 (Ethchlorvynol). A colourless to yellow, slightly viscous liquid having a characteristic pungent odour. It darkens on exposure to air and light. Immiscible with water; miscible with most organic solvents. Store in airtight containers of glass or polyethylene, using polyethylene-lined closures. Protect from light.

Dependence and Withdrawal

Prolonged use of ethchlorvynol may lead to dependence similar to that with barbiturates (see Amobarbital, p.962).

Adverse Effects

Adverse effects of ethchlorvynol include gastrointestinal disturbances, dizziness, headache, unwanted sedation and other symptoms of CNS depression such as ataxia, facial numbness, blurred vision, and hypotension. Hypersensitivity reactions include skin rashes, urticaria, and occasionally, thrombocytopenia and cholestatic jaundice. Idiosyncratic reactions include excitement, severe muscular weakness, and syncope without marked hypoten-

Acute overdosage is characterised by prolonged deep coma, respiratory depression, hypothermia, hypotension, and relative bradycardia. Pancytopenia and nystagmus have occurred.

Pulmonary oedema has followed abuse by intravenous injection.

Treatment of Adverse Effects

Treatment is as for barbiturate overdose (see Amobarbital. p.962). Haemoperfusion may be of value in the treatment of severe poisoning with ethchloryvnol.

Precautions

Ethchlorvynol should be used with caution in patients with hepatic or renal impairment or with depression, in patients with severe uncontrolled pain, and, as with all sedatives, in those with impaired respiratory function. It may cause drowsiness; affected patients should not drive or operate machinery.

Excessively rapid absorption of ethchlorvynol in some patients has been reported to produce giddiness and ataxia; this may be reduced by giving it with food.

Porphyria. Ethchlorvynol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The effect of ethchlorvynol may be enhanced by alcohol, barbiturates, and other CNS depressants. Ethchlorvynol has been reported to decrease the effects of coumarin anticoagulants.

Tricyclic antidepressants. Transient delirium has been reported from the use of ethchlorvynol with amitriptyline but details of such an interaction do not appear to have been published in the literature.

Pharmacokinetics

Ethchlorvynol is readily absorbed from the gastrointestinal tract, peak plasma concentrations usually occurring within 2 hours of ingestion. It is widely distributed in body tissues and is extensively metabolised in the liver, and possibly to some extent in the kidneys. It has a biphasic plasma half-life with a rapid initial phase and a terminal phase reported to last from 10 to 20 hours. Ethchlorvynol is excreted mainly in the urine as metabolites and their conjugates. Ethchlorvynol crosses the placenta.

Uses and Administration

Ethchlorvynol is a hypnotic and sedative with some anticonvulsant and muscle relaxant properties. It is given for the short-term management of insomnia (p.957) but has been largely superseded by other drugs. Use for periods greater than one week is not recommended. The usual oral hypnotic dose is 500 mg at night but doses ranging from 200 mg to 1 g have been given. Taking doses with food has been recommended-see Precautions,

Preparations

USP 31: Ethchlorvynol Capsules.

Ethyl Loflazepate (HNN)

CM-6912; Éthyle, Loflazépate d'; Ethylis Loflazepas; Loflazepato de etilo. Ethyl 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylate.

Этил Лофлазепат $C_{18}H_{14}CIFN_2O_3 = 360.8.$ CAS - 29177-84-2. ATC - N05BA18.ATC Vet - QN05BA18

Profile

Ethyl loflazepate is a long-acting benzodiazepine derivative with general properties similar to those of diazepam (p.986). It is used in the short-term treatment of anxiety disorders (p.952) in usual oral doses of 1 to 3 mg daily in a single dose or in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Victan; Belg.: Victan; Fr.: Victan; Jpn: Meilax; Mex.: Victan; Port.: Victan; Thoi.: Victan.