(p.2180) in whom organic pathology has been excluded. However, because of their potentially fatal toxicity in overdosage, there has been concern over the safety of using tricyclics in households with children. Most experience in nocturnal enuresis has been with imipramine, but other tricyclics such as amitriptyline, nortriptyline, and clomipramine have also been used. Their mechanism of action in nocturnal enuresis is unclear. It may be the result of their antimuscarinic and antispasmodic actions as well as their effect on sleep patterns and possible stimulation of antidiuretic hormone secretion. Imipramine appears to be most effective in older children, but many patients develop tolerance and increasingly higher doses are required.

Tricyclic antidepressants are also sometimes used in the management of **urinary incontinence** (p.2180).

References.

1. Glazener CMA, *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 24/11/05).

Narcoleptic syndrome. Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis associated with narcolepsy (p.2148). Imipramine has been widely used for these symptoms although some consider clomipramine more effective. The onset of action is quicker than when used for depression and doses required appear to be lower (typically 10 to 75 mg of imipramine daily) although tolerance may develop. Doses should be titrated to provide maximal protection for the time of day when symptoms usually occur.

Pain. Tricyclic antidepressants, usually amitriptyline, are useful in alleviating some types of pain when given in subantidepressant doses. An initial oral dose of amitriptyline hydrochloride 10 to 25 mg at night increased gradually if necessary to about 75 mg daily has been suggested by the *BNF* for the management of neuropathic pain in adults. Similar doses of amitriptyline hydrochloride are also suggested by the *BNFC* for the treatment of neuropathic pain in palliative care in children aged 12 years and over; in addition, younger children aged 2 years and above may receive an initial dose of 200 to 500 micrograms/kg (to a maximum of 25 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily. See also Choice of Analgesic on p.2. Chronic neuropathic pain as seen in cancer (p.5), central post-stroke pain (p.6), diabetic neuropathy (p.6), phantom limb pain (p.9), and postherpetic neuralgia (p.9) responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic orofacial pain (p.8), and may be of value for patients with complex regional pain syndrome (p.6). Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia (see Soft-tissue Rheumatism, p.13), a condition that responds poorly to analgesics and anti-inflammatory drugs. Patients with migraine or chronic tension-type headache may also benefit from tricyclics (see Headache, above). There is little evidence for an analgesic effect of tricyclics in acute or arthritic pain.

References.

1. Onghena P, Van Houdenhove, B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; **49:** 205–19.
2. McQuay HJ, *et al.* A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68:** 217–27.
3. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
4. McQuay HJ, Moore RA. Antidepressants and chronic pain. *BMJ* 1997; **314:** 763–4.
5. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 996–1000.
6. Arnold LM, *et al.* Antidepressant treatment of fibromyalgia: a meta-analysis and review. *Psychosomatics* 2000; **41:** 104–13.
7. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci* 2001; **26:** 30–6.
8. Reisner L. Antidepressants for chronic neuropathic pain. *Curr Pain Headache Rep* 2003; **7:** 24–33.

Pathological crying or laughing. Pathological crying or laughing can result from lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressants and favourable results have been reported in double-blind studies with amitriptyline[1] and nortriptyline.[2]

1. Schiffer RB, *et al.* Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; **312:** 1480–2.
2. Robinson RG, *et al.* Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993; **150:** 286–93.

Premenstrual syndrome. For reference to the tricyclic antidepressant, clomipramine, in premenstrual syndrome, see p.387.

Schizophrenia. Antidepressants such as the tricyclics are considered worth trying as an adjunct in the treatment of patients with schizophrenia (p.955) who develop depression during the recovery phase after an acute episode of psychosis. There is, however, no clear evidence that they are effective during acute psychotic episodes or for depression during periods of remission in patients with chronic schizophrenia.[1]

1. Anonymous. The drug treatment of patients with schizophrenia. *Drug Ther Bull* 1995; **33:** 81–6.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of tricyclic antidepressants (see Effects on Sexual Function in Adverse Effects, above). Such properties have been studied as a potential form of treatment for men with premature ejaculation (see Clomipramine, p.387).

Skin disorders. See under Doxepin, p.389, for use of tricyclic antidepressants in skin disorders.

Smoking cessation. Tricyclic antidepressants are among the drugs that have been tried with varying degrees of success as alternatives to nicotine replacement therapy (NRT) to alleviate the withdrawal syndrome associated with smoking cessation (p.2354). Nortriptyline is recommended by some as a second-line treatment in those patients who cannot tolerate or relapse after NRT.

References.

1. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Preparations

BP 2008: Amitriptyline Tablets;
USP 31: Amitriptyline Hydrochloride Injection; Amitriptyline Hydrochloride Tablets; Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Perphenazine and Amitriptyline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Tryptanol; Uxen; ***Austral.:*** Endep; Tryptanol; ***Austria:*** Saroten; Tryptizol; ***Belg.:*** Redomex; Tryptizol; ***Braz.:*** Amytril; Neurotrypt; Protanol; Tripsol; Tryptanol; ***Canad.:*** Elavil†; Novo-Triptyn; ***Denm.:*** Saroten; Tryptizol†; ***Fin.:*** Saroten†; Triptyl; ***Fr.:*** Elavil; Laroxyl; ***Ger.:*** Amineurin; Amioxid; Equilibrin; Novoprotect; Saroten; Syneudon; ***Gr.:*** Maxivalet; Saroten; Stelminal; ***Hong Kong:*** Qualitriptine; Tryptanol†; ***Hung.:*** Teperin; ***India:*** Sarotena; Tryptomer; ***Irl.:*** Lentizol†; ***Israel:*** Elatrol; Elatrolet; Tryptal; ***Ital.:*** Adepril; Laroxyl; Triptizol; ***Malaysia:*** Endep†; Tripta; Tryptanol; ***Mex.:*** Anapsique; Tryptanol; ***Neth.:*** Sarotex; Tryptizol; ***Norw.:*** Sarotex; Tryptizol†; ***NZ:*** Amitrip; ***Port.:*** ADT; Tryptizol; ***Rus.:*** Amyzol (Амизол); Eliwel (Элливел); Saroten (Саротен); ***S.Afr.:*** Noriline; Saroten; Trepiline; Tryptanol; ***Singapore:*** Tripta; ***Spain:*** Deprelio; Tryptizol; ***Swed.:*** Saroten; Tryptizol; ***Switz.:*** Saroten; Tryptizol; ***Thai.:*** Polytanol; Tripsyline†; Tripta; Triptyline; Tryptanol; ***Turk.:*** Laroxyl; Triptilin; ***UK:*** Elavil; ***USA:*** Elavil†; ***Venez.:*** Tryptanol.

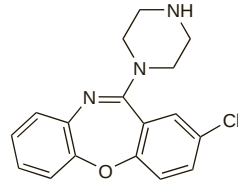
Multi-ingredient: ***Arg.:*** Mutabon D†; ***Austria:*** Limbitrol; ***Braz.:*** Limbitrol; ***Canad.:*** PMS-Levazine; Triavil†; ***Chile:*** Antalin; Limbatrilin; Morelin; Mutabon D†; Tiperin; ***Fin.:*** Klotriptyl; Limbitrol; Pertriptyl; ***Gr.:*** Minitran; ***India:*** Emotrip; ***Indon.:*** Limbritol; Mutabon-D; Mutabon-M; ***Ital.:*** Diapatol; Limbitryl; Mutabon; Sedans; ***Mex.:*** Adepsique; ***Port.:*** Mutabon; ***Rus.:*** Amixide (Амиксид); ***S.Afr.:*** Etrafon†; Limbitrol; ***Spain:*** Mutabase; Nobritol; ***Switz.:*** Limbitrol; ***Thai.:*** Anxipress-D†; Neuragon; Polybon; ***UK:*** Triptafen; ***USA:*** Etrafon; Limbitrol; Triavil†.

Amoxapine *(BAN, USAN, rINN)*

Amoksapiini; Amoksapin; Amoxapin; Amoxapina; Amoxapinum; CL-67772. 2-Chloro-11-(piperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.

Амоксапин

$C_{17}H_{16}ClN_3O$ = 313.8.
CAS — 14028-44-5.
ATC — N06AA17.
ATC Vet — QN06AA17.



Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Amoxapine). A white to yellowish crystalline powder. Practically insoluble in water; slightly soluble in acetone; freely soluble in chloroform; sparingly soluble in methyl alcohol and in toluene; soluble in tetrahydrofuran. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Rare cases of tardive dyskinesias and the neuroleptic malignant syndrome have been reported with amoxapine.

Antidopaminergic effects. Amoxapine is a derivative of the antipsychotic loxapine (p.1005) and possesses some antipsychotic activity. It also has dopamine-receptor blocking properties as do its hydroxylated metabolites. Adverse effects that are symptoms of such blockade have been reported and reviewed[1,2] and include akinesia, akathisia, withdrawal dyskinesia, reversible tardive dyskinesia, persistent dyskinesia, elevated serum concentration of prolactin, and galactorrhoea. Chorea[3] and oculogyric crisis[4] have also been reported.

1. Tao GK, *et al.* Amoxapine-induced tardive dyskinesia. *Drug Intell Clin Pharm* 1985; **19:** 548–9.
2. Devarajan S. Safety of amoxapine. *Lancet* 1989; **ii:** 1455.
3. Patterson JF. Amoxapine-induced chorea. *South Med J* 1983; **76:** 1077.
4. Hunt-Fugate AK, *et al.* Adverse reactions due to dopamine blockade by amoxapine. *Pharmacotherapy* 1984; **4:** 35–9.

Antimuscarinic effects. Amoxapine therapy has been reported to produce adverse effects associated with antimuscarinic activity (such as constipation, blurred vision, and dry mouth), but such reports did not reflect *in-vitro* findings that amoxapine had considerably less affinity for muscarinic binding sites than amitriptyline;[1] this was supported by results in healthy subjects. The adverse effects described as antimuscarinic could possibly be explained by amoxapine affecting noradrenergic mechanisms.

1. Bourne M, *et al.* A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 57–62.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the endocrine system. Reversible nonketotic hyperglycaemia developed in a 49-year-old woman with no history of diabetes mellitus within 5 days of oral therapy with amoxapine 50 mg three times daily.[1] She had previously had nonketotic hyperglycaemic coma after loxapine 150 mg daily. 7-Hydroxyamoxapine, a metabolite common to both amoxapine and loxapine, was implicated.

See also Antidopaminergic Effects, above, for mention of galactorrhoea and hyperprolactinaemia.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Overdosage. In overdosage, amoxapine is reported to cause acute renal failure with rhabdomyolysis,[1,2] coma, and seizures.[3-5] Although there has been some debate as to whether the incidence of seizures and death is higher with overdosage of amoxapine than with other tricyclic antidepressants, some[6] consider that evidence does seem to favour increased neurological consequences.

It has been reported that amoxapine is not cardiotoxic in overdosage[3] but later evidence would suggest that there is cardiotoxic potential.[6,7]

1. Pumariega AJ, *et al.* Acute renal failure secondary to amoxapine overdose. *JAMA* 1982; **248:** 3141–2.
2. Jennings AE, *et al.* Amoxapine-associated acute renal failure. *Arch Intern Med* 1983; **143:** 1525–7.
3. Kulig K, *et al.* Amoxapine overdose: coma and seizures without cardiotoxic effects. *JAMA* 1982; **248:** 1092–4.
4. Litovitz TL, Troutman WG. Amoxapine overdose: seizures and fatalities. *JAMA* 1983; **250:** 1069–71.
5. Jefferson JW. Convulsions associated with amoxapine. *JAMA* 1984; **251:** 603–4.
6. Leonard BE. Safety of amoxapine. *Lancet* 1989; **ii:** 808.
7. Sørensen MR. Acute myocardial failure following amoxapine intoxication. *J Clin Psychopharmacol* 1988; **8:** 75.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Amoxapine is readily absorbed from the gastrointestinal tract. It bears a close chemical relationship to loxapine (p.1005) and is similarly metabolised by hydroxylation. It is excreted in the urine, mainly as its metabolites in conjugated form as glucuronides.

Amoxapine has been reported to have a plasma half-life of 8 hours and its major metabolite, 8-hydroxyamoxapine, has been reported to have a biological half-life of 30 hours; 7-hydroxyamoxapine has been identified as another metabolite. Both metabolites are pharmacologically active. Amoxapine is about 90% bound to plasma proteins.

Amoxapine and its metabolite 8-hydroxyamoxapine are distributed into breast milk.

Uses and Administration

Amoxapine, the *N*-desmethyl derivative of loxapine (p.1005), is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). Amoxapine is one of the less sedating tricyclics and its antimuscarinic effects are mild; it also inhibits the reuptake of dopamine.

In the treatment of depression (p.373) amoxapine is given in oral doses of 50 mg two or three times daily initially, gradually increased up to 100 mg three times daily as necessary. In the USA, higher doses of up to 600 mg daily may also be given, if required, in severely depressed patients in hospital. A suggested dose for the elderly is 25 mg two or three times daily initially, increased after 5 to 7 days to up to 150 mg daily as necessary; in the USA further increases to a maximum of 300 mg daily are permitted, if required.

Once-daily dosage regimens, usually given at night, are suitable for amoxapine up to 300 mg daily; divided-dosage regimens are recommended for doses above 300 mg daily.

It has been claimed that, in the treatment of depression, amoxapine has a more rapid onset of action than amitriptyline or imipramine with a clinical effect possibly appearing 4 to 7 days after starting therapy, although this has been disputed.

Amoxapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Amoxapine has also been investigated for its potential as an antipsychotic.

◊ References.

1. Jue SG, *et al.* Amoxapine: a review of its pharmacology and efficacy in depressed states. *Drugs* 1982; **24:** 1–23.

2. Sa DS, *et al.* Amoxapine shows an antipsychotic effect but worsens motor function in patients with Parkinson's disease and psychosis. *Clin Neuropharmacol* 2001; **24:** 242–4.
3. Apiquian R, *et al.* Amoxapine shows atypical antipsychotic effects in patients with schizophrenia: results from a prospective open-label study. *Schizophr Res* 2003; **59:** 35–9.
4. Fitzgerald PB, *et al.* Amoxapine in schizophrenia: a negative double-blind controlled trial. *J Clin Psychopharmacol* 2004; **24:** 448–50.
5. Apiquian R, *et al.* Amoxapine as an atypical antipsychotic: a comparative study vs risperidone. *Neuropsychopharmacology* 2005; **30:** 2236–44.

Preparations

USP 31: Amoxapine Tablets.

Proprietary Preparations (details are given in Part 3)
Denm.: Demolox†; ***Fr.:*** Defanyl; ***India:*** Demolox; ***Indon.:*** Asendin; ***UK:*** Asendis†; ***USA:*** Asendin†.

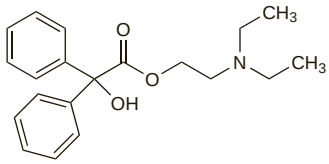
Benactyzine Hydrochloride *(BANM, rINNM)*

Amizylum; Bénactyzine, Chlorhydrate de; Benactyzini Hydrochloridum; Hidrocloruro de benacticina. 2-Diethylaminoethyl benzilate hydrochloride.

Бенактизина Гидрохлорид

$C_{20}H_{25}NO_3$,HCl = 363.9.

CAS — 302-40-9 (benactyzine); 57-37-4 (benactyzine hydrochloride).



(benactyzine)

Profile

Benactyzine has antidepressant and antimuscarinic activity. It has been used as the hydrochloride in the management of depression and associated anxiety. It is also used as a pharmacological tool. Methylbenactyzium bromide (p.1747), the methobromide of benactyzine, has been used for its antimuscarinic activity in the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Arg.:* Dimaval.

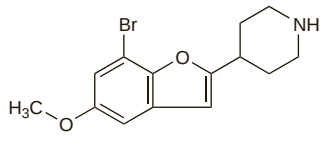
Brofaromine *(rINN)*

Brofaromina; Brofarominum; CGP-11305A (brofaromine hydrochloride). 4-(7-Bromo-5-methoxy-2-benzofuranyl)piperidine.

Брофаромин

$C_{14}H_{16}BrNO_2$ = 310.2.

CAS — 63638-91-5.



Profile

Brofaromine is a reversible inhibitor of monoamine oxidase type A (RIMA) (see Moclobemide, p.411). It has been studied in the treatment of depression and in anxiety disorders including social anxiety disorder.

Bupropion Hydrochloride

(BANM, USAN, rINNM)

Amfebutamone Hydrochloride; Bupropione, Chlorhydrate de; Bupropionhydroklorid; Bupropioni Hydrochloridum; Bupropionihydrokloridi; BW-323; Hidrocloruro de bupropión. (±)-2-(*tert*-Butylamino)-3′-chloropropiophenone hydrochloride.

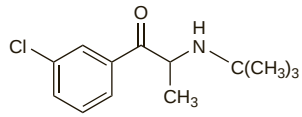
Бупропиона Гидрохлорид

$C_{13}H_{18}ClNO$,HCl = 276.2.

CAS — 34911-55-2 (bupropion); 31677-93-7 (bupropion hydrochloride).

ATC — N07BA02.

ATC Vet — QN07BA02.



(bupropion)

Pharmacopoeias. In *US.*
USP 31 (Bupropion Hydrochloride). A white powder. Soluble in water, in alcohol, and in 0.1N hydrochloric acid. Protect from light.

Adverse Effects and Treatment

Agitation, anxiety, and insomnia often occur during the initial stages of bupropion therapy. Other relatively common adverse effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Hypersensitivity reactions, ranging from pruritus and urticaria to, less commonly, angioedema, dyspnoea, and anaphylactoid reactions, have occurred, as have symptoms suggestive of serum sickness. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. Tachycardia, chest pain, and hypertension (sometimes severe), or occasionally vasodilatation, orthostatic hypotension, palpitations, and syncope have been reported. Psychotic episodes, confusion, nightmares, impaired memory, dysgeusia, anorexia with weight loss, paraesthesia, tinnitus, and visual disturbances have also been reported.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Seizures, which appear to be partially dose-related, may occur with bupropion and have been particularly notable in patients with anorexia nervosa or bulimia nervosa; the risk is also increased in patients with a history of seizure disorders or other predisposing factor. The manufacturers state that the overall incidence of seizure in patients receiving bupropion at recommended doses is about 0.1 to 0.4%.

Symptoms of overdosage include hallucinations, nausea and vomiting, tachycardia, loss of consciousness, and death (following massive overdose); seizures have occurred in about one-third of all bupropion overdose cases. Activated charcoal should be considered in adult patients who have taken more than 450 mg and in all children, if they present within 1 hour of ingestion; gastric lavage may also be used to decrease absorption. Treatment is supportive. Benzodiazepines may be tried for seizures. Diuresis, dialysis, and haemoperfusion are unlikely to be of benefit.

Incidence of adverse effects. Up to 24 July 2002 (the first 25 months of marketing), the UK CSM had received 7630 reports of suspected adverse reactions associated with the use of bupropion.[1] Of these reports, 60 were associated with a fatal outcome although in most cases underlying conditions could have been responsible. Cardiovascular and cerebrovascular disorders such as myocardial infarction and stroke were reported as the cause of death in 70% of cases. The CSM also commented that adverse reactions were mainly recognised ones and listed in the licensed product information.

In January 2005 the German pharmacovigilance network reviewed[2] 273 reports of adverse effects associated with bupropion, received between June 2000 and September 2004. The most frequent adverse effects were: psychiatric disorders (79.3%), including suicide attempts (17.6%), and tachycardia (11.15%), seizures (8.8%), and dyspnoea (8.8%). There were also 4 cases of pancreatitis and one of raised pancreatic enzyme activity three times greater than normal.

1. CSM/MCA. Zyban (bupropion hydrochloride) - safety update (issued 26th July 2002). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019524&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
2. Drug Commission of the German Medical Association. Increased pancreatic enzymes or acute pancreatitis induced by bupropion (Zyban)(from the UAW database). Available at: http://www.akdae.de/en/20/20/Archiv/2005/800_20050110.html (accessed 04/06/06)

Effects on the cardiovascular system. Up to the end of December 2001 the national pharmacovigilance centre in the Netherlands had received 591 adverse reaction reports associated with the use of bupropion for smoking cessation since its marketing 2 years earlier;[1] of these, 45 concerned cardiac complaints such as palpitations (21), arrhythmias (7), myocardial infarction (3), anginal pain (2), and cardiac arrest (1). Twenty-two reports also mentioned chest pain or tightness, although these were considered to be of noncardiac origin. In another report a 43-year-old male suffered an acute myocardial infarction 2 weeks after starting bupropion for smoking cessation;[2] he had experienced central chest and arm pain 3 days before the infarction. The authors of the report said that up to 30 April 2001 the UK CSM had received 238 reports of chest pain and 134 reports of chest tightness associated with bupropion use.

1. de Graaf L, Diemont WL. Chest pain during use of bupropion as an aid in smoking cessation. *Br J Clin Pharmacol* 2003; **56:** 451–2.
2. Patterson RN, Herity NA. Acute myocardial infarction following bupropion (Zyban). *QJM* 2002; **95:** 58–9.

Effects on the cerebrovascular system. A 67-year-old male had paraesthesia, dizziness, tinnitus, confusion, and gait impairment after taking bupropion for smoking cessation.[1] Although a transient ischaemic attack was suspected symptoms resolved on stopping bupropion and recurred on rechallenge.

1. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999; **33:** 305–7.

Effects on the pancreas. See under Incidence of Adverse Effects, above.

Effects on the skin. *Erythema multiforme* developed in a 31-year-old woman several weeks after starting modified-release bupropion for depression.[1] Symptoms resolved on drug withdrawal. In another report, 3 patients with controlled *psoriasis* had an exacerbation of their psoriatic symptoms after starting bupropion for smoking cessation.[2] All 3 patients required hospitalisation to control their symptoms. There have also been several reports of patients developing *generalised acute urticaria*;[3,4] systemic symptoms resembling serum sickness were also reported in 1 case[4] (see also Hypersensitivity, below).

1. Lineberry TW, *et al.* Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; **76:** 664–6.
2. Cox NH, *et al.* Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146:** 1061–3.
3. Fays S, *et al.* Bupropion and generalized acute urticaria: eight cases. *Br J Dermatol* 2003; **148:** 177–8.
4. Loo WJ, *et al.* Bupropion and generalized acute urticaria: a further case. *Br J Dermatol* 2003; **149:** 660.

Extrapyramidal effects. A 44-year-old man had acute head and neck dystonia while taking buspirone and modified-release bupropion.[1] No recurrence was noted on rechallenge with buspirone although symptoms did develop on rechallenge with bupropion when the dose was increased from 150 mg once daily to 150 mg twice daily. In another case, a 42-year-old woman had gross involuntary movements of her torso, arms, and legs (diagnosed as ballism) 8 days after starting bupropion for smoking cessation;[2] the dose had been increased from 150 mg once daily to 150 mg twice daily on the fourth day. She recovered when bupropion was stopped and treatment with haloperidol and oxazepam was given.

1. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; **36:** 251–4.
2. de Graaf L, *et al.* Ballism associated with bupropion use. *Ann Pharmacother* 2003; **37:** 302–3.

Hypersensitivity. Eosinophilia has been reported[1] in a patient 12 days after bupropion was added to her existing treatment regimen of glibenclamide and tolmetin. The eosinophil count returned to normal after all medication was stopped. Bupropion appeared to be the causative drug.

Serum sickness or symptoms suggestive of serum sickness has also been associated with bupropion use.[2-5] In one case,[5] although the initial presentation resembled serum sickness, the patient went on to develop multisystem complications that included hepatitis, cholestasis, and myocarditis.

See also Effects on the Skin, above.

1. Malesker MA, *et al.* Eosinophilia associated with bupropion. *Ann Pharmacother* 1995; **29:** 867–8.
2. Yolles JC, *et al.* Serum sickness induced by bupropion. *Ann Pharmacother* 1999; **33:** 931–3.
3. McCollom RA, *et al.* Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; **34:** 471–3.
4. Benson E. Bupropion-induced hypersensitivity reactions. *Med J Aust* 2001; **174:** 650–1.
5. Bagshaw SM, *et al.* Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann Allergy Asthma Immunol* 2003; **90:** 572–5.

Overdosage. Unlike the tricyclic antidepressants, bupropion appears to lack any significant cardiovascular or antimuscarinic adverse effects when taken in overdose. In an early review[1] of 58 overdose cases involving immediate-release bupropion alone, the most common symptoms were sinus tachycardia, lethargy, tremor, and seizures; other effects included confusion, lightheadedness, hallucinations, paraesthesias, and vomiting. Most patients had minor effects or none at all. Similar symptoms have also been noted in reviews of overdose cases involving modified-release bupropion.[2,3] UK licensed prescribing information for bupropion also lists ECG changes such as conduction disturbances, arrhythmias, and tachycardia although a literature review[4] concluded that cardiotoxicity appeared to be rare with