Cloxazolam *(rINN)*

Cloxazolamum; CS-370; Kloksatsolaami; Kloxazolam. 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

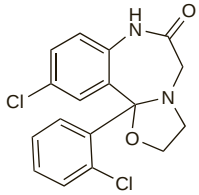
Клоксазолам

$C_{17}H_{14}Cl_2N_2O_2$ = 349.2.

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.



Pharmacopoeias. In *Jpn.*

Profile

Cloxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been given in oral doses of up to 12 mg daily in divided doses for the short-term treatment of anxiety disorders (p.952). A dose of 100 micrograms/kg may be used for premedication (p.1780).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tolestan; ***Belg.:*** Akton; ***Braz.:*** Anoxolan; Clozal; Elum; Eutonis; Olcadil; ***Port.:*** Cloxam; Olcadil; ***Switz.:*** Lubalix†.

Clozapine *(BAN, USAN, rINN)*

Clozapina; Clozapinum; HF-1854; Klotsapiini; Klozapin; Klozapina; Klozapinas. 8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo-[*b*,*e*][1,4]diazepine.

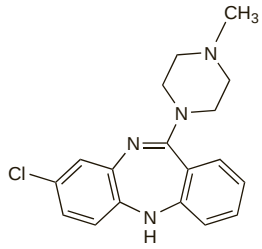
Клозапин

$C_{18}H_{19}ClN_4$ = 326.8.

CAS — 5786-21-0.

ATC — N05AH02.

ATC Vet — QN05AH02.



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

Ph. Eur. 6.2 (Clozapine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. It dissolves in dilute acetic acid.

USP 31 (Clozapine). A yellow crystalline powder. Insoluble in water; soluble in alcohol, in acetone, and in chloroform; sparingly soluble in acetonitrile.

Stability. A suspension of clozapine 100 mg in 5 mL, made by crushing clozapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for at least 18 days after preparation.[1]

1. Ramuth S, *et al.* A liquid clozapine preparation for oral administration in hospital. *Pharm J* 1996; **257:** 190–1.

Adverse Effects and Treatment

Although clozapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential (see Precautions, below). Eosinophilia may also occur. Anaemia, thrombocytopenia, and thrombocythaemia have been reported rarely.

Extrapyramidal disorders, including tardive dyskinesia, appear to be rare with clozapine. Clozapine has little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases, circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk of developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional adverse effects of clozapine include dizziness, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, faecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis. There have also been rare reports of dysphagia, parotid gland enlargement, confusion, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose homoeostasis and the onset of diabetes mellitus occur uncommonly; severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, has been reported very rarely. There have also been rare reports of hypercholesterolaemia and hypertriglyceridaemia. Many of the adverse effects of clozapine are most common at the start of therapy and may be minimised by gradual increase in dosage.

Effects on the blood. Clozapine can cause reversible neutropenia which, if the drug is not withdrawn immediately, may progress to a potentially fatal **agranulocytosis**. Particular concern over this adverse effect dates from 1975 when 17 cases of neutropenia or agranulocytosis, 8 of them fatal, were reported in Finland;[1] the calculated incidence[2] of agranulocytosis or severe granulocytopenia during this Finnish epidemic was 7.1 per 1000. These reports led to the withdrawal of clozapine in some countries or to restrictions in its use and intense haematological monitoring in others. After studies showing the efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[3] Clozapine was one of the individual drugs most frequently implicated, with 14 reports of agranulocytosis (1 fatal) and 119 of neutropenia (none fatal). Various estimates of the **incidence** of clozapine-associated agranulocytosis have been made; analysis of data from 11 555 patients given clozapine in the USA[4] showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1⁄ years with the risk being increased in elderly patients. The majority of cases of agranulocytosis occurred within 3 months of the start of treatment with the risk peaking in the third month. The manufacturers report a lower incidence of agranulocytosis of 4.8 per 1000 patients for the first 6 months[5] and an annual rate of 0.8 per 1000 patients during the next 2⁄ years. These figures were based on data on 56 000 patients in the USA given clozapine up to the end of March 1993. Analysis of data[6] on 6316 patients registered in the UK and Ireland between January 1990 and July 1994 to receive (although not necessarily given) clozapine produced a cumulative incidence of agranulocytosis of 0.7% during the first year and 0.8% over the whole study period. Most cases of agranulocytosis and neutropenia occurred during the first 6 to 18 weeks of treatment. The incidence of agranulocytosis (0.07%) and neutropenia (0.7%) seen during the second year of therapy was of the same order of magnitude noted for some phenothiazine antipsychotics.

These data[6] and comparable data from the USA[7] were considered to indicate that mandatory haematological monitoring (see Precautions, below) helped to reduce the risks of clozapine-induced neutropenia and agranulocytosis and associated deaths.

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune response.[8,9] **Predisposing factors** for development of agranulocytosis have not been identified, apart from a possible excess of cases in female patients and an increased risk with increasing age. Furthermore, both agranulocytosis and neutropenia do not appear to be dose-related effects with clozapine. A postulated higher incidence of agranulocytosis in patients of Jewish background may be related to genetic factors.[10] Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia[6] and it has been noted[11] that many patients from these ethnic groups are currently already excluded from treatment with clozapine because their normal white blood cell and neutrophil counts are below the recommended range for treatment (see Precautions, below). However, UK licensed product information recommends that patients who have low white blood cell counts due to benign ethnic neutropenia may begin clozapine treatment with the agreement of a haematologist.

Evidence would suggest that development of clozapine-induced leucopenia or granulocytopenia precludes **retreatment** with clozapine at any future date; in a series of 9 re-treated patients, all developed leucopenia or agranulocytosis again.[12] In the USA, patients who have had clozapine withdrawn because of moderate leucopenia (judged to be when counts fall to 2000 to 3000 cells/mm^3) are considered eligible for a return to clozapine treatment when this count returns to normal; such patients are considered to have a five- or sixfold greater risk of agranulocytosis.[5]

1. Idänpään-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11:** 193–8.
2. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11:** 199–201.
3. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329:** 162–7.
5. Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346:** 849.
6. Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169:** 483–8.
7. Honigfeld G, *et al.* Reducing clozapine-related morbidity and mortality: 5 years experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59** (suppl 3): 3–7.
8. Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338:** 262–3.
9. Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1–60.
10. Leiberman JA, *et al.* HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47:** 945–8.
11. Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313:** 1262.
12. Safferman AZ, *et al.* Rechallenge in clozapine-induced agranulocytosis. *Lancet* 1992; **339:** 1296–7.

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. However, a later review considered that there was overwhelming evidence that atypical antipsychotics induced more weight gain than classical antipsychotics.[2]

A separate review[3] calculated the average monthly weight gain associated with atypical antipsychotics to be:

- olanzapine (2.28 kg)
- zotepine (2.28 kg)
- quetiapine (1.76 kg)
- clozapine (1.72 kg)
- risperidone (0.96 kg)
- ziprasidone (0.80 kg)

Weight gain occurred most frequently during the first 6 to 12 months of treatment. It was recommended that if weight gain was more than 2 kg during the first 2 weeks, a strict dietary regimen should be started immediately. However, more recent opinion is that a change of antipsychotic may be necessary. Anti-obesity drugs have been tried although their routine use is not generally recommended.[2,4]

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.
2. Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16:** 75–85.
3. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24:** 59–73.
4. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (suppl 7): 22–31.

Effects on carbohydrate metabolism. Treatment with clozapine may be associated with an increased risk of glucose intolerance and diabetes mellitus; a similar association has also been noted for some other atypical antipsychotics.[1]

Data received by WHO indicated that up to December 2000, there had been 480 reports of glucose intolerance with clozapine, 253 with olanzapine, and 138 with risperidone.[2] In some cases weight gain was also reported, which may predispose to development of glucose intolerance. Other risk factors identified included an underlying diabetic condition, male gender, and use with some other medications including valproate, SSRIs, and buspirone. Regular monitoring of weight, blood glucose, and

blood lipids was recommended in patients receiving clozapine, olanzapine, and risperidone.

Glucose intolerance has also been reported for the atypical antipsychotic quetiapine.[3,4]

Other reviewers have also found similar evidence of an increased risk of diabetes with atypical antipsychotics.[5] In September 2003 the FDA therefore requested labelling changes for all atypical antipsychotics to include the following recommendations and warnings:

- patients with diabetes mellitus receiving atypical antipsychotics should be monitored regularly for worsening glucose control
- patients with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the start of, and during, treatment with atypical antipsychotics
- all patients given atypical antipsychotics should be monitored during treatment and those who develop hyperglycaemia should undergo fasting blood glucose testing
- in some cases hyperglycaemia resolved on withdrawal but some patients needed to continue antidiabetic therapy despite withdrawal

However, the American Diabetes Association and several other American medical associations[6] consider that the risks vary between atypical antipsychotics and have recommended that this should be taken into account when prescribing. The risk of weight gain, diabetes, and dyslipidaemia was considered to be greatest for clozapine and olanzapine, with risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having little effect (see also Effects on Body-Weight, above). They recommended that *baseline monitoring* should include:

- personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or cardiovascular disease
- weight, height, and waist circumference
- blood pressure
- fasting blood glucose
- fasting lipid profile

Patients at risk for diabetes should receive an atypical drug with a lower propensity for weight gain and glucose intolerance. *Follow-up monitoring* should consist of reassessment of weight at 4, 8, and 12 weeks, and it was recommended that a change of antipsychotic should be considered for any patient who gained more than 5% of their original weight during treatment. Fasting plasma glucose and blood pressure should be assessed at 3 months and annually or more frequently thereafter according to risk. Lipid levels should also be assessed after 3 months and, if normal, at 5-year intervals thereafter. Any patient with worsening glycaemia or dyslipidaemia should be changed to an antipsychotic that has not been associated with significant weight gain or diabetes.

1. Melkersson K, Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs* 2004; **64:** 701–23.
2. Hedenmalm K, *et al.* Glucose intolerance with atypical antipsychotics. *Drug Safety* 2002; **25:** 1107–16.
3. Griffiths J, Springuel P. Atypical antipsychotics: impaired glucose metabolism. *Can Adverse Drug React News* 2001; **11** (4): 3–6. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v11n4-eng.pdf (accessed 21/08/08)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Atypical antipsychotics and hyperglycaemia. *Aust Adverse Drug React Bull* 2004; **23:** 11–12. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0406.htm (accessed 25/05/05)
5. Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of diabetes mellitus. *Ann Pharmacother* 2003; **37:** 1849–57.
6. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27:** 596–601. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/2/596.pdf (accessed 24/05/05)

Effects on the cardiovascular system. The UK CSM[1] issued a warning in November 1993 of the risk of **myocarditis** with clozapine. Three patients who died while taking clozapine had evidence of myocarditis. The CSM had also received one other report of myocarditis and one of cardiomyopathy associated with clozapine. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) subsequently reported[2] another 5 cases of clozapine-associated myocarditis in November 1994. A later report[3] from Australia identified 15 cases of myocarditis, including 5 fatalities, between January 1993 and March 1999 (these figures were established using both data from ADRAC and the Australian manufacturers). Between September 1989 and December 1999 the FDA had received reports of 28 cases of myocarditis (18 fatal) and 41 of cardiomyopathy (10 fatal) temporally associated with clozapine use.[4] A review[5] by the pharmacovigilance authorities in New Zealand stated that by November 1999 the manufacturers (*Novartis*) had analysed 125 reports of myocarditis received worldwide including 35 fatalities; 53% had occurred during the first month of treatment but about 5% occurred more than 2 years after starting treatment. A more recent review[6] of reports submitted to ADRAC between 1993 and 2003 identified 116 cases of myocarditis; of these, 60 patients were known to have recovered and 12 died. Myocarditis developed within a median of 17 days of starting clozapine therapy. In a reminder article,[7] the CSM has also commented that myocarditis occurs most commonly in the first 2 months whereas cardiomyopathy generally develops later in therapy. Pericarditis and pericardial effusions have also been reported. As myocarditis can be difficult to diagnose and confirmation is not always possible, the CSM recommended that if there was a high clinical suspicion of myocarditis, antipsychotic medication should be stopped. Presenting features might include persistent tachycardia at rest, heart failure, arrhythmia, or symptoms mimicking myocardial infarction or pericarditis. Patients who have developed clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

There is also evidence that clozapine may be associated with fatal **thromboembolism**. Between February 1990 and December 1999, the FDA[8] had received 99 reports of venous thromboembolism associated with clozapine treatment. Of these reports, 83 mentioned pulmonary embolism with or without deep-vein thrombosis and 16 mentioned deep-vein thrombosis alone; 63 deaths were due to pulmonary embolism. The Swedish Adverse Reactions Advisory Committee had received reports[9] on 6 cases (5 fatal) of pulmonary embolism and 6 of venous thrombosis associated with clozapine treatment as of March 2000. The effect seemed to occur mainly in the first 3 months of treatment, and the majority of the cases involved men. However, analysis of data[10] from Germany and Switzerland suggests that the incidence of clozapine-associated thromboembolism is no different from that in psychiatric patients treated with classical antipsychotics or no antipsychotics at all.

There have been isolated reports[11,12] of **paradoxical hypertension** in patients receiving clozapine. Use with atenolol has controlled the hypertension and allowed clozapine therapy to be continued.

Some studies[13] have suggested that serious cardiovascular effects might occur more frequently and might be more severe in healthy subjects given clozapine than in patients with schizophrenia. The manufacturers had therefore requested that pharmacokinetic studies of clozapine should be performed in patients with treatment-resistant schizophrenia rather than in healthy subjects.

For further details of effects of clozapine on the cardiovascular system, see Benzodiazepines under Interactions, below.

1. CSM/MCA. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). *Current Problems* 1993; **19:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Clozapine and myocarditis. *Aust Adverse Drug React Bull* 1994; **13** (Nov): 14–15.
3. Kilian JG, *et al.* Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; **354:** 1841–5.
4. La Grenade L, *et al.* Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med* 2001; **345:** 224–5.
5. New Zealand Medicines and Medical Devices Safety Authority. Potentially fatal complications of clozapine therapy: myocarditis, venous thromboembolism and constipation. Available at: http://www.medsafe.govt.nz/profs/puarticles/cloz1.htm (accessed 24/05/05)
6. Haas SJ, *et al.* Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety* 2007; **30:** 47–57.
7. CSM/MCA. Clozapine and cardiac safety: updated advice for prescribers. *Current Problems* 2002; **28:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
8. Knudson JF, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252–3.
9. Hägg S, *et al.* Association of venous thromboembolism and clozapine. *Lancet* 2000; **355:** 1155–6.
10. Wolstein J, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252.
11. Gupta S. Paradoxical hypertension associated with clozapine. *Am J Psychiatry* 1994; **151:** 148.
12. Ennis LM, Parker RM. Paradoxical hypertension associated with clozapine. *Med J Aust* 1997; **166:** 278.
13. Pokorny R, *et al.* Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine. *Pharm Res* 1994; **11:** 1221.

Effects on fluid and electrolyte homoeostasis. Hyponatraemia has been reported to be associated with clozapine,[1] as with other antipsychotics (p.970). It was emphasised that hyponatraemia should be excluded as a possible trigger when considering the epileptogenic potential of clozapine.

1. Ogilvie AD, Croy MF. Clozapine and hyponatraemia. *Lancet* 1992; **340:** 672.

Effects on the gastrointestinal tract. The UK CSM had received 20 reports of serious gastrointestinal reactions resembling obstruction associated with clozapine treatment as of March 1999, of which 3 were fatal.[1] These reactions were thought to be due to the antimuscarinic actions of clozapine and, therefore, more likely to occur when clozapine was taken with other drugs with antimuscarinic actions such as tricyclic antidepressants, some antiparkinsonian drugs, and other antipsychotics; care was also warranted in those patients with a history of colonic disease or previous bowel surgery. It was also important to recognise and treat constipation in patients receiving clozapine to prevent the development of more serious complications such as obstruction and paralytic ileus.

1. CSM/MCA. Clozapine (Clozaril) and gastrointestinal obstruction. *Current Problems* 1999; **25:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Effects on the kidneys. There have been reports[1-3] of acute interstitial nephritis associated with clozapine treatment. All 3 patients had acute renal failure which resolved when the drug was stopped. The authors of 1 report noted that the UK CSM had received 7 reports of acute renal failure associated with clozapine treatment, including 1 death, between December 1989 and February 1999.[2]

1. Elias TJ, *et al.* Clozapine-induced acute interstitial nephritis. *Lancet* 1999; **354:** 1180–1.
2. Fraser D, Jibani M. An unexpected and serious complication of treatment with the atypical antipsychotic drug clozapine. *Clin Nephrol* 2000; **54:** 78–80.
3. Au AF, *et al.* Clozapine-induced acute interstitial nephritis. *Am J Psychiatry* 2004; **161:** 1501.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism, above.

Effects on the nervous system. As with other antipsychotics (see Convulsions, p.969), clozapine can lower the seizure threshold and cause EEG abnormalities, although treatment with clozapine appears to be associated with a higher frequency of seizures. A review[1] of 1418 patients treated with clozapine in the USA between 1972 and 1988 found that 41 had experienced generalised tonic-clonic seizures. It was considered that the risk of clozapine-induced seizures was dose-related. The seizure frequency was calculated to be:

- 1% at a dosage less than 300 mg daily
- 2.7% at 300 to 599 mg daily
- 4.4% with a dosage of 600 mg or more daily

Six of the patients had been taking other drugs reported to lower the seizure threshold. Therapy with clozapine was continued in 31 of the 41 patients by reducing the total daily dose of clozapine; antiepileptic drug therapy was begun in about half of the patients.

The UK CSM[2] considered that, although the epileptogenic effect of clozapine was claimed to be dose-related, the metabolism and plasma concentrations of clozapine were highly variable, and data from 8 cases reported to the CSM suggested that convulsions might possibly be related to high plasma concentrations in susceptible individuals. A low initial dosage followed by careful increases according to response and downward titration thereafter to a maintenance dose was recommended to avoid convulsions in susceptible individuals.

1. Devinsky O, *et al.* Clozapine-related seizures. *Neurology* 1991; **41:** 369–71.
2. CSM. Convulsions may occur in patients receiving clozapine (Clozaril , Sandoz). *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

Effects on the pancreas. There have been isolated reports of pancreatitis associated with clozapine therapy[1-3] and overdosage.[4] A systematic review[5] of the FDA's surveillance database and published case reports up to February 2002 found 192 patients who had pancreatitis (22 fatalities) after treatment with one or more antipsychotics. This included monotherapy with clozapine (72 patients), olanzapine (62), risperidone (31), and haloperidol (12). Most cases occurred within 6 months of starting therapy.

1. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry* 1992; **149:** 714.
2. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis. *Lancet* 1992; **340:** 251.
3. Garlipp P, *et al.* The development of a clinical syndrome of asymptomatic pancreatitis and eosinophilia after treatment with clozapine in schizophrenia: implications for clinical care, recognition and management. *J Psychopharmacol* 2002; **16:** 399–400.
4. Jubert P, *et al.* Clozapine-related pancreatitis. *Ann Intern Med* 1994; **121:** 722–3.
5. Koller EA, *et al.* Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. *Pharmacotherapy* 2003; **23:** 1123–30.

Extrapyramidal disorders. Clozapine retains a place in therapy, despite its propensity to cause agranulocytosis, because, in part, of its reduced rate of extrapyramidal effects (see also p.971). Other drugs in the class have since been developed. However, although atypical antipsychotics carry a lower risk of causing extrapyramidal disorders, the risk is not zero; acute effects and tardive syndromes have been reported with these drugs, and the developing tendency to use them for high-dose therapy may perhaps narrow the margin of advantage.[1]

1. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Safety* 2005; **28:** 191–208.

Hypersalivation. Hypersalivation has been reported[1] to occur in up to 54% of patients receiving clozapine. The pathophysiology for this effect is unclear, but proposed mechanisms include action at muscarinic (M_3 and M_4) receptors, blockade of

α_2-adrenoceptors, or distortion of the swallowing reflex. Management strategies have included chewing gum to increase frequency of swallowing or reduction of clozapine dosage in stabilised patients; antimuscarinics or α_2-agonists have been tried when other methods have failed. However, antimuscarinics could potentially exacerbate the antimuscarinic adverse effects of clozapine, and intranasal ipratropium bromide has been tried as an alternative with beneficial results in one small uncontrolled study.[2]

1. Davydov L, Botts SR. Clozapine-induced hypersalivation. *Ann Pharmacother* 2000; **34:** 662–5.
2. Calderon J, *et al.* Potential use of ipatropium [sic] bromide for the treatment of clozapine-induced hypersalivation: a preliminary report. *Int Clin Psychopharmacol* 2000; **15:** 49–52.

Neuroleptic malignant syndrome. A review of the literature[1] suggested that clozapine may produce fewer extrapyramidal effects and a lower rise in creatine kinase concentrations than classical antipsychotics. The incidence of neuroleptic malignant syndrome (NMS— p.972) with clozapine appeared to be similar to that with classical antipsychotics;[1] however, its presentation may differ, with fever and rigidity less frequent, and possibly less severe, but diaphoresis more common.[2] Nevertheless, a later review[3] concluded that manifestations of NMS associated with the atypical antipsychotics clozapine, olanzapine, quetiapine, and risperidone were of similar nature and severity to those associated with classical antipsychotics. NMS has also been reported[4] with the use of amisulpride and aripiprazole.

1. Sachdev P, *et al.* Clozapine-induced neuroleptic malignant syndrome: a review and report of new cases. *J Clin Psychopharmacol* 1995; **15:** 365–71.
2. Karagianis JL, *et al.* Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. *Ann Pharmacother* 1999; **33:** 623–30. Correction. *ibid.*; 1011.
3. Ananth J, *et al.* Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; **65:** 464–70.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Aripiprazole and neuroleptic malignant syndrome. *Aust Adverse Drug React Bull* 2007; **26:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0704.pdf (accessed 03/04/08)

Withdrawal. Abrupt withdrawal of clozapine may be associated with symptoms that have been described as 'cholinergic rebound' although the manifestations, which may include headache, profuse sweating, hypersalivation, bronchoconstriction, agitation, enuresis, and diarrhoea also have some common features with the serotonin syndrome (p.416); motor disorders and exacerbation of extrapyramidal disorders have also occurred. In addition, as with other antipsychotics, abrupt withdrawal of clozapine may be associated with rapid relapse of the original psychosis. In a retrospective case-note study of 29 schizophrenic patients whose clozapine treatment was withdrawn, abrupt withdrawal in 20 resulted in a marked, immediate deterioration in their mental state.[1] Of 3 further patients who experienced delirium with psychotic symptoms shortly after stopping clozapine, symptoms developed in 1 within 24 hours despite gradual withdrawal of clozapine over a 2-week period.[2] All the patients responded rapidly to resumption of low doses of clozapine.

1. Baker M, White T. Life after clozapine. *Med Sci Law* 2004; **44:** 217–21.
2. Stanilla JK, *et al.* Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry* 1997; **58:** 252–5.

Precautions

Clozapine should not be given to patients with uncontrolled epilepsy, alcoholic or toxic psychoses, drug intoxication, or a history of circulatory collapse. It should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. It is contra-indicated in patients with bone-marrow suppression, myeloproliferative disorders, or any abnormalities of white blood cell count or differential blood count. It is also contra-indicated in patients with a history of drug-induced neutropenia or agranulocytosis with the exception of that due to chemotherapy. It should not be used with drugs that carry a high risk of bone-marrow suppression (see Interactions, below).

Clozapine is contra-indicated in patients with severe renal impairment; caution is required in mild to moderate renal impairment. It should be used with caution in hepatic impairment and avoided in symptomatic or progressive liver disease or hepatic failure. Patients with a history of cardiac impairment or abnormal cardiac findings on examination should be referred to a specialist for further evaluation, which may include an ECG; treatment with clozapine should only then be started if the potential benefits clearly outweigh any risk. Clozapine should not be used in severe heart failure.

Clozapine possesses antimuscarinic properties and consequently it is contra-indicated in patients with paralytic ileus; it should also be used with caution in benign prostatic hyperplasia and angle-closure glaucoma.

Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes (see Effects on Carbohydrate Metabolism, above).

Monitoring the white blood cell and absolute neutrophil counts is mandatory during clozapine treatment and should be carried out in accordance with official recommendations; these may vary between countries (see Monitoring, below for further details). Patients or their carers should report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

Patients who develop tachycardia at rest, dyspnoea, arrhythmias, chest pain, or other signs and symptoms of heart failure should be investigated immediately and clozapine treatment stopped if a diagnosis of myocarditis or cardiomyopathy is suspected.

Because of an increased risk of collapse due to orthostatic hypotension associated with rapid dose escalation during initial titration of clozapine dosage, it is recommended that treatment should be begun under close medical supervision. In addition, patients with Parkinson's disease should have their blood pressure monitored for the first weeks of treatment.

On planned withdrawal, the dose of clozapine should be reduced gradually over at least a 1- to 2-week period in order to avoid the risk of rebound psychosis and other withdrawal symptoms (see above). If abrupt withdrawal is necessary then patients should be observed carefully.

Clozapine may affect the performance of skilled tasks such as driving.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of clozapine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Clozapine appears to be distributed into breast milk in relatively high concentrations.[2] Concentrations in a patient given 50 mg daily were 63.5 nanograms/mL in breast milk and 14.7 nanograms/mL in plasma; at 100 mg daily they were 115.6 nanograms/mL and 41.4 nanograms/mL, respectively.

The manufacturers have also stated that studies in *animals* suggest that clozapine is excreted into breast milk and has an effect on nursing infants; they recommend that mothers receiving clozapine should not breast feed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/05)
2. Barnas C, *et al.* Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. *Am J Psychiatry* 1994; **151:** 945.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics, including clozapine, in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs in this class. See under Risperidone, p.1024.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 24/05/05)

Monitoring. ***WHITE CELL COUNTS.*** A white blood cell count and a differential blood count must be performed before starting clozapine therapy and regularly throughout treatment. Treatment should not be started if the white blood cell count is less than 3500 cells/mm^3 and the absolute neutrophil count (ANC) is less than 2000 cells/mm^3, or if there is an abnormal differential count. Monitoring should continue throughout therapy and for 4 weeks after withdrawal.

In the EU, including the UK, monitoring is performed at weekly intervals for the first 18 weeks and then at least every 2 weeks between weeks 18 and 52; after 1 year of treatment with stable neutrophil counts, patients may be monitored at least every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 or the ANC falls to between 1500 and 2000 cells/mm^3 then monitoring should be performed **twice weekly** until values stabilise or increase.
- Clozapine should be **withdrawn** immediately if the white blood cell count falls below 3000 cells/mm^3 or the ANC drops below 1500 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In the USA, white blood cell and ANC are monitored weekly for the first 6 months and then every 2 weeks thereafter; after 1 year of therapy, patients may be monitored every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 and the ANC is above 1500 cells/mm^3 then monitoring should be performed **twice weekly**.
- If the white blood cell count falls below 3000 cells/mm^3 or the ANC is below 1500 cells/mm^3 then clozapine treatment should be **interrupted** and counts performed daily. Clozapine may be restarted if the white blood cell count recovers to above 3500 cells/mm^3 and the ANC to above 2000 cells/mm^3. After recovery, weekly monitoring is recommended for the next 12 months before reducing to every 2 weeks for 6 months, and then every 4 weeks thereafter.
- Clozapine should be **withdrawn** if the white blood cell count falls below 2000 cells/mm^3 or the ANC drops below 1000 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In patients with decreased white blood cell or ANC it is especially important that they or their carers report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

EOSINOPHIL COUNT. In the EU, clozapine should be withdrawn if the eosinophil count is greater than 3000 cells/mm^3; it should only be restarted once the count has fallen to below 1000 cells/mm^3.

Similar advice is given in the USA although the values differ: clozapine should be withdrawn if the eosinophil count is above 4000 cells/mm^3 and restarted once the count has fallen to below 3000 cells/mm^3.

PLATELET COUNT. European licensing information states that clozapine should be stopped if the platelet count falls below 50 000 cells/mm^3.

TREATMENT BREAK. If treatment with clozapine is interrupted for reasons other than abnormal haematological values then more frequent monitoring may be required following resumption of therapy.

In the EU, patients who have taken clozapine for at least 18 weeks and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 4 weeks if the counts are stable; a break of 4 weeks or more would require weekly monitoring for the next 18 weeks.

US licensed product information recommends resuming weekly monitoring for 6 months in patients whose therapy has been interrupted for more than 1 month; frequency of monitoring is then reduced as described in White Cell Counts, see above. Those who have taken clozapine for at least 6 months and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 2 weeks for 6 months if the counts are stable; those on clozapine for over 1 year may be monitored every 4 weeks after initial weekly monitoring for 6 weeks.

Pregnancy. A review of the literature[1] between 1993 and April 2004 suggested that clozapine and olanzapine do not appear to increase the risk of fetal teratogenicity; literature regarding aripiprazole, quetiapine, risperidone, and ziprasidone was incomplete or not available. The rate of spontaneous abortions in pregnant women exposed to clozapine or olanzapine was not found to be higher than that of the general population; however, these 2 drugs increased the risk of hyperglycaemia in pregnant women. A prospective comparative study[2] of pregnancy outcomes in women taking clozapine, olanzapine, quetiapine, and risperidone also concluded that atypicals do not appear to be associated with an increased risk for major malformations when compared to the baseline risk in the general population. The authors recommended that benefits and risks be weighed carefully in each case and optimal control of the psychiatric disorder be maintained throughout pregnancy and postpartum together with careful monitoring.

1. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. *Ann Pharmacother* 2004; **38:** 1265–71.
2. McKenna K, *et al.* Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 2005; **66:** 444–9.

Interactions

Clozapine may enhance the central effects of MAOIs and CNS depressants including alcohol, antihistamines, benzodiazepines, and opioid analgesics.

Clozapine should not be used with drugs that carry a high risk of bone-marrow suppression including carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulfonamides, antineoplastics, or pyrazolone analgesics such as azapropazone. Long-acting depot antipsychotics have myelosuppressive potential and should not be used with clozapine as they cannot be withdrawn rapidly should neutropenia occur. Additive effects may occur when clozapine is given with drugs that possess antimuscarinic, hypotensive, or respiratory depressant effects. Clozapine may reduce the effects of alpha-adrenoceptor agonists such as noradrenaline.

The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit or act as a substrate to this isoenzyme may affect plasma concentrations of clozapine and the dose of clozapine may need to be altered. Increased plasma-clozapine concentrations, with an increased risk of adverse effects, may be seen in patients who suddenly stop smoking. Use with phenytoin or other enzyme-inducing drugs may accelerate the metabolism of clozapine and reduce its plasma concentrations.

◊ References.

1. Taylor D. Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 1997; **171:** 109–12.

Antibacterials. A patient with schizophrenia controlled with clozapine therapy had a tonic-clonic seizure 7 days after starting treatment with *erythromycin*.[1] It appeared that erythromycin had inhibited the metabolism of clozapine and raised its serum concentrations. Increased drowsiness and hypersalivation have been seen in a patient receiving clozapine and *ampicillin*; he recovered when ampicillin was replaced with doxycycline.[2]

Giving clozapine with *rifampicin* has resulted in decreased clozapine concentrations with consequent return of paranoid thoughts in a patient with a complicated history of schizophrenia.[3] An improvement was seen after rifampicin was replaced with ciprofloxacin. The interaction was thought to be due to the induction of cytochrome P450 isoenzymes, particularly CYP1A2, by rifampicin, resulting in the accelerated metabolism of clozapine.

1. Funderburg LG, *et al.* Seizure following addition of erythromycin to clozapine treatment. *Am J Psychiatry* 1994; **151:** 1840–1.
2. Csík V, Molnár J. Possible adverse interaction between clozapine and ampicillin in an adolescent with schizophrenia. *J Child Adolesc Psychopharmacol* 1994; **4:** 123–8.
3. Joos AAB, *et al.* Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with atypical mycobacterial infection. *J Clin Psychopharmacol* 1998; **18:** 83–5.

Antidepressants. Rises in serum concentrations of clozapine have been found in patients receiving clozapine after addition of *fluoxetine*[1] or *fluvoxamine*[2] to therapy. Increased serum concentrations of clozapine have also been reported when *paroxetine* or *sertraline* was added to therapy.[3] A possible serotonin syndrome (p.416) has been reported[4] in a patient receiving *clomipramine* after clozapine was gradually withdrawn from the treatment regimen, although the symptoms were also similar to those of clozapine withdrawal (see above). There has been an isolated report[5] of a patient who developed myoclonic jerks 79 days after fluoxetine was added to treatment with clozapine and lorazepam, although some[6] doubt whether the effects were entirely due to an interaction. Giving clozapine with *lithium* may increase the risk of neuroleptic malignant syndrome. For reference to neurological reactions in patients receiving lithium with clozapine, see p.405.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Jerling M, *et al.* Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16:** 368–74.
3. Centorrino F, *et al.* Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996; **153:** 820–2.
4. Zerjav-Lacombe S, Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. *Ann Pharmacother* 2001; **35:** 180–2.
5. Kingsbury SJ, Puckett KM. Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473.
6. Baldessarini RJ, *et al.* Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473–4.

Antiepileptics. Use of *phenytoin* or other *enzyme-inducing antiepileptics* may accelerate the metabolism of clozapine and reduce its plasma concentrations. Studies have found that addition of *sodium valproate* to clozapine therapy may increase[1] or decrease[2] plasma concentrations of clozapine. Although no increase in clozapine-related adverse effects or loss of control of psychotic symptoms were reported in these studies, there has been a report[3] of a patient who experienced sedation, confusion, slurring of speech and other functional impairment after valproate was given with clozapine.

See also under Benzodiazepines, below.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* 1994; **36:** 487–8.
3. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* 1995; **15:** 139–41.

Antipsychotics. Giving *risperidone* to a patient with schizoaffective disorder partially controlled by clozapine produced clinical improvement but was associated with a 74% rise in serum-clozapine concentrations over a 2-week period.[1] Although no adverse effects occurred in this patient, the potential for serious adverse effects requires caution if these drugs are used together. Neuroleptic malignant syndrome associated with use of clozapine with *haloperidol* has been reported.[2]

See also under Chlorpromazine, p.974.

1. Tyson SC, *et al.* Pharmacokinetic interaction between risperidone and clozapine. *Am J Psychiatry* 1995; **152:** 1401–2.
2. Garcia G, *et al.* Neuroleptic malignant syndrome with antidepressant/antipsychotic drug combination. *Ann Pharmacother* 2001; **35:** 784–5.

Antivirals. Although the UK manufacturers of *ritonavir* have stated that it may increase plasma concentrations of clozapine with a resultant increase in the risk of toxicity, there is evidence to suggest that, in fact, ritonavir may decrease the plasma concentrations of clozapine.[1] Ritonavir has been noted to induce the cytochrome P450 isoenzyme CYP1A2 and hence, as clozapine is primarily metabolised via this isoenzyme, an acceleration of the metabolism of clozapine would be expected. US prescribing information has been amended accordingly.

1. Penzak SR, *et al.* Comment: significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999; **33:** 1372–3.

Benzodiazepines. Concern has been expressed over reports of cardiorespiratory collapse in patients taking both clozapine and benzodiazepines.[1,2] In response, the manufacturers of clozapine outlined[3] similar cases reported to them in the USA. Of 7 cases of respiratory arrest or depression only 2 involved recent use of a benzodiazepine; among 26 cases of orthostatic hypotension with syncope reported during the first year the drug was marketed, only 8 included recent benzodiazepine use. The manufacturers concluded that an increased risk of such reactions in patients taking both drugs simultaneously was possible but not established, and advised caution when starting clozapine therapy in patients taking benzodiazepines.

Hypersalivation associated with clozapine and benzodiazepines may be exacerbated when these drugs are used together. A patient[4] experienced increased hypersalivation, salivary thickening, and distension of the parotid glands when *clonazepam* was added to treatment with clozapine. Adverse effects reported in 5 other patients given clozapine and benzodiazepines together included hypersalivation, sedation, ataxia, and symptoms of delirium.[5,6]

1. Sassim N, Grohmann R. Adverse drug reactions with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry* 1988; **21:** 306–7.
2. Friedman LJ, *et al.* Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518.
3. Finkel MJ, Schwimmer JL. Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518–19.
4. Martin SD. Drug-induced parotid swelling. *Br J Hosp Med* 1993; **50:** 426.
5. Cobb CD, *et al.* Possible interaction between clozapine and lorazepam. *Am J Psychiatry* 1991; **148:** 1606–7.
6. Jackson CW, *et al.* Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry* 1995; **7:** 139–41.

Buspirone. Potentially fatal gastrointestinal bleeding, accompanied by severe acidosis and hyperglycaemia, developed in a patient given buspirone with clozapine.[1] The patient had previously been taking clozapine for over a year without adverse effect, and was subsequently maintained on clozapine alone without a recurrence of symptoms.

1. Good MI. Lethal interaction of clozapine and buspirone? *Am J Psychiatry* 1997; **154:** 1472–3.

Gastrointestinal drugs. A patient stabilised on clozapine developed increased serum clozapine concentrations and signs of clozapine toxicity after starting treatment with *cimetidine*.[1] Cimetidine was withdrawn and ranitidine substituted without recurrence of toxicity.

A marked reduction in plasma-clozapine concentrations was seen in 2 smokers stabilised on the antipsychotic who began treatment with *omeprazole*,[2] which is a known inducer of the cytochrome P450 isoenzyme CYP1A2. However, a small retrospective analysis of the effect of stopping omeprazole in 13 patients taking both drugs suggested that the effect of omeprazole was only significant in non-smokers, and the clozapine dose did not need to be adjusted in any of these patients.[3]

1. Szymanski S, *et al.* A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 1991; **52:** 21–2.
2. Frick A, *et al.* Omeprazole reduces clozapine plasma concentrations: a case report. *Pharmacopsychiatry* 2003; **36:** 121–3.
3. Mookhoek EJ, Loonen AJ. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm World Sci* 2004; **26:** 180–2.

Xanthines. *Caffeine* may inhibit the metabolism of clozapine.[1,2] Care should be taken before stopping or starting caffeine-containing beverages in patients stabilised on clozapine treatment.

1. Carrillo JA, *et al.* Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998; **18:** 311–16.
2. Hägg S, *et al.* Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000; **49:** 59–63.

Pharmacokinetics

Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by first-pass metabolism. Peak plasma concentrations are achieved, on average, about 2.5 hours after oral doses. Clozapine is about 95% bound to plasma proteins and has a mean terminal elimination half-life of about 12 hours at steady state. It is almost completely metabolised and routes of metabolism include *N*-demethylation, hydroxylation, and *N*-oxidation; the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect. It is distributed into breast milk.

◊ References.

1. Jann MW, *et al.* Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993; **24:** 161–76.
2. Lin S-K, *et al.* Disposition of clozapine and desmethylclozapine in schizophrenic patients. *J Clin Pharmacol* 1994; **34:** 318–24.
3. Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? *Clin Pharmacokinet* 1997; **32:** 93–100.
4. Olesen OV. Therapeutic drug monitoring of clozapine treatment: therapeutic threshold value for serum clozapine concentrations. *Clin Pharmacokinet* 1998; **34:** 497–502.
5. Guitton C, *et al.* Clozapine and metabolite concentrations during treatment of patients with chronic schizophrenia. *J Clin Pharmacol* 1999; **39:** 721–8.
6. Dettling M, *et al.* Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. *Psychopharmacology (Berl)* 2000; **152:** 80–6.
7. Renwick AC, *et al.* Monitoring of clozapine and norclozapine plasma concentration-time curves in acute overdose. *J Toxicol Clin Toxicol* 2000; **38:** 325–8.
8. Frazier JA, *et al.* Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. *J Clin Psychopharmacol* 2003; **23:** 87–91.
9. Tang Y-L, *et al.* Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *Br J Clin Pharmacol* 2007; **64:** 49–56.

Bioavailability. Mean plasma concentration of clozapine increased from 329 to 629 nanograms/mL in 10 patients when switched from an extemporaneous liquid formulation to conventional tablets.[1]

1. Coker-Adeyemi F, Taylor D. Clozapine plasma levels in patients switched from clozapine liquid to tablets. *Pharm J* 2002; **269:** 650–2.

Uses and Administration

Clozapine is a dibenzodiazepine derivative and the prototype of the atypical antipsychotics. It has relatively weak dopamine receptor-blocking activity at D_1, D_2, D_3, and D_5 receptors but has a high affinity for the D_4 receptor. Clozapine possesses alpha-adrenergic blocking, antimuscarinic, antihistaminic, antiserotonergic, and sedative properties.

Clozapine is used for the management of schizophrenia; however, because of the risk of agranulocytosis, it is reserved for patients who fail to respond to other antipsychotics, including other atypicals, or who experience severe neurological effects with such drugs. In the USA, it may also be used for reducing the risk of recurrent suicidal behaviour in those with schizophrenia or schizoaffective disorder who are at chronic risk for suicidal behaviour. In the UK, it is also used in the management of treatment-resistant psychoses associated with Parkinson's disease.

Clozapine use must be accompanied by strict procedures for the monitoring of white blood cell counts (see Precautions, above). To minimise the incidence of ad-

verse effects, clozapine therapy should be introduced gradually, beginning with low doses and increasing according to response.

In the treatment of **schizophrenia**, including reducing the risk of suicidal behaviour, the usual oral dose is 12.5 mg once or twice on the first day followed by 25 mg once or twice on the second day. Thereafter the daily dosage may be increased gradually in steps of 25 to 50 mg to achieve a daily dose of up to 300 mg within 14 to 21 days (in the USA, up to 450 mg daily is permitted by the end of 2 weeks). Subsequent increases in steps of 50 to 100 mg may be made once or twice weekly; a daily dosage of 900 mg should not be exceeded. Once a therapeutic response has been obtained, a gradual reduction of dosage to a suitable maintenance dose is recommended; most patients respond to 200 to 450 mg daily. The total daily dose is given in divided doses; a larger portion may be given at night. Daily maintenance doses of 200 mg or less may be given as a single dose in the evening. If clozapine is to be withdrawn, this should be done gradually over a 1- to 2-week period. However, immediate withdrawal with careful observation is essential if neutropenia develops or if myocarditis or cardiomyopathy is suspected (see Precautions, above).

Elderly patients may require lower doses of clozapine and it is recommended that treatment should start with a dose of 12.5 mg on the first day and that subsequent dose increments should be restricted to 25 mg.

For patients who are restarting treatment after an interval of more than 2 days, 12.5 mg may be given once or twice on the first day. If this dose is well tolerated it may be possible to increase the dosage more quickly than when first starting. However, patients who have had respiratory or cardiac arrest with initial dosing, but were then successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after a break of even 24 hours. Additional monitoring of blood cell counts may also be required if treatment is interrupted, see Treatment Break, under Monitoring, above.

It is recommended that oral therapy with other antipsychotics should be withdrawn gradually before treatment with clozapine is started.

Clozapine has also been given by intramuscular injection.

In the management of treatment-resistant **psychoses in Parkinson's disease**, the initial oral dose of clozapine is no more than 12.5 mg once daily in the evening. Thereafter, the daily dosage may be increased in increments of 12.5 mg up to twice a week; a dose of 50 mg daily should not be reached before the end of the second week. The usual dose ranges from 25 to 37.5 mg daily. Increases in the daily dose above 50 mg should only be made in exceptional cases in increments of 12.5 mg at weekly intervals up to a maximum of 100 mg daily. The total daily dose should preferably be given as a single dose in the evening. Dosage of antiparkinsonian drugs may be increased when there has been complete remission of psychotic symptoms after at least 2 weeks of clozapine therapy. If psychotic symptoms recur after increases in antiparkinsonian therapy, the dose of clozapine may need to be increased in line with the above guidance. As in patients with schizophrenia, planned withdrawal of clozapine in patients with Parkinson's disease should also be gradual in decrements of 12.5 mg over 1 to 2 weeks.

Action. Antipsychotics are thought to work through inhibition of dopamine D_2-receptors (see p.975), but this hypothesis fails to explain the activity of the atypical antipsychotics such as clozapine. How clozapine produces its antipsychotic activity is not clear; it has a high affinity for a number of different receptors.[1]

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164:** 141–8.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of clozapine. Although some reports indicate that it is perfectly possible to switch from branded to generic clozapine,[1-4] the need for monitoring and concerns about any requirement for retitration of doses (because of potential lack of bioequivalence[5]) have to be taken into account. There have been a few reports of exacerbation of psychotic symptoms in patients who were switched to a generic formulation.[6,7]

1. Sajbel TA, *et al.* Converting patients from brand-name clozapine to generic clozapine. *Ann Pharmacother* 2001; **35:** 281–4.
2. Makela EH, *et al.* Branded versus generic clozapine for treatment of schizophrenia. *Ann Pharmacother* 2003; **37:** 350–3.
3. Stoner SC, *et al.* A program to convert patients from trade-name to generic clozapine. *Pharmacotherapy* 2003; **23:** 806–10.
4. Bazire S, Burton V. Generic clozapine in schizophrenia: what is all the fuss about? *Pharm J* 2004; **273:** 720–1.
5. Lam YW, *et al.* Branded versus generic clozapine: bioavailability comparison and interchangeability issues. *J Clin Psychiatry* 2001; **62** (suppl 5): 18–22.
6. Kluznik JC, *et al.* Clinical effects of a randomized switch of patients from clozaril to generic clozapine. *J Clin Psychiatry* 2001; **62** (suppl 5): 14–17.
7. Mofsen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. *Clin Ther* 2001; **23:** 1720–31.

Bipolar disorder. Clozapine is of benefit for the treatment of mania in patients with bipolar disorder (p.372), and the use of atypical antipsychotics in the management of such patients is increasing. However, the adverse effects of clozapine may restrict its use.

Dementia. Although atypical antipsychotics such as clozapine have been tried in elderly patients with dementia, the licensing authorities in the USA now recommend against such use, see under Precautions, above. For further discussion of the management of disturbed behaviour, see p.954.

Parkinsonism. Clozapine is used as an alternative to classical antipsychotics in the management of **treatment-resistant psychoses** in patients with Parkinson's disease (p.791). Some neurologists even consider clozapine to be the antipsychotic of choice in these patients,[1] although this remains to be determined. A review[2] in 1994 considered that there was little evidence to support clozapine as first choice given the quality of the available studies and the need for extensive monitoring. However a subsequent double-blind, placebo-controlled study[3] showed that low-dose clozapine treatment (up to 50 mg daily) significantly improved drug-induced psychosis without worsening parkinsonism. Adverse effects noted in this study were generally mild, although in the clozapine group of 30 patients, there was 1 report of leucopenia. A similar study also reported benefit,[4] although 7 of 32 patients noted some aggravation of parkinsonism, usually mild and transient, while receiving clozapine. Adverse effects reported from other individuals have also included a patient with parkinsonism who had worsening of psychotic symptoms when her dose of clozapine was increased,[5] and the sudden return of psychosis in another patient with parkinsonism whose psychosis was successfully treated with clozapine for 5 years.[6]

Low-dose clozapine (about 40 mg daily) also appears to be of benefit in the management of **levodopa-induced dyskinesias** in patients with severe Parkinson's disease.[7]

1. Klein C, *et al.* Clozapine in Parkinson's disease psychosis: 5-year follow-up review. *Clin Neuropharmacol* 2003; **26:** 8–11.
2. Pfeiffer C, Wagner ML. Clozapine therapy for Parkinson's disease and other movement disorders. *Am J Hosp Pharm* 1994; **51:** 3047–53.
3. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340:** 757–63.
4. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; **353:** 2041–2.
5. Auzou P, *et al.* Worsening of psychotic symptoms by clozapine in Parkinson's disease. *Lancet* 1994; **344:** 955.
6. Greene P. Clozapine therapeutic plunge in patient with Parkinson's disease. *Lancet* 1995; **345:** 1172–3.
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Schizophrenia. Clozapine is an effective antipsychotic for the management of schizophrenia (p.955) but its use is limited by its blood toxicity. Its effectiveness and superiority over classical antipsychotics was shown in a multicentre study.[1] Patients refractory to at least 3 different antipsychotics and who failed to improve after a single-blind trial of haloperidol, were randomised, double-blind, to treatment for 6 weeks with either clozapine up to 900 mg daily, or chlorpromazine hydrochloride up to 1800 mg daily with benzatropine mesilate up to 6 mg daily. Of the 267 patients included in the evaluation, 5 of 141 (4%) improved with chlorpromazine and benzatropine, and 38 of 126 (30%) improved with clozapine. Clozapine was superior to chlorpromazine in the treatment of negative as well as positive symptoms. Reviews[2,3] of clozapine indicate that these findings have been well replicated both in subsequent studies and in clinical practice. It is, however, unclear for how long clozapine should be tried: although 1 study[4] identified new responses up to 12 months after starting therapy, others have indicated that if improvement was not seen within the first 6 to 24 weeks, it was unlikely to occur.[2,5]

Clozapine is also used to reduce suicide risk in patients with refractory chronic schizophrenia.[6] The reported suicide rate of 0.05% per year in 6300 patients in the UK given clozapine since 1990 was considered to be tenfold less than expected.[7] A subsequent study[8] found it to be more effective than olanzapine in preventing suicide attempts in patients with schizophrenia or schizoaffective disorder at high risk.

Clozapine has shown consistent clinical benefit in schizophrenic patients with persistent aggressive or violent behaviour.[2,9] Whether this is due to a sedative effect, a specific antiaggressive action, or just reflects an overall improvement in psychosis is unknown.

Clozapine has been advocated for use in schizophrenic patients with moderate to severe tardive dyskinesia. It is still unclear whether clozapine can itself cause tardive dyskinesia but some patients with established tardive dyskinesia have experienced improvement in their symptoms when using clozapine.[10,11]

1. Kane J, *et al.* Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45:** 789–96.
2. Buckley PF. New dimensions in the pharmacologic treatment of schizophrenia and related psychoses. *J Clin Pharmacol* 1997; **37:** 363–78. Correction. *ibid.* 1998; **38:** 27.
3. Wahlbeck K, *et al.* Clozapine versus typical neuroleptic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 24/05/05).
4. Meltzer HY, *et al.* A prospective study of clozapine in treatment-resistant schizophrenic patients I: preliminary report. *Psychopharmacology (Berl)* 1989; **99:** S68–S72.
5. Conley RR, *et al.* Time to clozapine response in a standardized trial. *Am J Psychiatry* 1997; **154:** 1243–7.
6. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 1995; **152:** 183–90.
7. Kerwin RW. Clozapine: back to the future for schizophrenia research. *Lancet* 1995; **345:** 1063–4.
8. Meltzer HY, *et al.* Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60:** 82–91. Correction. *ibid.* 735.
9. Volavka J, *et al.* Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol* 2004; **24:** 225–8.
10. Tamminga CA, *et al.* Clozapine in tardive dyskinesia: observations from human and animal model studies. *J Clin Psychiatry* 1994; **55** (suppl B): 102–6.
11. Nair C, *et al.* Dose-related effects of clozapine on tardive dyskinesia among "treatment-refractory" patients with schizophrenia. *Biol Psychiatry* 1996; **39:** 529–30.

Preparations

USP 31: Clozapine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lapenax; Sequax; ***Austral.:*** Clopine; Clozaril; ***Austria:*** Lanolept; Leponex; ***Belg.:*** Leponex; ***Braz.:*** Leponex; Zolapin†; ***Canad.:*** Clozaril; ***Chile:*** Leponex; ***Cz.:*** Leponex; ***Denm.:*** Leponex; ***Fin.:*** Froidir; Leponex; ***Fr.:*** Leponex; ***Ger.:*** Elcrit; Leponex; ***Gr.:*** Leponex; ***Hong Kong:*** Clozaril; ***Hung.:*** Leponex; ***India:*** Lozapin; Sizopin; ***Indon.:*** Clozaril; Sizoril; ***Irl.:*** Clozaril; ***Israel:*** Leponex; Lozapine; ***Ital.:*** Leponex; ***Malaysia:*** Clozaril; Zapine; ***Mex.:*** Clopsine; Leponex; ***Neth.:*** Leponex; ***Norw.:*** Leponex; ***NZ:*** Clopine; Clozaril; ***Philipp.:*** Leponex; ***Pol.:*** Klozapol; Leponex; ***Port.:*** Leponex; Ozapim; ***Rus.:*** Leponex (Лепонекс); ***S.Afr.:*** Cloment; Leponex; ***Singapore:*** Clozaril; ***Spain:*** Leponex; ***Swed.:*** Leponex; ***Switz.:*** Clopin; Leponex; ***Thai.:*** Cloril; Clozaril; ***Turk.:*** Leponex; ***UK:*** Clozaril; Denzapine; Zaponex; ***USA:*** Clozaril; FazaClo; Fazalco†; ***Venez.:*** Leponex.

Cyamemazine *(rINN)*

Ciamemazina; Cyamémazine; Cyamemazinum; Cyamepromazine; RP-7204. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile.

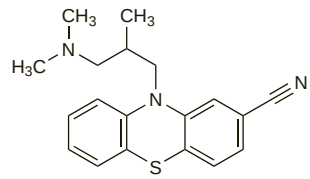
Циамемазин

$C_{19}H_{21}N_3S$ = 323.5.

CAS — 3546-03-0 (cyamemazine); 93841-82-8 (cyamemazine tartrate).

ATC — N05AA06.

ATC Vet — QN05AA06.



Profile

Cyamemazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is used in the management of a variety of psychiatric disorders including anxiety disorders (p.952) and aggressive behaviour (p.954).

Cyamemazine has been given orally as the base or the tartrate and by injection as the base. Doses are expressed in terms of the base; cyamemazine tartrate 36.6 mg is equivalent to about 25 mg of cyamemazine. Oral doses have ranged from 25 to 600 mg daily, depending on the individual and the condition being treated; the daily dosage is given in 2 or 3 divided doses. Doses given by intramuscular injection have ranged from 25 to 200 mg daily.

Cyamemazine should be given in reduced dosage to elderly patients; the parenteral route is not recommended for the elderly.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Tercian; ***Port.:*** Tercian.