sis project. We heard some disturbing rumours from the gaol, but 10 days later the ophthalmologist reappeared looking quite fit and free of any charge. He said that he had been well looked after in prison for he was related to most of the gaolers.

Well outside Wau was a smart German leprosy hospital of scrupulously clean red roofed buildings surrounded by the tropical colour of bourganvillia, flame trees, and the fragrant blossom of frangipani. The hospital houses 50 inpatients and its clinics served many more outpatients, displaying the whole spectrum of the disease from pure lepromatous to pure tuberculous cases, and all stages from the earliest innocuous looking macules to the disease of many years standing with severe mutilation. A farm next to the hospital compound provided work for some of the patients. Cobblers made orthopaedic shoes to protect anaesthetic feet and there were advisers to instruct patients in the limitations and dangers of anaesthetic limbs and to aid rehabilitation. One of the oldest patients was employed as the gate keeper. Dressed in a green uniform and sporting a topee he would salute with a fingerless hand and teased me mercilessly for stalling my motorcycle in front of the gate.

At Wau the river waters were becoming very low. An old and sickly hippo was stranded in one of the pools. As the water level dropped the hippo's back became exposed and the children took

to stoning the creature until a game warden put it out of its misery. The river trips were becoming less productive for fly catching as the dry season progressed, but the bird population swelled with migrants and the area provided a fascinating interface between the familiar pale arctic species and the more exotic residents of the tropical forest and woodland savannah. In a comparatively small area over 180 species were seen.

The steamer made good time on the return journey from Juba to Khartoum, leaving me with several days free before my return flight. The steps where General Gordon was killed are hidden behind the guarded walls of the palace, but over the river in Omdurman I could visit the Khalifa's house and the Mahdi's tomb and on a Friday afternoon watch some dervishes whirl themselves into a dizzy trance. On the bank of the Blue Nile lies the wreck of Gordon's paddlesteamer, *Bordein*, and Kitchener's gunboat, *Melik*, is now the sailing club house. My hosts took me for picnics on the Blue Nile, supposedly free of bilharzia. Two early morning sandgrouse shoots on the White Nile gave me a final view of that great river, to whose waters, once drunk, it is said, one must return. I hope the saying is true.

(Accepted 20 April 1983)

New Drugs

Antidepressants

BRIAN R BALLINGER, JOHN FEELY

The classification of depression presents many problems, but most psychiatrists group depressions into psychotic and neurotic (or endogenous and reactive). Depressive symptoms may also be secondary to other psychiatric illness such as schizophrenia or organic syndromes and may be a side effect of drugs. Antidepressant treatment should usually be considered only after detailed consideration of the nature of the symptoms and causes. Not all patients with depressive symptoms require drugs, and in some individuals other forms of treatment may be important, such as electroconvulsive therapy, psychotherapy, and, possibly, cognitive therapy and behaviour therapy.

Tricyclic antidepressant drugs

Imipramine was the original tricyclic antidepressant and has been used for over 20 years. Most trials have shown it to be superior to placebo, resulting in improvement in about two thirds of cases. Amitriptyline, introduced subsequently, was shown to be as effective but more sedative.

The disadvantages of the original tricyclic antidepressants that have become apparent over the years include inefficacy in some cases of depression, slow onset of action, and various side effects including the commonly occurring anticholinergic side effects as well as danger when taken in overdose.

A succession of newer tricyclic antidepressants and similar drugs has been introduced subsequently, often with claims of speedier action and fewer side effects. They have different degrees of sedative effect but generally seem to have a similar range of activity to each other and to the older drugs. The results of most trials support their claims to be effective antidepressants, although many of the studies have been comparisons with established agents. In patients with less severe depression an apparently favourable result from a trial against another antidepressant may just indicate that both drugs have a sedative effect or that spontaneous remissions occur. Small numbers make many trials difficult to interpret.

Newer tricyclic antidepressants include dothiepin, which has some sedative action and fewer anticholinergic side effects than amitriptyline. Dothiepin is an effective antidepressant and usually well tolerated. Clomipramine, on the other hand, has a particularly pronounced effect on the uptake of serotonin. This drug is not particularly sedative but anticholinergic side effects may sometimes be a problem. It has been used as an intravenous infusion, but there is no evidence that this has any specific advantages. It has been claimed that clomipramine may be particularly effective in treating obsessional neurosis, although this may be partly an effect on associated depressive symptoms.

Lofepamine (Gamanil) is a very recently introduced tricyclic

Royal Dundee Liff Hospital, Dundee DD2 5NF

BRIAN R BALLINGER, FRCP, FRCPsych, consultant psychiatrist

Department of Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY

JOHN FEELY, MD, MRCP, lecturer

Correspondence to: Dr B R Ballinger.

antidepressant which is claimed to have fewer anticholinergic side effects and to be less cardiotoxic in overdose than amitriptyline.

There is evidence that most tricyclic antidepressants inhibit the reuptake of noradrenaline and serotonin into neurones. Some drugs act predominantly on the uptake of serotonin—for instance, amitriptyline, imipramine, and clomipramine—and others on noradrenaline—for instance, nortriptyline, desipramine. This action is linked to the amine hypothesis of depression which suggests that symptoms are caused by changes in amine metabolism. It is by no means totally certain, however, that this is the basis of the antidepressant action of these drugs.

Being lipid soluble, these drugs are readily absorbed and undergo first pass metabolism in the liver. Their rate of metabolism varies considerably, in part due to genetic control that results in a large variation in plasma steady state concentrations in patients given the same dose and a wide variation in the elimination half life. Many tricyclics produce demethyl metabolites that are pharmacologically active and ring hydroxylation leads to inactive metabolites excreted by the kidneys. Tricyclic antidepressants are widely distributed throughout the body and being 90% protein bound they are not susceptible to active elimination techniques in overdose. Preliminary evidence suggests that plasma concentrations may be higher in elderly people and that lower doses are required.

New antidepressant drugs resembling tricyclics

Various new antidepressants have been introduced, including those with a two (bicyclic) or four (tetracyclic) ring nucleus, although the clinical importance of the structural differences is uncertain. These and other agents appear in the table. In no case has the efficacy of the newer antidepressants been shown to exceed those of the tricyclics, but most have fewer anticholinergic side effects than amitriptyline.

Some established tricyclic and new antidepressant drugs*

Approved name	Proprietary name	Elimination half life of active drug (h)	Usual dose range (mg/day)
Tricyclics:			
Amitriptyline	Domical, Elavil, Lentizol, Saroten, Tryptizol	30–45	50–150
Imipramine	Praminil, Tofranil	10–20	75–150
Clomipramine	Anafranil	20–40	30–100
Dothiepin	Prothiaden	45–56	75–150
Bicyclic:			
Viloxazine	Vivalan	2–5	150–400
Zimelidine	Zelmid	7–17	200–300
Tetracyclic:			
Maprotiline	Ludiomil	30–50	50–150
Mianserin	Bolvidon, Norval	10–17	30–120
Others:			
Nomifensine	Merital	2–4	75–200
Trazodone	Molipaxin	5–8	100–400

* Full prescribing instructions should be consulted and lower doses may be appropriate in some elderly patients and higher in refractory depressions.

BICYCLICS

Viloxazine is completely absorbed and extensively metabolised in the liver. Unlike the tricyclics it is not highly protein bound and has a short elimination half life that has led to the suggestion that it should be given two or three times daily. Some controlled trials have shown little difference in antidepressant effects from the standard drugs. Viloxazine has little sedative action and few anticholinergic and cardiac side effects. Nausea has been reported as a frequent side effect and seems to be dose related, which possibly limits its usefulness.

Zimelidine—Extensive metabolism in the liver results in an active metabolite norzimelidine with a longer elimination half

life (about 17 hours) than the parent drug (about seven hours). Elimination is reduced in elderly people, and 100 mg is the recommended dose for this age group. Acting predominantly on the reuptake of serotonin, zimelidine may not interact with the hypotensive adrenergic neurone blockers. Trials have shown it to have a similar antidepressant effect as traditional drugs and to have little sedative action. It has relatively few anticholinergic and cardiac side effects but nausea, insomnia, and headache have been reported in some patients. Experience of this drug is still relatively limited in Britain.

TETRACYCLICS

Maprotiline—As with most of the extensively metabolised antidepressants, maprotiline shows considerable variation among individuals in steady state concentrations. It seems to be an effective antidepressant and is claimed to have fewer anticholinergic side effects than older drugs. Maprotiline is sedative and does not differ greatly from the tricyclic antidepressants.

Mianserin is extensively metabolised in the liver, and its profile of action differs considerably from the tricyclic antidepressants as it does not block amine uptake. It has negligible anticholinergic side effects and is relatively safe in patients with heart disease. Nevertheless, occasional blood dyscrasias and arthropathy have been reported. Mianserin is a widely used antidepressant with a pronounced sedative effect and is relatively safe in overdose.

Other new antidepressant drugs

Nomifensine—Although metabolised to a glucuronide after a single dose, during chronic treatment unchanged nomifensine is present in the plasma. This is excreted by the kidney, and the drug should be avoided in chronic renal failure because it accumulates. Because of a short elimination half life the drug should be given two to three times daily, although it is not certain that this is essential. Nomifensine inhibits the reuptake of noradrenaline and dopamine to nerve endings and has little sedative effect. It is apparently an effective antidepressant and is claimed to have fewer anticholinergic side effects and to be relatively free of cardiovascular side effects, although sleep disturbance, restlessness, and nausea have been reported. Its action on dopamine metabolism led to the suggestion that it may be effective in treating patients with parkinsonism and depression, but this has not been fully established. Also unlike many other antidepressants it does not appear to be epileptogenic.

Trazodone—Chemically unrelated to other agents this antidepressant blocks postsynaptic serotonin receptors. Trazodone is metabolised in the liver with a relatively short elimination half life and is often given in divided doses with the larger portion at bedtime. It is claimed to be a quick acting antidepressant with anxiolytic properties and fewer anticholinergic and cardiac side effects than amitriptyline. Time will tell whether it has any clear advantages.

Use of tricyclic and allied antidepressant drugs

Various general considerations apply to the older and newer tricyclic and allied antidepressants.

Response—These drugs are generally more effective in psychotic (endogenous) depressions. Their antidepressant action does not appear for one to three weeks and further improvement may occur later. The claims that some newer drugs act more quickly have not been fully substantiated.

Duration of treatment—When these drugs are effective in treating depression there is evidence that their use should be continued for several months, and trials have suggested that some patients benefit from at least six months' treatment.

Longer term treatment may prevent depressive episodes in some patients liable to recurrent depression, although lithium is at least as effective.

Dosage—Dose requirement varies, and plasma concentrations vary widely among individuals. There is no evidence that very small doses of antidepressants should be used in mild depression. Many of the tricyclic antidepressants have similar dose ranges, and dosage should be increased over a few days to minimise side effects. Elderly patients generally require lower doses.

Manner of administration—These drugs are almost always given by mouth, and there are no clear advantages for parenteral administration. Several trials have shown that administration once daily is as effective as the traditional divided doses, although a few patients tolerate divided doses better. The dose is often best given in the evening, particularly with the more sedative drugs.

Plasma concentrations—There is evidence that intermediate plasma concentrations of tricyclic antidepressants may be more effective than higher or lower concentrations, and plasma concentrations vary substantially among different individuals given the same dose. Monitoring services have been introduced in some centres, but it is still not clear whether their routine use would be justified as a therapeutic range is not clearly established. They provide a useful index of patient drug compliance in non-responders, although urine testing may be simpler.

Side effects—Side effects have been a serious limiting factor in the use of these drugs, and they tend to start before the therapeutic effect is apparent. Side effects include the anticholinergic symptoms such as dry mouth, visual accommodation difficulties, constipation, and hesitant micturition. These are particularly pronounced with amitriptyline but occur in the whole group, and although a nuisance and occasionally hazardous may sometimes be a guide to the need to adjust the dose. The problem in their evaluation is that some of the symptoms resemble those of depressive illness. Sedation may be a problem, although this may be minimised by selecting an appropriate drug. Other side effects include precipitation of epilepsy, tremor, nausea, and psychiatric complications including hypomania and confusional state. Cardiovascular side effects, including orthostatic hypotension, tachycardia, flattening of the T wave, and conduction defects on the electrocardiogram, have been reported and occasional sudden cardiac deaths may be a hazard, perhaps particularly with amitriptyline. Cardiac effects may be a major problem in overdose. These drugs should be used with great caution in pregnancy.

Drug interactions may occur with other sedative drugs including alcohol. By blocking the uptake of adrenergic neurone blockers—for example, guanethidine—methyldopa, and clonidine, tricyclics can reverse their antihypertensive effect.

Other antidepressant drugs

Other drugs that differ from the tricyclic and related antidepressants include monoamine oxidase inhibitors, tryptophan, some neuroleptics, and lithium. Monoamine oxidase inhibitors such as phenelzine, tranylcypromine, and isocarboxazid retain a place in the management of some patients with depression. Trials of these agents have given variable results, and side effects have led to caution in their use, particularly with regard to hypertensive interactions with certain foodstuffs and drugs (including tricyclic antidepressants). Many psychiatrists believe that monoamine oxidase inhibitors still have a place in the treatment of depression, particularly in certain patients with "atypical" symptoms including some types of neurotic depression with anxiety and phobic symptoms. They do not appear to be the agents of choice in most psychotic depressions.

Tryptophan is the precursor of the indolamines, and its use

as an antidepressant was suggested by the amine hypothesis of depression. Some trials suggested that it may be effective but this has not always been confirmed. The place of tryptophan in antidepressant treatment remains uncertain, although it may potentiate monoamine oxidase inhibitors such as phenelzine.

Neuroleptics are mainly used in the treatment of schizophrenia, and indeed depression has been described as a possible side effect of some of them. Nevertheless, flupenthixol (Fluanxol), a thioxanthene derivative, has been advocated as an antidepressant. This is not fully established, but it may be worth trying in certain refractory cases, at a dose range of 1.5–3 mg daily.

Lithium is not a new drug, but after initial reports of toxic effects its introduction was delayed. It has been used widely since the 1960s for the prophylaxis of bipolar manic depressive psychosis using plasma concentration control. Recently, however, there has been a growing realisation that lithium is effective in the prophylaxis of recurrent depression. It has also been shown to have some effect in acute depression, but it should not be recommended as the usual treatment for this at present.

Place of newer antidepressant drugs

The place of newer antidepressants alongside the older agents such as imipramine and amitriptyline has been the matter of some debate. The newer drugs have fewer side effects but they are less well tried, and there are still some lingering doubts about the efficacy of some of them. The newer drugs are generally more expensive.

The older drugs still have a major place in treating depression, but the new agents should be considered in some conditions, such as patients with heart disease, frail older patients, patients intolerant of anticholinergic and other side effects of imipramine and amitriptyline, and in the presence of serious suicidal risk.

We thank Dr G J Naylor for helpful comments.

Bibliography

- Brogden RN, Heel RC, Speight TM, Avery GS. Mianserin: a review of its pharmacological properties and therapeutic efficacy in depressive illness. *Drugs* 1978; **16**:273-301.
- A full review of the pharmacology and clinical use of mianserin, including information about clinical trials and side effects.
- Carlsson A, Gottfries C, Holmberg G, Modigh K, Svensson T, Ogren S, eds. Recent advances in the treatment of depression. *Acta Psychiatrica Scand* 1981; **63**, suppl 290.
- A conference symposium partly about zimelidine but also includes papers on other aspects of depression and its treatment.
- Gershon S, Lader MH, Caldwell ADS, eds. *New directions in antidepressant therapy. International congress and symposium*. Series No 46. London: Royal Society of Medicine, 1981.
- This is partly related to trazodone but also contains a review of other aspects of treatment with antidepressants.
- Hollister LE. Current antidepressant drugs: their clinical use. *Drugs* 1981; **22**:129-52.
- An up to date review of the clinical pharmacology of newer agents, a consideration of the amine hypothesis, and a general discussion on how and when these drugs should be used.
- Mindham RHS. Tricyclic antidepressants and amine derivatives. In: Paykel ES, ed. *Handbook of affective disorders*. Edinburgh: Churchill Livingstone, 1982:231-45.
- A useful and well balanced summary of the use of tricyclic and similar antidepressants, including a brief review of the newer agents.
- Paykel ES, Coppen A, eds. *Psychopharmacology of affective disorders*. Oxford: Oxford University Press, 1979.
- An excellent collection of reviews of the drug treatment of depression, including the newer preparations.
- Stonier PD, Jenner FA, eds. *Nomifensine—international congress and symposium*. Series No 25. London: Royal Society of Medicine, 1980.
- This symposium is mainly devoted to the pharmacology and clinical use of nomifensine but also summarises other aspects of the treatment of depression.