Burrows
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Editors: GRAHAM D. BURROWS
Department of Psychiatry
University of Melbourne

JOHN S. WERRY
Department of Psychiatry
University of Auckland

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LIST OF CONTRIBUTORS

Michael G. Aman	Department of Psychiatry, School of Medicine, University of Auckland, New Zealand
Thomas A. Ban	Tennessee Neuropsychiatric Institute, Vanderbilt University, Nashville
Graham D. Burrows	Department of Psychiatry, University of Melbourne, Australia
Paul E. Debenham	Department of Psychiatry, University of Melbourne, Australia
Yasuo Fujii	Department of Neuropsychiatry, Keio University, Tokyo, Japan
Silvio Garattini	Mario Negri Institute for Pharmacological Research, Milan, Italy
Kazuo Ichikawa	Department of Internal Medicine, Tokai University, Tokyo, Japan
Hitoshi Itoh	Department of Neuropsychiatry, Keio University, Tokyo, Japan
G. Laakmann	Psychiatric Hospital, University of Munich, West Germany
Malcolm Lader	Institute of Psychiatry, De Crespigny Park, Denmark Hill, London
Josee E. Leysen	Department of Biochemical Pharmacology, Janssen Pharmaceutica, Beerse, Belgium
Kay P. Maguire	Department of Psychiatry, University of Melbourne, Australia
Norbert Matussek	Psychiatric Hospital, University of Munich, West Germany

Trevor R. Norman — Department of Psychiatry, University of Melbourne, Australia

William M. Petrie — Tennessee Neuropsychiatric Institute, Vanderbilt University, Nashville

Hannes Petursson — Institute of Psychiatry, De Crespigny Park, Denmark Hill, London

Walter Rosser — Department of Family Medicine, University of Ottawa School of Medicine

Rosario Samanin — Mario Negri Institute for Pharmacological Research, Milan, Italy

Earl Usdin — National Institute of Mental Health, Rockville, Maryland, now at the Department of Psychiatry, University of California, Irvine

Simon N. Young — Department of Psychiatry, McGill University, Montreal, Canada

PREFACE TO VOLUME THREE

In this third volume of the series, recent research has been approached from two directions. The more clinical aspects are presented in Section I. Improvements in "second generation" antidepressant drugs, finer control over neuroleptics through plasma level measurement and an expert reevaluation of benzodiazepines begin this section. The next chapter presents a successful study in educating physicians to optimum use of prescriptions. From drugs to aid learning in the mentally retarded, we pass to the use of drugs in the elderly. Finally, sleep studies promise important insights into brain function.

Section II presents highly significant research indicating how drugs work. This wide-ranging section covers basic research strategies, the use of precursors for bioactive amines, and drug-related endocrine effects. There is a chapter on a recent breakthrough, measurement of receptors for neuroleptic drugs. The complexities of anorexia mechanisms are elaborated in the last chapter.

We hope that these essays will provide pleasure in the reading, as well as easy access to otherwise widely scattered information about recent and significant advances in psychopharmacology.

GRAHAM D. BURROWS
JOHN S. WERRY
Series Editors

CONTENTS

SECTION I

PHARMACOKINETICS AND CLINICAL ASPECTS

NEW ANTIDEPRESSANTS—CLINICAL STUDIES

Trevor R. Norman, Kay P. Maguire, and Graham D. Burrows

Recent years have seen the introduction of a number of new antidepressant drugs into clinical practice and a larger number for clinical evaluation. Many more compounds are tested and discarded after preclinical evaluation. Inevitably the question is posed: Why more antidepressants? Clearly some agents do not provide significant advances over the standard drugs, imipramine and amitriptyline, and have been ignored in prescribing habits. On the other hand, some minor chemical modifications of the basic tricyclic nucleus have produced drugs with advantages; for example, doxepin, an oxygenated derivative of amitriptyline, has produced less cardiac complications than another congener of amitriptyline, nortriptyline (Burrows et al., 1981). The past decade has seen a shift away from modifications of the tricyclics to diverse chemical structures with more specific actions on neurotransmitters. The promise of these new antidepressants is that

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Table 1. Some Advantages of Newer Antidepressants

	Anticholinergic effects	*Cardiovascular effects*	*Drug interactions*	*Extra clinical effect*	*Side effects*
Mianserin	low	very low	+vely with alcohol none with antihypertensives or anticoagulants	anxiolytic	sedation weight gain
Trazodone	low	possibly low			
Nomifensine	low	very low	none with alcohol	some anxiolytic effect rapid onset of action	no sedation
Zimelidine	low	low		phobic anxiety	
Amoxapine	less than tricyclics	not known		possible rapid onset of action	
Citalopram	negligible	low			
Bupropion	low	very low			may exacerbate psychotic symptoms, DA reuptake blocker

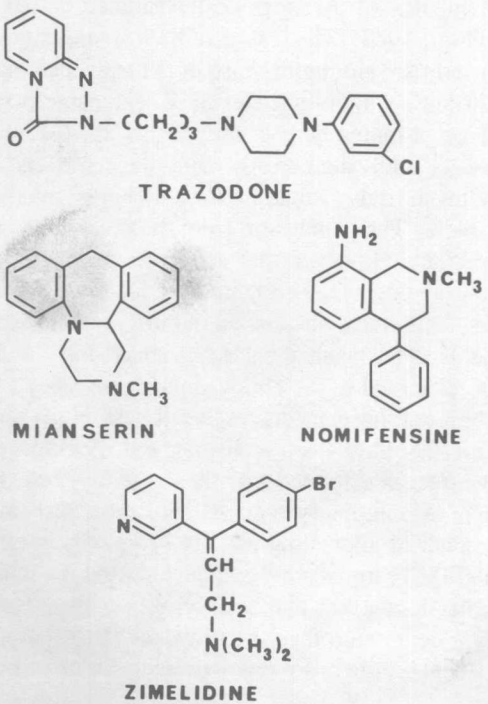
they will prove to be more effective than the older ones, both in terms of the side effects experienced by the patients and in response rates to the drug.

Coppen and Perris (1976) have suggested that about 30% of depressed patients will respond to a placebo. A certain percentage of patients do not respond to any treatment. Further, the tricyclics have associated cardiotoxic effects and numerous side effects. Anticholinergic effects occur commonly and dry mouth is the most frequent problem. Blurred vision, perspiration, tachycardia, dizziness, faintness, postural hypotension, nausea, and constipation are other effects commonly reported. Less frequently, micturition difficulties, delayed ejaculation, impotence and paralytic ileus have been reported, particularly at toxic doses. Another major disadvantage of the tricyclics is that they take up to 2 weeks or more to produce their clinical effects. These shortcomings of the tricyclics have provided the impetus for the development of new drugs.

MIANSERIN

Mianserin is the first example of a tetracyclic antidepressant (see Figure 1). It was developed as an antihistamine and antiserotonin compound and conse-

Figure 1.



quently has a pharmacological profile distinct from the tricyclics (van den Burg et al., 1970). The central antiserotonergic action of mianserin was confirmed by studies in mice, rats, and rabbits (Maj et al., 1978). Mianserin also has a presynaptic α_2-adrenoreceptor blocking activity (Fludder and Leonard, 1979). Mishra et al. (1980) demonstrated that chronic administration of mianserin to the rat caused subsensitivity of the noradrenaline receptor-coupled adenylate cyclase system. The α_2 blocking properties of mianserin could be responsible for this effect. Like nomifensine, mianserin has few anticholinergic effects (Brogden et al., 1978).

Metabolism of mianserin in man occurs predominantly by N-oxidation, N-demethylation, and aromatic hydroxylation, the major metabolites being 8-hydroxymianserin, N-desmethylmianserin and mianserin-N-oxide. Their pharmacological activity is unknown, but one or all may be active on peripheral serotonin uptake mechanisms (Coppen et al., 1978). Most of an administered dose of mianserin is excreted in the urine within 24 hours (Brogden et al., 1978).

Pharmacokinetics of mianserin have been studied after oral administration and intravenous infusion (Jansen, 1978). It was rapidly absorbed and distributed (half-life 1.4 hours) and slowly eliminated (half-life 17 hours). The volume of distribution in females was almost twice that observed in males. In 8 male volunteers pharmacokinetic parameters were similar to those reported by Jansen, except that the estimates of apparent oral clearance varied between the two studies (Maguire et al., 1982). The results of both studies suggest that the kinetic properties of mianserin are similar to those of the tricyclics, namely large apparent volume of distribution, high oral clearance, extensive first pass metabolism and slow elimination. Montgomery et al. (1978b) have shown that single and divided doses produce equivalent steady state plasma levels.

A selection of clinical trials evaluating the antidepressant activity of mianserin is presented in Table 2. The conclusion from these studies is that the drug is an effective antidepressant. However, the study of Perry and colleagues (1978) found no difference among mianserin, imipramine, and placebo in 46 patients treated for 3 weeks. This study was carried out in a predominantly neurotic group of depressed patients. The result then is not surprising, as the best effects of antidepressants are observed in the endogenous depressions. The dose of mianserin giving the best response in depressive illness is 60 mg/day, but higher doses up to 130 mg/day have been well tolerated. A single oral dose at night produces the same effect as a divided daily dose and may be beneficial in patients with initial insomnia (Montgomery et al., 1978b). Mianserin also has an efficacy equivalent to diazepam in alleviating anxiety symptoms in general practice patients (Murphy, 1978). There is some evidence, based on analysis of individual items of rating scales to suggest that mianserin is more effective in improving certain symptoms of depression than the tricyclics (Vogel et al., 1976). Further studies in larger patient numbers are required to elaborate this differential effect.

Table 2. Some Clinical Trials of Mianserin in Depressive Illness

No. of Patients	*Diagnosis*	*Dose mg/d*	*Duration of Trial*	*Comparative Substance*	*Results*	*References*
55	Mixed[§]	50–130	4–6 wks	nil (open study)	66% response	Marriott et al. (1981)
192	Mixed	10–130	5 wks	nil (open study)	65% response	Hopman (1980)
21	Endogenous	30	2 wks	placebo	M > P	Smith et al. (1978)
24	Mixed	30–120	6 wks	DIAZ	M > DIAZ	Russell et al. (1978)
17	Mixed	60	6 wks	AMI	M = AMI	Coppen et al. (1976)
57	Depression[†]	60–120	3 wks	AMI	M = AMI	Jaskari et al. (1977)
23	Mixed	60	4 wks	AMI	M = AMI	Vogel et al. (1976)
29	Endogenous	30–80	3 wks	CMI	M = CMI	Blaha et al. (1980)
30	Mixed	60 mg	4 wks	IMI	M = IMI	Pull et al. (1980)
20	Endogenous	50 mg	3 wks	AMI	M = AMI	Kretschmar (1979)

[§]A mixed group of endogenous and reactive depressions.
[†]Type of depression not stated.

ABBREVIATIONS USED IN THE TABLES

AMI	*amitriptyline*	*MAP*	*maprotiline*
CMI	*chlomipramine*	*M*	*mianserin*
DMI	*desipramine*	*N*	*nomifensine*
DOTH	*dothiepin*	*P*	*placebo*
DIAZ	*diazepam*	*T*	*trazodone*
IMI	*imipramine*	*Z*	*zimelidine*

Mianserin in the dosages used in clinical trials is well tolerated and in comparative studies with the tricyclics has significantly fewer side effects. Peet (1977) reviewed the side effect data from six comparative trials of mianserin against amitriptyline or imipramine. In contrast to the tricyclics where total side effect scores increased from baseline, the scores in patients receiving mianserin decreased. In particular, mianserin had a very low incidence of anticholinergic side effects. Kopera (1978a) measured pupil diameter and salivary production in 18 male volunteers who received amitriptyline, mianserin, or placebo for 8 days (6 volunteers per treatment). Mianserin was without significant anticholinergic effects in contrast to amitriptyline. The major side effect noted by Peet was drowsiness. The severity of this effect is usually mild, and tolerance develops

after the first week or two. Weight gain due to unusual appetites in patients receiving mianserin has also been noted (Harris and Harper, 1980). Hopman (1980) reported increased appetite in the majority of patients and an average weight gain of 2.13kg in 10% of patients. Other drug-related effects reported in clinical trials and causing withdrawal of the patients have been skin allergy, acute psychotic symptoms, and severe restlessness. This latter effect was also noted by Maguire et al. (1982) in a single dose pharmacokinetic evaluation of mianserin.

The effect of mianserin on psychomotor performance has been evaluated by Mattila et al. (1978). Twenty volunteers received amitriptyline, mianserin, or placebo for 2 weeks in a double-blind crossover study. Mianserin did not affect learning and memory or interact with alcohol in these tasks. However, coordination and reaction skills were impaired by mianserin on the first day. Mianserin interacted additively with alcohol. Amitriptyline impaired psychomotor skills up to day 7. Further studies are required to confirm this report and to assess the effect of mianserin on tasks related to car driving.

Some severe adverse reactions to mianserin have been reported. Agranulocytosis was reported in a female alcoholic patient treated with thyroxine and mianserin (Curson and Hales, 1978). After 5 weeks of mianserin treatment (60 mg/day) she presented feeling unwell with a sore throat and hyperpyrexia. The reaction was attributed to the mianserin. Tulloch (1978) reported hypotensive reactions in 2 female patients soon after commencing mianserin therapy, while Brooks (1980) reported an idiosyncratic pulmonary reaction in a 42-year-old male. Leucopenia was reported in a 73-year-old female 12 days after commencing mianserin (McHarg and McHarg, 1979). All drugs were ceased and the patient made a complete recovery after ampicillin treatment. Four cases of neutropenia associated with mianserin therapy have been reported (ADRAC, 1980). All 4 patients recovered without further serious complications.

Few studies have been carried out to evaluate drug interactions with mianserin. As described above, mianserin appears to interact additively with alcohol. Co-administration of mianserin and adrenergic-neurone-blocking drugs, such as bethanidine or guanethidine, or β-adrenergic blocking drugs (e.g. propranolol or propranolol+hydrallazine) did not produce any effect on blood pressure (Coppen et al., 1978; Burgess et al., 1978). Kopera (1979) found no effect of mianserin on the anticoagulant doses of phenprocoumon. Clearly further studies are required to assess pharmacodynamic and pharmacokinetic drug interactions with mianserin.

Interest in mianserin as an antidepressant has been stimulated by several reports of its apparent lack of effect on the cardiovascular system—a distinct advantage for the drug over the tricyclics. No consistent electrocardiographic effects were noted in 13 depressed patients receiving 80 to 120 mg of mianserin for 3 weeks (Peet et al., 1977). In a comparative study of mianserin, amitriptyline and placebo administered to healthy volunteers for 7 days, mianserin in

doses of up to 60 mg/day lacked the postural hypotension associated with amitriptyline treatment (Kopera, 1978a). Kopera (1978b) also studied the effects of mianserin on cardiological parameters in 54 patients stabilized on phenprocoumon treatment. They were randomly allocated to mianserin 60 mg/day, mianserin 30 mg/day, or placebo and treated for a 3-week period. Heart rate, blood pressure and electrocardiogram were monitored throughout the trial. Statistical analysis revealed no significant differences between the 3 patient groups in heart rate, systolic or diastolic blood pressure or electrocardiographic parameters. Burgess et al. (1979) studied the cardiac effects of mianserin 60 mg nocte in 8 depressed inpatients using systolic time intervals (STI) and high speed surface ECG. Cardiac parameters were evaluated during a placebo period and then after 4–6 weeks on drug therapy. No effects on the ECG were noted, but some changes were observed in the STI from the control period. The changes observed seemed to indicate a mixed and paradoxical effect on the heart: a positive inotropic effect (shortening of the QS_2) and decreased contractility (increased PEP:LVET ratio). The authors concluded that mianserin exerted these effects via the peripheral circulation.

Using His-bundle electrography, Burrows et al. (1979) observed no effect of mianserin on cardiac conduction. Mianserin was administered at 60 mg/day for 3 weeks to 10 depressed in-patients. No significant changes in heart rate or blood pressure (supine or standing) were observed.

On overdosage, mianserin does not cause the severe complications of most other antidepressants. In 21 adults who ingested mianserin alone, Crome et al. (1978) report that there were no serious cardiovascular problems. In another report, no ECG abnormalities were observed in a 53-year-old woman who overdosed on 600 mg of mianserin and 10 g of carbromal-like monoureides (Jansen, 1978). Plasma mianserin was 780 μg/L 5 hours after ingestion. In another case, first degree heart block was observed in a 39-year-old female who overdosed on 580 mg of mianserin, 35 mg diazepam and 30 mg nitrazepam (Green and Kendall-Taylor 1977). After 9 hours the ECG had returned to normal. One death has been reported in a woman who ingested 600 mg mianserin and a large dose of lorazepam (Crome and Newman, 1977).

These studies support the notion that mianserin is without significant cardiological effects and may be useful in the treatment of the depressed patient with heart disease.

Comparatively few studies have attempted to define the relationship between plasma concentration and clinical response for mianserin. Coppen et al. (1976) studied 17 depressed inpatients for 6 weeks and found no relationship between mianserin concentration and clinical response. On the other hand both Montgomery et al. (1978b) and Perry et al. (1978) demonstrated a relationship. Both studies found a significant negative relationship between clinical improvement and plasma level, that is, high plasma concentrations have a deleterious effect on improvement. Montgomery et al. suggested that a curvilinear relationship, with a