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A RANDOMISED DOUBLE-BLIND, MULTICENTRE PARALLEL GROUP STUDY TO COMPARE THE TOLERABILITY AND EFFICACY OF MOCLOBEMIDE ADMINISTERED IN THREE DIFFERENT DOSAGE REGIMENS IN DEPRESSED OUTPATIENTS IN PSYCHIATRIC PRACTICE

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A dissertation submitted to the Faculty of Medicine in part fulfilment of the requirements for the degree of Master of Medicine in Psychiatry at the University of the Witwatersrand

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ABSTRACT

Moclobemide is a reversible monoamine oxidase inhibitor. It is a short acting antidepressant, and previously studies were done comparing 300 to 600 mg dosages administered three times daily. Data on a twice daily dosage schedule is limited. This study compares the efficacy and tolerability of Moclobemide 150 mg twice daily as compared to two different three times a day schedules with total daily dosages of 300 to 450 mg respectively.

Thirty one adult outpatients with major depressive disorder (as defined by DSM-IIIR) were included in this trial. It was controlled in a randomised double-blind manner.

All treatments were found to be effective and no clinically significant differences between treatments could be demonstrated in this respect. Group 3 (150 mg b.d.) was found to be slightly more effective than the other two groups. Moclobemide was found to be effective at all dosage regimens with respect to treating co-morbid symptoms of anxiety and agitation. There were no differences between the groups with respect to type and frequency of adverse events. Overall tolerability was found to be good in all the treatment groups. Since the twice daily dosage is more convenient, it has been suggested that compliance will be enhanced on this regimen. The treatment response rates obtained confirm this conclusion.

DECLARATION

I declare that this dissertation is my own unaided work. It is being submitted for the degree of Master of Psychiatry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination at any other university.

_____

K.M. VUKOVIC

_____ day of _____ 1995

To Ivan, Bentley, Nina and Alice.

PREFACE

"One should always distrust the insane. They are of bad faith somehow and they know it. But they don't know how to alter it, and you doctors don't know how to cure it".

Lawrence Durrell
Monsieur
The Avignon Quartet

Do we know how to cure 'it'? We have been dazzled by eloquent research in psychopharmacology. How much closer are we going to get to understanding the complexities of the mind, and the neurochemistry behind the illness? Despite all of this, do we really know what we are doing when we administer medication? Do we really understand the nuances behind the drugs we use daily?

The motivation behind my study was an attempt at understanding better the clinical and practical implications at using a commonly prescribed antidepressant medication at different dosage regimens. Also to determine the most effective dosages and the various clinical outcomes thereof.

I wish to express thanks to Dr Michael Berk, who was my supervisor and co-investigator on this trial. For his continuous guidance, inspiration and keen interest in psychopharmacology.

With thanks to Dr David Franklin of the Medicine Department at Baragwanath Hospital, for his endless patience and good humoured assistance in creating accurate graphical representation of my data. Thanks to Dr Robert Schall of the Pharmacology Department of the Orange Free State for processing my raw data.

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CHAPTER ONE

1.1 ANTIDEPRESSANTS - AN OVERVIEW

It was postulated by the ancients, that melancholia was caused by an excess of "black bile", and, despite the failure of the investigators to identify the nature of this substance over the past 2000 years, the search for its identity continues. The importance of this search lies in its emphasis on the biochemical basis of affective disorders, and, in recent years, there have been a multitude of studies to suggest that such disorders arise as a consequence of malfunctioning of one or more neuronal limbic pathways. Neurones containing norepinephrine and 5-Hydroxytryptamine (5-HT) as neurotransmitters have been considered as the most likely candidates to be functionally abnormal in the affective disorders. Other transmitters and neuromodulators such as the neuropeptides and prostoglandins may also be involved; their precise role however, remains uncertain (Leonard, 1993a).

In the 1960s, it was known that most drugs that were clinically effective in treating depression, increased the availability of monoamines in the synapse. Early studies showed that reserpine, an antihypertensive agent that depletes neurones of norepinephrine, serotonin and dopamine, produced clinically significant depression in 15% or more of patients. These observations led to the early hypothesis that depression was caused by inadequate neurotransmission of monamines, most notably norepinephrine. The monoamine theory of depression postulates, that symptoms of the illness arise as a consequence of a deficit in the availability of norepinephrine and serotonin.

Direct evidence from the analysis of the body fluids of non-drug-treated depressed patients is equivocal. Indirect investigations of changes in the densities and/or functional activities of peripheral receptors of the noradrenergic and serotinergic systems provide more compelling evidence (Leonard, 1986). Studies of van Praag et al. (1970; 1973; 1979; 1982) and Asberg et al. (1976), have suggested that there could be a subgroup of depressed patients whose depressive symptoms are primarily related to a deficit in the availability of serotonin. Asberg et al. (1976) suggested that such patients, who were identified as having a markedly reduced concentration of the main serotonin metabolite, 5-hydroxy indoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF), were more prone to violent suicide attempts than those depressed patients free from such a severe deficit in serotonin. If such a subgroup of depressed patients exists, it would seem reasonable to speculate that antidepressants which selectively facilitate central serotinergic transmission should be particularly beneficial. Montgomery (1982) in an attempt to test this hypothesis, studied the response of a group of depressed patients either with or without low CSF 5-HIAA concentrations, after the administration of a serotonin selective (zimelidine) or nor-epinephrine selective (maprotiline) reuptake inhibitor. Results of this double-blind study, showed that the response to treatment did not correlate with the biochemical status of the patient. This study, as well as those of Veith et al. (1983), and Potter et al. (1985), in which the concentrations of metabolites in the urine were measured to assess the neurotransmitter status, raised doubts regarding the relationship between the CSF amine metabolite concentrations, and the response of the depressed patient to an amine selective reuptake inhibitor.

Despite these clinical observations, a plethora of antidepressants with the profiles that show a high degree of selectivity for the serotinergic or noradrenergic systems have been developed. There appears to be no clinical evidence to suggest that these drugs are more effective, or have a faster onset of action, than the older non-specific tricyclic antidepressants. Their major advantage appears to be reduction in their anticholinergic effects and a relative lack of cardiovascular toxicity in overdose or in patients with pre-existing disease of the myocardial conduction system (Leonard, 1993b).

Antidepressants have been developed that show a high degree of selectivity for the noradrenergic, serotinergic, or dopaminergic systems. Also, other drugs with antidepressant properties have been developed; they show selectivity for the GABA-ergic system, modulate benzodiazepine receptors, or act as partial agonists for a subpopulation of 5-HT receptors. Figure 1, records a list of antidepressants that have been developed in recent years (Bech, 1993).

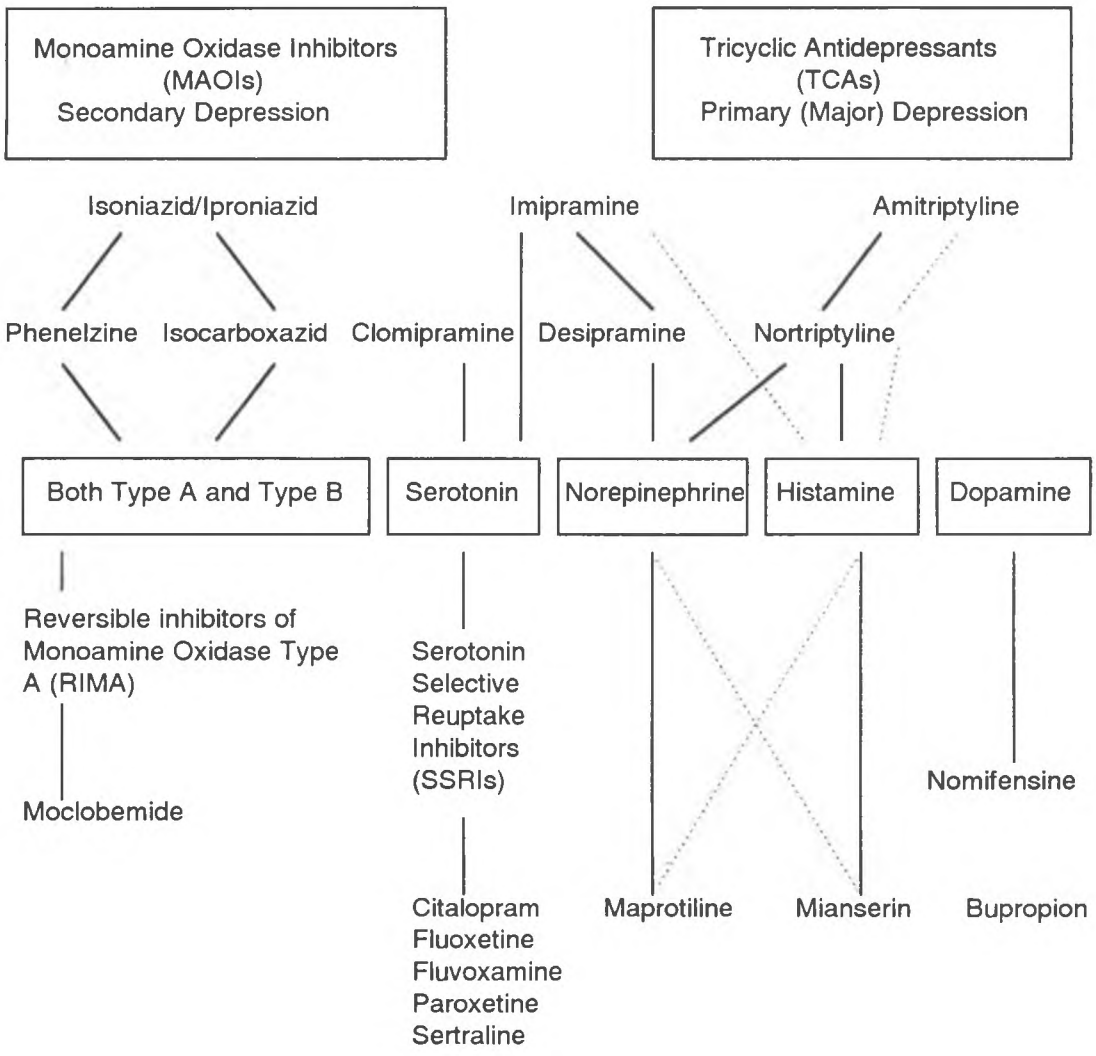


Figure 1: **Systems affected by old and new generations of anti-depressants**

Whilst there is no evidence that second generation antidepressants are therapeutically more effective than the "classical" antidepressants such as imipramine or phenelzine, there is evidence from those that have been widely used (for example, mianserin, fluoxetine and lofepramine) that they are less cardiotoxic and better tolerated by the patient. The question arises whether antidepressants have a common mode of action, that is not directly related to presumed specificity of action on a neurotransmitter in the brain.

Also, the new generation antidepressants differ from the old generations by being more specific than them or by acting predominantly on other systems, for example Dopamine (figure 1) (Bech, 1993). Thus, moclobemide, is a reversible inhibitor of monoamine oxidase type-A (RIMA) and fluoxetine, is a selective serotonin reuptake inhibitor (SSRI). Maprotiline is a norepinephrine reuptake inhibitor considered to be more specific than desipramine or nortriptyline, but it still seems to be closer to the older than to the new generations of antidepressants. Another tetracyclic antidepressant, mianserin, has a weak effect on norepinephrine and no effect on serotonin reuptake, but has a strong effect on histamine and is an α_2 antagonist. Bupropion, has a stimulatory action on the reuptake of dopamine, which is a relatively new action, compared with those of the older generations of antidepressants and is similar to nomifensine (Bech, 1993).

1.2 CLASSIFICATION OF DEPRESSION (THE SPECTRUM APPROACH)

The accuracy of psychiatric diagnosis was improved with the introduction of the DSM-IIIR. The diagnosis of depression referred to a descriptive

dimension; that is, it is based only on symptoms, their duration and severity; rather than referring to aetiologic functions (for example psychogenic versus endogenous depression). DSM-IIIR confirmed the descriptive validity of the diagnosis, often referred to as the spectrum of depression. The subdivision of depressive disorders, was therefore, made with reference to the severity of illness (symptoms) for example, major depression, less than major depression (for example dysthymia) and more than major depression (for example psychotic depression). Within these categories of depression, a further subdivision along a dimension of severity was not possible because the DSM-III-R algorithms are resistant to qualification (Bech, 1991; 1993).

1.2.1 Major Depression

The DSM-III-R symptomatological algorithm of major depression states that at least five of the following symptoms must be present for at least two weeks: depressed mood, lack of interest, significant changes in appetite and/or body weight, significant changes in sleep, psychomotor retardation or agitation, fatigue, guilt feelings, concentration difficulties, and suicidal thoughts or impulses. It furthermore states that this diagnosis should be discarded if superimposed on schizophrenia, schizophreniform disorders, delusional disorder, or other psychotic disorders. Brief depression, means a major depression lasting less than two weeks, whilst atypical depression means a clinical picture with hyperphagia, and hypersomnia, because depression is usually associated with loss of appetite and reduced sleep.

1.2.2 Less than Major Depression

The DSM-III-R algorithm of dysthymia is the prototype for less than major depression. At the symptomatological level, this algorithm says that at least two of the following symptoms must cluster with depressed mood, and have been present for most days within the last two years: Changes in appetite, insomnia, fatigue, low self-esteem, poor concentration or indecision, and feelings of hopelessness.

It also states that the diagnosis of dysthymia should be discarded, if the patient during the two year period has fulfilled the algorithm of major depression. Also, there has never been a Manic Episode, a Mixed Episode (mania and depression) and criteria have never been met for Cyclothymic Disorder. Dysthymia is subdivided into primary type and secondary type (for example secondary to panic disorders, substance use disorder, alcoholism, a physical disorder such as rheumatoid arthritis, or chronic pain syndrome). Patients with dysthymic disorders developing major depression might be described as having a "double depression" (Keller et al., 1983).

"Double depression" essentially, is a manifestation of the stage of illness. Similarly, the chronic form of panic disorder goes from the stage of increased awareness of body functions (neurotic only sometimes, hypochondriasis or neuroticism), to a stage of dysthymia which in a later stage goes onto a major depression (Sheenan, 1983). Akiskal et al. (1983), describes a person who suffers from dysthymia, as an individual who is "habitually gloomy, introverted, broody and over conscientious".

The International Classification Diseases (ICD-10), includes mixed anxiety - depression to emphasise that patients who do not fulfill the symptomatic criteria for major depression, often have anxiety as the predominating feature (WHO International Classification of Diseases tenth revision: 1992; Boulenger, 1993; Tyrer, 1989).

1.2.3 More than Major Depression

The DSM-III-R algorithm of psychotic depression, refers to the severe degree of major depression, in which either delusions or hallucinations are present. Furthermore, it should be specified whether the delusions are mood congruent or mood incongruent (Schatzberg, 1992).

1.3 CLINICAL CLASSIFICATION OF ANTIDEPRESSANTS

Historically, two different systems based on clinical symptoms have been used to classify antidepressants. These are the profile approach (for example the triple component system of antidepressants) and the intensity approach.

1.3.1 The Triple Component System of Antidepressants

Kielholz found antidepressants to have mood elevating, activating and sedative-anxiolytic properties. Antidepressants are therefore separated into three different categories depending on these properties. For example, the monoamine oxidase inhibitors (MAOIs), nomifensine and desipramine have activating properties. Desipramine, imipramine and amitryptilline were found to be mood elevating. Mianserin and thioridazine have sedative anxiolytic properties. Overlap occurs in the different groups, for example amitriptyline

and mianserin are sedative-anxiolytic, as well as mood elevating (Bech, 1993).

1.3.2 The Intensity Classification System

The Hamilton Rating Scale for Depression (HAM-D) is the most frequently used scale to measure outcome of the acute treatment of depression. The scale is more sensitive to change than self-rating scales in the acute treatment of depression. In clinical trials with antidepressive therapy, the HAM-D has most frequently been used to describe the intensity of the response to treatment (Hamilton, 1960).

1.4 THE MONOAMINE OXIDASE INHIBITORS (MAOI)

Iproniazid, was the first MAOI, to be synthesised as an anti-tuberculosis drug in the 1950s. It was noted to have stimulant and antidepressant properties and was subsequently shown to be an inhibitor of the enzyme monoamine oxidase (MAO). Other MAOIs have subsequently been developed and are in use. Iproniazid, however, is no longer in use due to its hepatotoxicity.

MAO is found primarily on membranes of mitochondria, and is the enzyme primarily responsible for the intracellular metabolism of biogenic amines. MAO in the presynaptic nerve terminals metabolises catecholamines that are found outside their storage granules. MAO, found in the liver and gut, metabolises bioactive amines that are ingested in foods, thus serving an important protective function. MAO enzyme activity may vary markedly among individuals, and appears to increase with ageing (Hyman and Arana, 1991).

Two subtypes have been described - monoamine oxidase A and B. Monoamine oxidase-A, preferentially metabolises norepinephrine and serotonin; MAO-B acts preferentially on phenylethylamine and benzylamine. Selective MAOIs have been developed; for example reversible MAOIs viz. moclobemide, however most MAOIs affect both A and B forms of the enzyme (see table 1, Hyman & Arana, 1991).

Table 1: Comparison of Monoamine Oxidase A and B

TYPE	LOCATION	PREFERRED SUBSTRATES	SELECTIVE INHIBITORS
A	Central nervous system, sympathetic terminals, liver, gut, skin	Norepinephrine, Serotonin, Dopamine, Tyramine, Octopamine, Tryptamine	Clorgyline
B	Central nervous system, liver, platelets	Dopamine, Tyramine, Tryptamine, Phenylethylamine, Benzylamine, N-methylhistamine	Deprenyl

Since the cellular compartementalisation of MAO-A and MAO-B in the central nervous system and peripheral organs determines which substrate has access to which isoenzyme, knowledge of the tissue distribution and cellular localisation of the enzymes is essential (Sau-wah Kwan et al., 1992).

Monoamine oxidases (MAO) oxidatively deaminate neurotransmitter and xenobiotic amines in the central nervous system and peripheral organs. Isoenzymes (MAO-A and MAO-B) have been identified by their substrate selectivity and their inhibitor sensitivity. In rodent brain, serotonin, dopamine and noradrenaline are preferentially metabolised by MAO-A, the trace amines

phenylethylamine and methylhistamine by MAO-B, and tyramine and octopamine by both enzymes (in human brain, a similar situation prevails except that dopamine is a substrate for both enzymes). The isoenzymes are integral flavoproteins of outer mitochodrial membranes in neurones, glia and other cells.

The physiological role of MAO is probably twofold: firstly, to maintain a low cytosolic amine concentration in monoaminergic neurons and other cells (for example glia) in order to further the uptake of monoamines by the respective transporters (that is, to facilitate, indirectly, the inactivation of released neurotransmitter amines), and secondly to prevent various natural substrates from accumulating in monoaminergic neurons, where they could interfere with the storage, release, uptake and receptor function of physiological neurotransmitter amines (Sau-Wah Kwan et al., 1992).

Phenelzine and isocarboxazid are hydrazine derivatives and are irreversible blockers of MAO whereas tranylcypromine reversibly inhibits MAO. Tranylcypromine is the only available non-hydrazine MAOI; it has structural characteristics similar to amphetamines and it also has some stimulant properties (Hyman and Arana, 1991).

1.4.1 Phenelzine - A Hydrazine Derivative of MAOI

This is the most durable MAO inhibitor (MAOI), and its use has become more widespread over recent years. It's pharmacokinetics have been extensively evaluated, and because it has less inhibitory activity than iproniazid in the liver, and more in the brain, it is less hepatotoxic. A major route of metabolism

is acetylation by hepatic acetyl transferase. The rate of acetylation is genetically determined and is bimodally distributed in the population: persons are either slow or fast acetylators. There also appears to be racial differences with respect to acetylation - approximately 50 percent of whites and blacks, and a high percentage of Asians are slow acetylators (Hyman and Arana, 1991).

It is well absorbed orally, and there appear to be no parenteral forms available. It appears to inhibit MAO in nerve terminals in the central nervous system, peripheral sympathetic nervous system and non-nervous system, for example liver and gut. It also partially inhibits other enzymes, but this effect is of little clinical consequence. With repeated dosing, maximal inhibition of MAO occurs within days. Onset of action is with two to four weeks which is approximately equivalent to the latency of onset of cyclic antidepressants.

For phenelzine, inhibition of greater than 85 percent of baseline platelet MAO type B activity correlates with therapeutic efficacy. Doses of greater than 45 mg per day are necessary to achieve this level of inhibition.

When patients taking MAOIs ingest vasoactive amines in foods, they are not catabolised, but enter the bloodstream and are taken up by sympathetic nerve terminals. These exogenous amines cause release of endogenous catecholamines, which can result in a hyperadrenergic crisis with severe hypertension, hyperpyrexia and other symptoms of sympathetic overactivity including tachycardia, diaphoresis, tremulousness, and cardiac arrhythmias. Amines in foods may induce these sympathomimetic crises in MAOI-treated

patients. For this reason, foods containing tyramine and other vasoactive amines and sympathomimetic drugs, should not be ingested by patients on MAOIs (see table 2 - sample instructions for patients taking MAOIs) (Hyman and Arana, 1991).

Phenelzine is thought to be the safest of the non-rima MAOIs, and is regarded by some as the standard MAOI. Most comparative trials regard it to be superior to placebo. Phenelzine has a greater incidence of side effects compared to tranylcypromine (viz., weight gain, drowsiness, anticholinergic-like effects, for example dry mouth and greater incidence of impotence and anorgasmia). Despite the fact that hepatotoxicity is uncommon, the hydrazines have a greater risk of causing fatal or serious hepatotoxicity than tranylcypromine. Phenelzine has been found to be as effective in imipramine in 32 patients with dysthymic disorder (Vallejo et al., 1987). Atypical depressions, characterised by having a mood reactive to situations, hyperphagia, hypersomnolence, leaden feeling, and sensitivity to rejection, responded better to phenelzine than to placebo or to imipramine (Quitkin et al., 1988). Thus it appears that MAOIs have selected areas in which they excel. Older trials in which MAOIs appeared to be less effective than tricyclics suffered from poor patient selection, and more importantly, doses of MAOIs were used that would now be considered subtherapeutic.

More recently, controlled studies (for example more than 45 ml/day of phenelzine) have shown equivalent efficacy of MAOIs with tricyclics. In clinical practice, the drugs compliment each other because MAOIs can help some patients who are tricyclic non responders (especially atypical

depression) and vice versa. MAOIs may also be the first choice agent in depression with panic symptoms. In the treatment of panic anxiety complicated by polyphobic behaviour, at least one study has found phenelzine to be more effective than imipramine (Quitkin et al., 1988).

Table 2: Sample Instructions for Patients taking Monoamine Oxidase Inhibitors (Hyman and Arana, 1991)

1. Certain foods and beverages must be avoided:
All cheese except for fresh cottage cheese or cream cheese.

MEAT
Beef liver
Chicken liver
Fermented sausages
Pepperoni
Salami
Bologna
Other fermented sausages
Other cured unrefrigerated meats

FRUITS
Overripe fruits, canned figs

BEVERAGES
Chianti wine
Some imported beers

FISH
Caviar
Cured, unrefrigerated fish
Herring (dried or pickled)
Dried fish, shrimp paste

VEGETABLES
Overripe avocados
Fava beans
Sauerkaut

OTHER FOODS
Yeast extracts(e.g. Marmite, Bovril)

SOME FOODS AND BEVERAGES SHOULD BE USED ONLY IN MODERATION
Chocolate Coffee Beer Wine

2. If you visit other physicians or dentists, inform them that you are taking an MAOI. This precaution is especially important if other medications are to be prescribed or if you are to have dental work or surgery.

3. Take no medication without a doctor's approval.
Avoid all over-the-counter pain medications except plain aspirin, acetaminophen (Tylenol), and ibuprofen.
Avoid all cold or allergy medications except plain chlorpheniramine (Chlortrimeton) or brompheniramine (Dimetane).
Avoid all nasal decongestants and inhalers.
Avoid all cough medications except plain guaifenesin elixir (plain Robitussin).
Avoid all stimulants and diet pills.

4. Report promptly any severe headache, nausea, vomiting, chest pain, or other unusual symptoms. If your doctor is not available, go directly to an emergency room.

Before beginning therapy with MAOIs it is important to educate the patient about the risks and interactions with amine containing foods, beverages and medications. Patients must clearly understand the need for dietary restrictions and it is recommended that the physician describe these issues before medication is prescribed. Casual prescription of MAOIs (non-rima), must be avoided because of the risks inherent in their use require a cautious approach and a co-operative patient. It is most useful to have a sheet of restrictions (see table 2) that can be given to the patient; and also it is of extreme importance to enlist family support in planning meals that avoid prescribed foods. In addition to dietary restriction, it is important to educate patients regarding common side effects, especially postural hypotension, insomnia, and possible sexual dysfunction. Informing patient about latency of therapeutic effects will minimise discouragement and noncompliance (Leonard, 1993c).

Phenelzine is commenced at 15 mg per day and may be increased to a twice daily dose (7,5 to 10 mg per day in the elderly). Dosages may be increased by 15 mg weekly to at least 60 mg. Usual doses of phenelzine are 45 to 90 mg per day (Robenson et al., 1978). Doses as high as 90 mg may be required.

At higher doses (more than 45 mg per day), it's effectiveness in certain types of patients becomes apparent. Phobic patients particularly seem to benefit, as do patients with symptoms of irritability, somatic anxiety, and hypochondriasis. Cases of 'endogenous' depression may also respond to higher doses.

Therapeutic effects often are not evident for two to four weeks. As with tricyclics, the aim is to achieve a therapeutic effect with the least possible toxicity. Before abandoning a trial of phenelzine as a failure, it is useful to obtain a platelet MAO level. If there is inadequate suppression (85 percent of baseline of an initial measurement was made or 85 percent of normal otherwise), a higher dose should be administered (Hyman and Arana, 1991).

It is prudent to taper MAOIs for a week or so when discontinuing them, psychoses have been reported with abrupt discontinuation. When MAOIs are stopped, MAO levels do not immediately return to normal. Thus, it is prudent to wait 14 days before discontinuing phenelzine. During changes from a MAOI (non-rima) to a cyclic antidepressant, similar waiting periods should be observed. Severe and even fatal interactions have been reported when tricyclics have been added to MAOIs (non-rima) (Leonard, 1993c).

There is little experience with the use of MAOIs in pregnancy. For this reason, their use should be avoided.

1.4.2 Side Effects and Toxicity

Fear of toxicity has severely limited the use of MAOIs. Nonetheless, in compliant patients these drugs can be used safely and effectively.

Postural hypotension is dose-related, and may limit therapy. This may be compounded by concomitant use of diuretics or antihypertensives. Episodes of hypotension almost always respond to a supine position. In severe cases

of hypotension intravenous fluids are required; pressor amines should be avoided if at all possible. Lower doses should be considered if insomnia and agitation occur. These side effects may also be treated with benzodiazepines. Severe daytime somnolence may occur with phenelzine, reducing the dose may improve this side effect (Hyman and Arana, 1991).

Hyperadrenergic crises are caused by ingestion of sympathomimetic drugs or pressor amines, such as tyramine, which is found in some foods and beverages. These reactions are serious and may cause stroke or myocardial infarction. All sympathomimetic drugs can lead to crises, as can L-dopa and tricyclic antidepressants. Symptoms include severe headache, diaphoresis, mydriasis, neuromuscular irritability, hypertension and cardiac arrhythmias. Other side effects include weight gain, impotence and anorgasmia, constipation and urinary retention (particularly in the elderly). Alternatively, nausea and diarrhoea have also been reported by some patients. Sweating, flushing or chills may also occur. Hepatitis may occur, this is a serious but rare side effect. Muscle twitching and electric-shock like sensations may also occur (Hyman and Arana, 1991).

1.4.3 Tranylcypromine

Tranylcypromine is the only available nonhydrazine MAOI antidepressant. It has structural characteristics similar to amphetamine and therefore also has some stimulant properties (see figure 2) (Hyman and Arana, 1991). It is rapidly absorbed and almost entirely metabolized and eliminated within 24 hours. Parenteral forms are not available. Tranylcypromine inhibits MAO in nerve terminals in the central nervous system, peripheral sympathetic

nervous system and non-nervous tissues such as liver and gut. Repeated dosing results in maximal inhibition of MAO in several days. Onset of action for antidepressant effect with MAOIs is two to four weeks, approximately equivalent to the latency of onset in cyclic antidepressants. Tranylcypromine reversibly inhibits MAO; thus, enzyme activity returns to normal within three to four days after discontinuation of the drug (Hyman and Arana, 1991).

Acetylation occurs in the liver, and the rate of acretylation is not thought to be clinically significant for this class of drugs. Tranylcypromine's metabolism does not seem to be affected by anticonvulsants. Tranylcypromine is atypical both in its inhibition and in its possession of amphetamine-like properties. Monoamine oxidase inhibition is quicker in onset and offset than with iproniazid, suggesting a different mode of monoamine oxidase inhibition (Hyman and Arana, 1991). Tranylcypromine is more effective against type B monoamine oxidase. In animals, tranylcypromine increases spontaneous activity, induces hypersensitivity to external stimuli, and results in sympathomimetic effects. Moderate doses of tranylcypromine produces EEG activation. Like amphetamine, tranylcypromine releases nor-adrenaline from its storage vesicles and inhibits its re-uptake (Hyman and Arana, 1991).

As is the case with tranylcypromine, there is an interaction with tyramine and other amines and for this reason they should be avoided by patients taking MAOIs. It is therefore important to educate these patients about the risks of interactions with amine-containing foods, beverages and medications. It is also important to educate the patient about common side effects, especially postural hypotension, insomnia, and possible sexual dysfunction. Informing

patients about the latency of onset of therapeutic effects will minimise discouragement and noncompliance (Leonard, 1993c).

Tranylcypromine, has a lower incidence of side effects as compared to phenelzine; it causes insomnia which may be severe in a minority of patients. Preliminary reports suggest that trazodone 25 to 50 mg at bedtime may safely and effectively treat insomnia. Though there may be a slightly higher risk of hypertensive crisis with tranylcypromine, MAO enzyme function returns to normal more quickly when this drug is discontinued than when hydrazine drugs are discontinued. Tranylcypromine may be the first choice MAOI in patients who are intolerant of sedation (Hollister, 1990).

MAOIs are administered at low doses, with gradual increases as side effects allow. Some tolerance may develop to side effects, including postural hypotension. Tranylcypromine in started at 10 mg twice or three times a day (5 to 10 mg/day in the elderly). Dosages can be increased by 10 mg weekly (as side effects allow) to 30 to 40 mg/day, dosages may be as high as 90 mg per day, however this is considered to be an extremely high dose and side effects must be monitored. Once depressive symptoms remit, lower dosages may be adequate for continuation and maintenance therapy (Leonard, 1993).

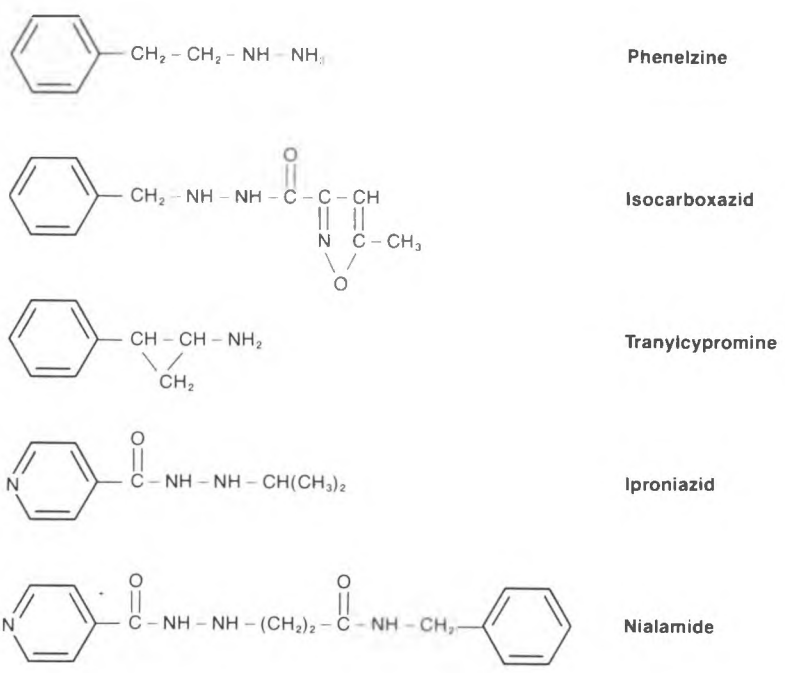


Figure 2: **Formulae of some monoamine oxidase inhibitors**

Therapeutic effects may not be evident for two to four weeks. The aim is to achieve a therapeutic effect with the least possible toxicity. This empirical process takes patience and careful dosage adjustment. MAOIs should be tapered before discontinuation, and when MAOIs are stopped MAO levels take some time to return to normal. It is also important to wait at least seven days before discontinuing MAOI dietary restrictions after discontinuing tranylcypromine. Severe and fatal interactions have been reported when tricyclics were added to tranylcypromine. Generally it is recommended that tricyclics be stopped for seven to ten days and fluoxetine for four to six weeks before starting tranylcypromine (Leonard, 1993c).

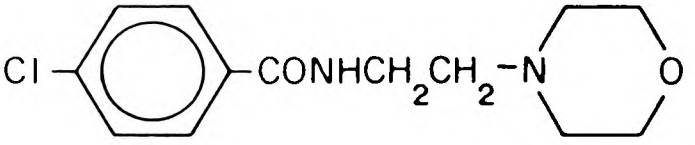
Adverse effects are much the same as for phenelzine; postural hypotension is dose related, and tends to limit therapy. This may be exacerbated in patients who are on antihypertensive agents or diuretics. Patients are advised to deal with this problem symptomatically - they are advised to be careful when changing posture. Pressor amines should be avoided (Hyman and Arana, 1991).

CHAPTER TWO

Monoamine oxidase inhibitors (MAOIs) were introduced in the 1950s for the treatment of depressive disorders, and despite their clinical efficacy, their use has been compromised by reports of hepatotoxicity, postural hypotension, and hypertensive crises resulting from concurrent administration of sympathomimetics particularly tyramine. The severe dietary restrictions and poor efficacy in initial trials resulted in the decline in clinical use of first generation, irreversible, nonselective MAO inhibitors. These agents were increasingly replaced with the tricyclic antidepressants.

A resurgence of interest in the use of MAO inhibitors for the treatment of depression resulted from the discovery of distinct subtypes of MAO - viz. MAO-A and MAO-B.

By selectively and competitively inhibiting MAO-A (the enzyme primarily responsible for deamination of monoamines implicated the aetiology of depression); whilst leaving MAO-B unaffected, these compounds can be expected to result in antidepressant action without the risk of development of a hypertensive crisis. The benzamide derivative, moclobemide (figure 3), a member of this second generation reversible, selective MAO-A inhibitors, is effective in the treatment of major depressive disorders and is devoid of the drawbacks associated with the non-selective MAO inhibitors (Fitton et al., 1992).



Moclobemide (MAO-A specific)

Figure 3: **Structural formulae of the benzamide derivative moclobemide**

2.1 PHARMACODYNAMIC PROPERTIES OF MOCLOBEMIDE

Affective disorders have been associated with a deficiency in the functional activity of central monoamines - serotonin and/or noradrenaline (Leonard, 1989).

Almost all presently available antidepressant drugs appear to enhance central monoaminergic (serotinergic and or nor-adrenergic) neurotransmission by increasing the synaptic availability of serotonin and/or noradrenaline or by sensitising of the post synaptic serotonergic or alpha-one-adrenergic receptor (Sulser, 1987). Long term administration of these drugs results in desensitisation of the noradrenaline-coupled adenyl cyclase system, which is generally associated with B-adrenoceptor down regulation (Sulser, 1987).

Monoamine oxidase, is an enzyme present in outer mitochondrial membranes both in neuronal and non-neuronal cells (Greenwalt, 1972). It is responsible for oxidative deamination of endogenous monoamines (noradrenaline, adrenaline, dopamine and serotonin) and trace exogenous amines (tyramine, octopamine, Z-phenylethylamine and tryptamine) in the central nervous system (CNS) and the periphery (Arana and Hyman, 1991). MAO exists in two functional forms: MAO-A and MAO-B, which are distinguished by differences in substrate preference, inhibitor specificity and tissue distribution (Arana and Hyman, 1991). MAO-A preferentially deaminates nonpolar aromatic amines such as phenethylamine and benzylamine (Knoll and Magyar, 1972). Tyramine and dopamine are substrates for both forms of MAO. Most human tissues contain both MAO subtypes, in the CNS MAO-A is

present in the basal forebrain and locus ceruleus, whereas MAO-B is present in the serotinergic neurones of the dorsal raphe nucleus. MAO-A predominates in the periphery in sympathetic nerve terminals and intestinal mucosa, where it is involved in the deamination of exogenous monamines derived from food, for example tyramine whereas MAO-B, however, predominates in the liver and lungs (Da Prada et al., 1988). MAO-A appears to be the predominant target enzyme in the treatment of depression, since it is the enzyme primarily responsible for the deamination of central noradrenaline and serotonin. Clinical findings confirm that inhibitors of MAO-A rather than MAO-B are effective antidepressants, particularly when used at low doses enabling MAO specificity to be maintained (Youdim and Finburg, 1983).

2.1.1 Effects on Monoamine Oxidase Activity

In vitro moclobemide produces a highly selective yet relatively weak inhibition of rat brain MAO-A activity, and is virtually devoid of MAO-B inhibitory activity. The MAO-A inhibitory potency of moclobemide in vitro is approximately 500 to 1000 times lower than that of selective MAO-A inhibitors, for example clorgiline, harmaline, cimoxatone and brofaromine (Da Prada et al., 1989; Kettler et al., 1990).

Despite its weak MAO-A inhibitory activity *in vitro*, moclobemide induces pronounced inhibition of the enzyme in *vivo*, thereby suggesting that biotransformation of the drug may be necessary for full expression of its MAO inhibitory effect (Burton et al., 1984; De Prada et al., 1983). In *ex vitro* experiments, moclobemide (≤300 μmol/kg administered orally two hours prior

to decapitation) selectively inhibited rat brain and liver MAO-A activity (doses producing 50% inhibition of specific rat brain MAO-A and MAO-B activities (ED_{50}) = 7.6 and 78 μmol/kg, respectively), displaying an MAO-A inhibitory potency comparable to that of clorgline and brofaromine and two to four times greater than that of cimoxatone and harmaline (Da Prada et al., 1989b; Kettler et al., 1990). Orally administered moclobemide was equipotent in inhibiting rat liver MAO-A and MAO-B activities *ex vivo* (ED_{50} values of 8.4 and 6.6 μmol/kg, respectively), suggesting a lack of selectivity in the periphery (Da Prada et al., 1989). This phenomenon may be due to the generation of moclobemide metabolites with MAO-B inhibitory activity (Da Prada et al., 1990a).

The inhibitory effects of moclobemide on rat brain MAO activities *ex vivo* were unaltered by repeated oral dosing (Da Prada et al., 1981) or inhibition of the microsomal cytochrome P450 hydroxylating system (Da Prada et al., 1983), indicating that the drug does not accumulate or cause microsomal enzyme induction.

The onset of *ex vivo* inhibition of rat brain and liver MAO-A, activity following single dose oral moclobemide (10 to 16 mg/kg) administration was rapid with maximum effect (80 percent inhibition) occurring with 30 minutes post dose (Da Prada et al., 1983; 1989). In contrast, inhibition of MAO-B was delayed in liver, complete enzyme inhibition occurred at one to two hours post dose, while in the brain the maximum inhibition of MAO-B activity (approximately 40 percent) occurred more than two hours post dose, providing further support for the notion that MAO-B inhibitory activity is due in part to moclobemide

metabolites (Da Prada et al., 1983; 1989). At both sites, moclobemide induced inhibition of MAO-A and MAO-B activities was short lived; in comparison with that produced by the irreversible MAO inhibitors tranylcypromine and phenelzine (> 48 hours) with recovery being achieved within 16 hours (Da Prada et al., 1983; 1989; 1990a). An even shorter lasting inhibition of MAO-A and MAO-B activities was produced by moclobemide in rat kidney and rat intestine, of approximately eight hours duration (Da Prada et al., 1989). Similarly *ex vivo* inhibition of platelet MAO-B activity induced in human volunteers by oral moclobemide (200 to 300 mg) was of short duration (four to eight hours) and of only moderate intensity) (approximately 30 to 50 percent inhibition) (Da Prada et al., 1989; Koulu et al., 1989).

Marked *ex vivo* depression of rat brain and liver MAO-A activity induced by orally administered moclobemide (30 to 80 mg/kg) is reversed, in a temperature- and time-dependent fashion, during *in vitro* dialysis or incubation of inhibitor-free medium (Da Prada et al., 1988a; 1989; 1990a). Reversibility of this inhibitor-enzyme interaction suggests that moclobemide (or its active metabolite) readily dissociates from MAO-A or is transformed by MAO-A itself into an inactive derivative.

The kinetics of moclobemide's *in vitro* interaction with MAO-A changes, from a competitive inhibition (seen on simultaneous addition of moclobemide and [14C] serotonin substrate to rat brain homogenates) to a mixed competitive non-competitive inhibition on pre-incubation (Callingham, 1989; Da Prada et al., 1989). However, this latter pattern of non-competitive inhibition may slow dissociation from MAO-A; and consequent failure to achieve full equilibration

during the incubation period, rather than a truly irreversible interaction with MAO-A (Waldemeier and Stocklin, 1990). As with irreversible and several other reversible MAO-A inhibitors, the apparent *in vitro* inhibitory potency of moclobemide increases with incubation time (Da Prada et al., 1988; 1989). This kinetic pattern of time-dependent inhibition and non-competitive inhibition or pre-incubation suggests, that moclobemide behaves as a mechanism-based, enzyme-activated inhibitor of MAO-A undergoing conversion by MAO-A to a more reactive intermediate, which reversibly inhibits the enzyme without prior release from the active site (Burkard et al., 1989; Burton et al., 1984; Da Prada et al., 1989).

MAO-A inhibitory activity appears to reside almost completely in moclobemide and its N-oxide derivative. The primary amine RO 16-6491, a metabolite of moclobemide in the rat but not in humans (Schoerlin and Da Prada, 1990), is however a potent reversible inhibitor of rat brain MAO-B *in vitro* (Da Prada et al., 1989; 1990a), and appears responsible for the marked *ex vivo* inhibition of MAO-B produced by moclobemide in rat periphery (Da Prada et al., 1989; Schoerlin and Da Prada, 1990). Moclobemide's selectivity for MAO-A inhibition in humans consequently, may be attributed to a less extensive biotransformation process than that seen in other species.

2.2 EFFECTS ON CENTRAL NEUROTRANSMITTER SYSTEMS

The effects of a single oral dose of moclobemide (5 to 50 mg/kg) on rat regional and whole brain monoamine levels are those typically observed with MAO-A inhibitors, comprising moderate increases in levels of noradrenaline, dopamine, serotonin and methylated catecholamine metabolites

normetenephrine and 3-methoxytyramine, and dose related reductions in levels of deaminated metabolites homovanillic acid (HVA), 3,4 dihydroxyphenylacetic acid (DOPAC), 3-methoxy -4- hydroxyphenylolycol (MHPG) and 5 hydroxyindoleacetic acid (5-HIAA) (Da Prada et al., 1981). The increase in brain serotonin and decreases in brain DOPAC and HVA levels were particularly pronounced, and their temporal change roughly paralleled the time course of rat brain MAO-A inhibition *ex vitro* (Da Prada et al., 1981; 1989; 1990a, b).

In vitro and *ex vivo* findings indicate that the pharmacological actions of moclobemide on the central monoaminergic system are entirely related to MAO inhibition, and that moclobemide does not modify the activity of enzymes involved in monoamine biosynthesis - viz. tyrosine hydroxylase, dopa decarboxylase, dopamine - B hydroxylase, or phenylethanolamine-N-methyltransferase (Keller et al., 1978). Prolonged (14 days) oral administration of moclobemide (20 mg/kg/day) to rats resulted in no change in density (Bmax) or antagonist binding affinity (ka) of dopamine D1, D2 or α_2 adrenergic receptors in the striatum and limbic forebrain, but of slight increase in the agonist binding affinity of α_1 adrenoceptors (Klimek et al., 1990).

Radioligand binding studies have demonstrated that moclobemide (10 to 100 mmd/L), does not interact to any appreciable extent *in vitro* with muscarinic, dopaminergic, serotinergic, adrenergic, histaminergic (H1), benzodiazepine, opioid ($\mu\lambda\kappa$) or excitatory amino acid binding sites in rat, mouse and guinea

pig brain membranes (Da Prada et al., 1989). *In vivo* studies have shown a lack of antimuscarinic activity (Burkard et al., 1989).

In contrast to tranylcypromine and selegiline, moclobemide (50 mg/kg intraperitoneally) did not induce dopamine release *in vivo* as demonstrated by its failure to produce stereotyped turning behaviour in rats with unilateral 6-hydroxydopamine-induced lesions in the (dopaminergic) medial forebrain bundle (Da Prada et al., 1981).

2.3 NEUROENDOCRINE EFFECTS

Moclobemide does not appear to affect sympatho-adrenal function, as reflected in unaltered basal catecholamine levels in healthy volunteers. In fasting volunteers and those on low-tyramine or tyramine-free diets, no significant changes in plasma nor adrenaline, adrenaline or dopamine levels were seen after a single oral dose of moclobemide 100 to 300 mg (Da Prada et al., 1981; Koulu et al., 1989); or multiple doses of moclobemide 50 to 200 mg three times daily for seven to fourteen days (Cusson et al., 1991). There was an increase in plasma levels of conjugated noradrenaline and dopamine was observed in volunteers receiving a tyramine free meal (but not in fasting volunteers) after a single 200 mg dose of moclobemide (Da Prada et al., 1981): the selective effect is indicative of moclobemide-induced inhibition of hepatic/gastrointestinal MAO and emphasises the influence of dietary intake on the plasma catecholamine response to moclobemide administration.

As a consequence of MAO inhibition, single oral doses of moclobemide 100 to 300 mg produced sustained ($\leq$ 24 hours), dose-related reductions in

plasma levels of the deaminated catecholamine metabolites DOPAC and 3,4-dihyroxyphenylethylglycol (DHPG) and decreased urinary excretion of HVA and 3 methoxy-4-hydrodoxymandelic acid (vanillylmandelic acid: VMA), while increasing urinary excretion of methylated, non-deaminated metabolites metaphrine, Nor-metanephrine and 3 methoxytyramine in healthy volunteers (Koulu et al., 1989). Similarly multiple dose moclobemide administration, 150 mg three times a day for seven days to healthy volunteers was associated with significant reductions in plasma DHPG, HVA and 5-HIAA levels, and increased urinary excretion of methylated, nondeaminated metabolites metanephrine, normetanephrine, and 3-methoxytyramine in healthy volunteers (Koulou et al., 1989). Multiple dose administration of moclobemide, viz. 150 mg three times daily for seven days to healthy volunteers was associated with significant reductions in plasma DHPG, HVA and 5-HIAA levels, and increased urinary excretion of normetanephrine and 3-methoxytyramine (Berlin et al., 1990). It has been suggested that plasma DHPG may provide a specific index of intraneuronal MAO-A inhibition in humans (Brown and Monks, 1983; Koulu et al., 1989).

In healthy volunteers single oral doses of moclobemide 100 to 300 mg produced transient (approximately three hours), dose-related (≤ 270 percent) in plasma prolactin levels in the absence of concomitant alterations in plasma growth hormone or cortisol levels (Koulu et al., 1989).

Multiple dose administration of moclobemide (400 to 600 mg/day for two to four weeks) given to depressed male patients, was associated with a significant isolated increase (approximately 0.53 percent) in plasma

testosterone levels in absence of concomitant changes in plasma prolactin, lutentising hormone or follicle-stimulating hormone levels (Markianos et al., 1991). The stimulatory effect on testosterone is thought not to be mediated via the hypothalmic-hypophyseal axis, but may be due to moclobemide-induced augmentation of circulating noradrenaline levels.

2.4 POTENTIATION OF THE TYRAMINE PRESSOR EFFECT

Tyramine is an indirectly acting sympathomimetic amine, exerting its pressor effect through active uptake into sympathetic nerve terminals and noradrenaline displacement from intravesicular stores. Use of first-generation MAO inhibitors have been restricted by an acute pressor effect, which is likely to occur when patients on these compounds ingest foodstuffs rich in tyramine (the so-called 'cheese effect') (Blackwell and Marley, 1966).

Humans deaminate dietary tyramine, in intestinal mucosa, where MAO-A activity predominates (> 90 percent of total MAO activity); tyramine escaping degradation at this site is transported to the liver via the Portal circulation, where MAO-B activity occurs (approximately 70 percent of total), and may be further deaminated in the lung, before gaining access to the systemic circulation (Da Prada et al., 1988). Less than one percent of dietary tyramine passes unchanged into the systemic circulation, consequently high doses of oral tyramine (400 to 500 mg) are required to produce threshold changes in systolic blood pressure (30 mmHg) in untreated volunteers (Simpson and White, 1984).

MAO inhibitors potentiate pressor effects of tyramine in two ways:

(a) By reducing the presystemic deamination of tyramine in intestinal mucosa and liver following oral administration.

(b) By increasing the release of noradrenaline from sympathetic nerve terminals as the result of intraneuronal MAO-A inhibition (Hollister and Csernasky, 1990).

The resulting rise in systolic blood pressure following on administration (intravenous or oral) of tyramine forms the basis of the tyramine pressor test. Tyramine sensitivity is defined as the amount of tyramine required to increase systolic blood pressure by 30 mmHg (Pace et al., 1988).

One should administer moclobemide on completion of a meal to avoid tyramine absorption coinciding with the development of intestinal MAO inhibition (Korn et al., 1988a). It has been concluded that a tyramine does of at least 150 mg was required to raise systolic blood pressure by 30 mm Hg in healthy volunteers receiving moclobemide 600 mg/day (Zimmer et al., 1990). A recent systematic analysis of the tyramine content of European foods and beverages indicates that most meals contain less than 40 mg of tyramine in total (Da Prada et al., 1988). In conclusion, therefore, food containing up to 150 mg of tyramine can be safely consumed with minimal risk of a pronounced pressor response by subjects receiving therapeutic doses of moclobemide, as long as the latter is administered as recommended (that is, postprandially).

Oral tyramine pressor tests have indicated that the risk of a pressor effect after ingestion of food is considerably lower with moclobemide than with the irreversible and nonselective MAO inhibitors. The pressor response to moclobemide 450 mg/day normalised within three days of its discontinuation, whereas that to tranylcypromine 20 mg/day normalised after four weeks (Bieck and Antonin, 1989). Moclobemide's relatively weak potentiation of the tyramine pressor effect may be related to its selective inhibition of MAO-A, leaving MAO-B free to deaminate tyramine, and the competitive nature of its interaction with MAO-A, permitting displacement of the inhibitor from the enzyme's active site by high concentrations of tyramine (Strolin and Dostert, 1987).

2.5 CENTRAL NERVOUS SYSTEM EFFECTS

2.5.1 Effects on Sleep Patterns

Moclobemide's antidepressant action appears to be characterised by the absence of any pronounced supressant effect on REM sleep: rather, an improvement in the quality and architecture of sleep accompanies the improvement in depressive symptoms. Monti (1989), demonstrated that moclobemide produces a REM sleep habituation phenomenon, and that a slight REM sleep rebound effect occurred during early withdrawal. The observed neuroelectrophysiological changes appear to be specific for moclobemide.

2.5.2 Effects on Cognitive and Psychomotor Function

In healthy young volunteers single oral doses of moclobemide 200 to 400 mg were devoid of any detrimental effect on psychomotor activity and cognitive

function. Elderly volunteers (60 to 75 years) receiving single oral doses of moclobemide 100 to 300 mg displayed only slight impairment of mental efficiency (reduced number vigilance) whilst showing some evidence of memory improvement (improvement in verbal recognition and memory scanning) (Wesnes et al., 1989). In healthy volunteers, a therapeutic moclobemide dose 450 mg per day for eight days did not affect psychometric evaluations of vigilance or short and long term memory (Berlin et al., 1990; Allain et al., 1992). Young depressed out-patients receiving treatment of moclobemide 450 mg/day for six weeks showed improvement in both vigilance (critical flicker fusion frequency) and attention (reaction time), as well as pneumonic performance (general memory score, facial recognition, delayed verbal recall) (Allain et al., 1992) .

Elderly patients with major depression associated with cognitive impairment or dementia, were reported to show significant improvements in orientation and memory recall ability following six weeks treatment with moclobemide 400 mg/day as compared to those on placebo (Baumhackl et al., 1991).

2.6 ABSORPTION AND BIOAVAILABILITY

Moclobemide appears to be rapidly and almost completely absorbed from the gastrointestinal tract on oral administration (> 95 percent) with mean peak plasma concentrations (Cmax) of approximately 0,3 to 2,7 mg/L occurring at one to two hours (Tmax) after a single oral dose of moclobemide 50 to 300 mg to healthy volunteers. Moclobemide is subject to substantial first-pass hepatic metabolism, resulting in oral bioavailability of approximately 55 percent after a single 100 mg dose (Schoerlin et al., 1987), and is higher on

multiple dosing, increasing from 56 percent (single 100 mg dose) to 86 percent on administration of 100 mg three times daily for a week (Schoerlin et al., 1987). The first-pass hepatic metabolism is either a saturable process or is subject to auto-inhibition as is demonstrated by the positive correlation between oral bioavailability and dose (Schoerlin et al., 1987), and the associated nonlinear relationship between dose (100 mg to 400 mg orally) and Cmax. Ingestion of food 30 minutes before oral administration of a single dose of moclobemide 100 mg tended to reduce the rate of drug absorption in healthy volunteers, however the extent of moclobemide's absorption and its bioavailability remain unchanged (Schoerlin et al., 1988).

Accumulation of moclobemide was evident in healthy volunteers on moclobemide 100 mg or 150 mg three times daily for 15 days, as reflected in significant increases in minimum and maximum plasma concentrations over the first week of drug administration (Schoerlin et al., 1987). Steady-state plasma moclobemide concentrations in depressed patients are thought to correlate with dose.

2.7 DISTRIBUTION

Moclobemide is almost 50 percent bound to human plasma protein (albumin predominantly). It has been suggested by studies done on post partum women, that the breast-fed infant of a nursing mother receiving therapeutic doses of moclobemide would be exposed to only small amount, of moclobemide and its metabolites (0,05 mg/kg/day) representing less than one percent of the maternal dose (Schoerlin and Da Prada, 1990).

2.8 METABOLISM AND EXCRETION

Moclobemide is extensively metabolised in the liver, less than 0,5 percent of the parent compound is excreted in the urine unchanged, following oral administration (Jauch et al., 1990).

Metabolism of moclobemide comprises an oxidative attack on the morphine moiety, aromatic hydroxylation and deamination representing the other primary metabolic reactions (Jauch et al., 1990). All urinary metabolites account for one percent or more of the orally administered dose have been identified (Jauch et al., 1990). The four major urinary metabolites (M7A, M7B, M8 and M9) are carboxylic acids, and collectively account for approximately 50 percent of the administered dose (Jauch et al., 1990). The pattern of plasma metabolites is qualitatively similar to that in urine, with the carboxylic acids M7A, M8 and M9 and the lactam derivative M15 predominating. Of the identified moclobemide metabolites, only metabolites M4 and M5 (moclobemide-N-oxide) (Jauch et al., 1990) retain modes MAO-A inhibitory activity in humans. The observation that moclobemide is a more potent MAO-A inhibitor *ex vivo* than *in vitro* (section 2.1.1) suggests that the probable existence of a more active, but as yet unidentified plasma intermediary.

Moclobemide metabolism is rapid, with peak plasma concentrations (Cmax) of metabolite, M15 (0,49 mg/L) and M5 (0,1 mg/L) occurring within two hours (Tmax) of single oral dose administration of moclobemide 100 mg to volunteers (Schoerlin et al., 1987). The accumulation of parent compound observed on multiple oral dosing of moclobemide 100 mg three times daily for

15 days in healthy volunteers has been associated with an increase in minimum steady-state plasma concentrations of metabolite M5 and a decrease in those of metabolite M15 (mean values, 0,07 and 0,23 mg/.L, respectively over the second week) (Schoerlin et al., 1987). Moclobemide displays first-order elimination kinetics, plasma concentrations declining exponentially following single oral (50 to 200 mg) and intravenous (50 mg) dose administration in healthy volunteers (Wiesel et al., 1985). Elimination kinetics studies have suggested that the drug has a short plasma elimination half-life (approximately one to two hours) and a relatively high systemic clearance (0,5 to 1.0 L/min). Renal clearance is extremely low (approximately 2,5 ml/min) (Schoerlin et al., 1987). Following oral administration of 14 C - labelled moclobemide 50 mg to a healthy volunteer, 92% of total radioactivity was recovered in the urine after the first 12 hours, and combined urinary and faecal recovery of radioactivity over 96 hours accounted for all the administered dose. Most urinary metabolites are excreted in an unconjugated form (Jauch et al., 1990).

Pretreatment of healthy volunteers with moclobemide 100 mg three times daily for 15 days altered the elimination of subsequent single intravenous dose of moclobemide 150 mg. Similarly oral clearance of moclobemide in these volunteers, declined significantly (from 1.39 to 0.59 L/min) during the first week of multiple oral dosing with the drug (Schoerlin et al., 1987). The mechanism responsible for this reduction in hepatic clearance of moclobemide is unclear, but it may involve anti-inhibition or metabolite induced inhibition of moclobemide metabolism.

2.9 INFLUENCE OF AGE AND DISEASE STATE

Absorption, distribution and elimination characteristics of moclobemide following single intravenous (100 mg) or oral (50 mg) dose administration did not differ significantly between healthy young (22 to 33 years) and elderly (65 to 77 years) volunteers or between younger (20 to 56 years) or older (60 to 77 years) depressed patients (Stoeckl et al., 1990). Similarly, after oral administration of moclobemide 100 mg three times daily for two weeks the absorption and elimination kinetics of the drug (Cmax, tmax, bioavailability, steady-state plasma concentrations, terminal elimination half-life and clearance) in the two age groups were comparable (Stoeckel et al., 1990). Modification of moclobemide regimens in the elderly is therefore unwarranted.

In patients with moderate to severe renal impairment (creatinine clearance $\leq$ 40 ml/min; n = 13), absorption, distribution and elimination kinetics of moclobemide, following oral and intravenous dosing (100 mg) are essentially similar to those in normal (healthy) volunteers (Schoerlin et al., 1990; Stoeckel et al., 1990). Mean absorption time was higher in those with renal impairment (1.05 vs. 0.47 hours). These findings are consistent with the low renal clearance of moclobemide (< one percent of system i.e. (systemic) clearance) described by Schoerlin et al. (1987), and it suggests that renal impairment per se does not influence the disposition of the parent compound. Renal function, however, does influence the accumulation of the active metabolite M5, following intravenous and oral dosing with moclobemide in patients with renal impairment (Schoerlin et al., 1990).

Patients with hepatic impairment displayed significant prolongation of plasma terminal elimination half-life (3.9 vs. 1.7 h) and mean residence time (7.2 vs. 2.4 h), a decreased systemic clearance (14.6 vs. 37.7 L/h) and unchanged steady-state volume of distribution and renal clearance values for moclobemide following intravenous administration of 90 mg dose (Stoeckel et al., 1990). The Cmax value of metabolite M15 was significantly reduced (18 percent) while that of metabolite M5 was significantly elevated (83 percent). Hepatic cirrhosis is associated with significantly increased oral bioavailability (84 vs. 56 percent) and Cmax value (1.6 vs. 0.58 mg/L) and reduced oral clearance (20.2 vs. 78.8 L/h) of moclobemide following a 100 mg oral dose (Stoeckel et al., 1990). The Cmax value of metabolite M15 (but not metabolite M5) was significantly reduced (29 percent). A two-to three-fold reduction in moclobemide dosage in patients with hepatic dysfunction therefore appears necessary in order to ensure that the plasma level remains within the therapeutic range; alternatively the interval between dose administration may be extended.

2.10 COMPARISONS WITH PLACEBO

Moclobemide at doses of $\leq$ 600 mg/day has been shown to have superior antidepressant efficacy to placebo in several short term (four to six week) comparative studies involving patients with endogenous or neurotic/reactive depression (Botte et al., 1990; Cassachia et al., 1984; Versiani et al., 1989). In the largest randomised, double-blind comparison with placebo performed, 63 percent of depressed patients receiving moclobemide 300 to 600 mg/day (n = 158) for up to six weeks showed a 50 percent or greater reduction in total HDRS score compared with 29 percent of placebo treated patients (n =

156) (Versiani et al., 1989). In this study, moclobemide proved equally effective, and superior to placebo, in patient subgroups with unipolar/bipolar endogenous depression (response rate 64 vs. 28 percent) and neurotic/reactive depression (response rate 58 vs. 32 percent). The mean reduction in total HDRS score was significantly greater with moclobemide (52 percent) than with placebo (28 percent) ($p < 0,001$ between treatments), and the investigators assessed overall antidepressant efficacy as good/very good in 70 percent of moclobemide recipients and 28 percent of placebo recipients. Premature treatment termination, due to lack of treatment response, was significantly less common with moclobemide (11 percent of patients) than with placebo (25 percent). Individual HDRS items of depressed mood, inhibition, guilt and suicidal ideation were most markedly improved by moclobemide in patient populations with mixed endogenous and neurotic depression, indicating that the drug has the greatest influence on clinical features of depression and psychomotor retardation (Casacchia et al.., 1984). Therapeutic response to moclobemide was not substantially altered by concomitant benzodiazepine administration (Versiani et al., 1989).

In contrast to the abovementioned findings, another study confined to patients with mild-to-moderate neurotic/reactive or reactive depression and marked by relatively high response rates to placebo failed to demonstrate any significant advantage of moclobemide 300 to 500 mg/day over placebo (Larsen et al., 1989). It is important to note that placebo response has previously been associated with mild nonendogenous depression making it difficult to establish antidepressant efficacy in such cases.

2.11 COMPARISON WITH OTHER ANTIDEPRESSANTS

2.11.1 Tricyclic Antidepressants

Randomised, double-blind, non-placebo controlled studies (typically employing fewer than 30 patients in each treatment group) have shown that moclobemide, in doses of up to 600 mg/day had demonstrated comparable antidepressant efficacy to amitriptyline in doses of 125 to 250 mg/day (Beckers et al., 1990; Newburn et al., 1990), desipramine in doses of 50 to 175 mg/day (Stefanis et al., 1989), clomipramine in doses of 75 to 150 mg/day (Civeira et al., 1990; Dierick et al., 1990; Larsen et al., 1984; 1989) and imipramine in doses of 75 to 150 mg/day (Casacchia and Rossi, 1989) over a four to six week treatment period in patients presenting with a major depressive disorder (DSM III-R criteria) of an endogenous or nonendogenous type. The small size of the treatment groups used in these active control studies may be expected to preclude identification of any small differences in therapeutic efficacy that may exist between moclobemide and the tricyclic antidepressants.

Despite the fact that moclobemide does not appear to be of superior efficacy in any particular subtype of depression; a small-scale study done by Dierick et al. (1990), reported that moclobemide was more effective in nonendogenous depression. The scores of depression and somatic complaints on the Hamilton Depression Rating Scale improved similarly in response to moclobemide and clomipramine in patients with endogenous and non-endogenous depression, whereas improvements in agitation and anxiety were more marked on moclobemide (Cattiez et al., 1990). Amitriptyline (150 to 250 mg/day) and moclobemide (150 to 450 mg/day) displayed comparable

anxiolytic efficacy in mixed endogenous/non-endogenous depression; as assessed by the improvement in HDRS items of psychic and somatic anxiety (Norman et al., 1985). Moclobemide 150 to 300 mg/day, tended to be more activating and less anxiolytic than imipramine 75 to 150 mg/day in major depressive disorder and dysthymic disorder (Casacchia and Rossi, 1989).

Randomised, multicentre, double-blind studies comparing moclobemide 300 to 600 mg/day with clomipramine 100 to 200 mg/day over six to twelve week periods in a total of 315 patients with endogenous (Guelfi et al., 1992) or non-endogenous depression (Lecrubier and Guelfi, 1990) have shown that the two drugs were of comparable antidepressant efficacy on objective (HDRS, Montgomery-Asberg Depression Rating Scales) and subjective global evaluation, producing similar improvements (approximately 60 to 65 percent reductions) in total HDRS score on analysis of end point scores.

Anxiety, assessed on the Covi Anxiety Scale, improved equally with moclobemide and clomipramine in non-endogenous depression (Lecrubier and Guelfi, 1990). Both studies noted a significantly earlier antidepressant response with moclobemide (day ten) than with clomipramine (day thirteen). Improvement of psychomotor retardation occurred more rapidly in moclobemide as opposed to clomipramine in both endogenous (Guelfi et al., 1992) and non-endogenous depression (Lecrubier and Guelfi, 1990). In two randomised, double-blind, multicentre trials involving heterogeneous populations (total of 670 patients) with endogenous and non-endogenous (reactive/neurotic, symptomatic/organic) depression; moclobemide 300 to 600 mg per day was found to be as effective as imipramine 75 to 200 mg/day in

relieving depressive symptoms (Baumhackl et al., 1989; Versiani et al., 1989).

2.12 SECOND GENERATION ANTIDEPRESSANTS

Moclobemide (at doses of 600 mg/day), is thought to have similar antidepressant efficacy to Maprotiline (75 to 225 mg/day) and Mianserin (75 to 150 mg/day) in major depressive disorders, particularly in the elderly (De Vanna et al., 1990; Tiller et al., 1990) and to Fluvoxamine (100 to 200 mg/day) used in mixed endogenous and non-endogenous depression (Bougerol et al., 1992).

2.13 TETRACYCLIC ANTIDEPRESSANTS

Several studies comparing antidepressant efficacy and tolerability have been done comparing moclobemide and fluoxetine (Lonnquist et al., 1994; Geerts et al., 1994) and fluvoxamine (Bougerol et al., 1992). Moclobemide at doses of 300 mg per day was found to be as effective an antidepressant as 20 mg of fluoxetine and 100 mg of fluvoxamine. All treatments tended to be well tolerated, however, moclobemide tended to have a more favourable side effect profile when compared to either fluoxetine or fluvoxamine.

2.14 META ANALYSIS OF COMPARATIVE TRIALS

Studies have been made, in an attempt to assess whether moclobemide is equally effective in certain diagnostic subgroups of depression. Efficacy data pooled from the double-blind comparative studies of moclobemide compared to standard antidepressants (imipramine, clomipramine, desipramine, amitriptyline and second-generation antidepressants) have been subjected to

a retrospective meta-analysis (Angst and Stabl, 1992). A total of 1987 patients were evaluated using HDRS (17-item) and Clinical Global Impression ratings (CGI).

The therapeutic efficacy of moclobemide, assessed in terms of the proportion of patients receiving good/very good CGI ratings were comparable in unipolar and bipolar depression (66 percent vs. 60 percent responses rate respectively), agitated and retarded depression (76 percent vs. 61 percent response rate, respectively). It was also found that the response rate of moclobemide did not differ significantly between the elderly (> 65 years) and younger patients (< 65 years) (patients 62 percent vs. 65 percent response rate, respectively). The observed tendency for those concomitantly receiving benzodiazepines, was to lower response rate to moclobemide than those receiving moclobemide monotherapy (59 percent vs. 66 percent respectively). This may be a simple reflection of differences in severity of depression in these two subgroups.

2.15 TOLERABILITY AND SAFETY

Clinical studies, of less than 12 weeks duration have shown that moclobemide is tolerated by depressed patients almost as well as placebo when administered in doses of up to 600 mg per day. Few patients have withdrawn due to adverse reactions to the drug.

In the most recent safety file on moclobemide, comprising a total of 1102 moclobemide-treated patients with endogenous or non-endogenous depression, the data is drawn primarily on the data pooled from the major

multicentre study (n = 490) of Versiani et al. (1989) and numerous smaller double-blind comparative studies (n -1656) of moclobemide versus tricyclic antidepressants (amitriptyline, desipramine, imipramine and clomipramine) and/or placebo (Moll and Hetzel, 1990; Stabl et al., 1989; Versiani et al., 1990).

Among the patients who received moclobemide in placebo-controlled studies (n = 285), only nausea occurred more frequently in moclobemide than with placebo (10 percent vs. 5 percent respectively): dry mouth (13 percent), headache (10 percent); dizziness (10 percent), insomnia (7 percent), constipation (5 percent), anxiety (5 percent); agitation (4 percent), epigastric discomfort (4 percent), fatigue (4 percent), tachycardia (3 percent), tremor (3 percent), diarrhoea (3 percent), blurred vision (3 percent) and orthostatic hypotension (2 percent) were no more frequent with moclobemide than with placebo (Stabl et al., 1989). Moclobemide tended to be better tolerated in comparison with the tricyclic antidepressants being largely devoid of the latter's anticholinergic effects.

Dry mouth, constipation, blurred vision and tremor were significantly less frequent with moclobemide (n = 164) than with imipramine (n = 164) during short term treatment (< six weeks) of major depression (Versiani et al., 1989).

Tolerance and safety after administration of single repeated doses of moclobemide was determined in eight studies (Moll and Hetzel, 1990: Stabl et al., 1989, Versiani et al., 1990). The range of administered single doses was 50 to 1200 mg and multiple doses was 100 to 900 mg per day. Results

showed that single doses of ≤ 400 mg were well tolerated. With 800 mg, headache, tiredness and dizziness occurring. Since adverse events were also systematically collected in other human studies - information on tolerance is available from 728 subjects. Taking all these studies together, adverse events after a single moclobemide dose ≤ 200 mg were not more frequent than placebo. With single doses > 200 mg, dizziness occurred more frequently, six percent more subjects complained about sedation but also four percent more subjects complained of the stimulatory effects from moclobemide. During repeated dose administration, complaints of adverse effects after moclobemide occurred with a lower frequency than during placebo treatment. Complaints about palpitations were more frequent with placebo. The incidence of adverse events was lowest when moclobemide was taken during a meal.

Even with the highest repeated doses of 900 mg/day, moclobemide was tolerated with no statistically significant changes in vital signs. The electrocardiogram readings remained unchanged compared to baseline or placebo after single and repeated moclobemide doses.

In contrast to the irreversible non-selective MAO inhibitors, which are characterised by a relatively high incidence of CNS adverse effects (insomnia, irritability, agitation and restlessness). Moclobemide appears to produce little central excitation (Baumhackl et al., 1989; Stabl et al., 1989). While moclobemide and the reversible MAO inhibitor toloxatone, are both well tolerated in major depression, moclobemide, tended to display the more pronounced anticholinergic effect (Lemoine and Mirabaud, 1992).

Overall assessments of tolerability have favoured moclobemide over second generation antidepressants maprotiline and fluvoxamine (Bougerol et al., 1992) on account of its lower incidence of anti-cholinergic effects (vs. maprotiline) and gastrointestinal symptoms and headache (vs. fluvoxamine). In the elderly moclobemide is tolerated as well as maprotiline (75 to 150 mg/day) (De Vanna et al., 1990). Proconvulsant activity has not been observed with moclobemide (Amrein et al., 1988).

No consistent, clinically relevant changes in heart rate or systemic blood pressure were noted in depressed patients during treatment with moclobemide at doses ranging from 100 to 600 mg/day (Bakish et al., 1992; Baumhackl et al., 1989; Casacchia and Rossi, 1989; Newburn et al., 1990). Hypertensive episodes arising in 0.7 percent of patients overall (n = 2300) (Versiani et al., 1990).

In the majority of cases (12 of 15), the hypertensive responses were attributed to an episodic deterioration of pre-existing, predominantly labile, hypertension or *de novo* onset of essential hypertension, and occurred in the absence of exposure to tyramine-rich food (Versiani et al., 1990). Postural changes in systolic blood pressure during moclobemide treatment tended to be slight and clinically insignificant (< 10 mmHg) (Newburn et al., 1990).

Orthostatic hypotension (standing systolic pressure < 90 mmHg), occurring in approximately twenty percent of patients on tricyclics and irreversible MAO inhibitors (Blackwell, 1981) occurred in about one percent of patients on

moclobemide. It's incidence is comparable to that seen in placebo (Versiani et al., 1990).

Moclobemide was found to have no effect on body weight or on haematological parameters (Bakish et al., 1992; Baumhackl et al., 1989; Versiani et al., 1990); no abnormalities in alanine or aspartate aminotransferase activities were observed, a finding consistent with moclobemide's documented lack of hepatotoxicity in animals.

Moclobemide tends to be well tolerated in elderly patients (> 60 years) with depression, as it is in their younger counterparts on short term administration (< 12 weeks). Tolerability in patients on long term moclobemide therapy (> one year) at doses of up to 600 mg/day (n = 115), appeared to be good or very good in 95 percent of cases, with dizziness, headache, dry mouth (all 8 percent), tremor (6 percent), insomnia, nausea, somnolence, sweating, and tachycardia (all 5 percent) representing the most frequently reported adverse effects (Versiani et al., 1990). This figure is probably an overestimation of moclobemide's true tolerability, as patients displaying early intolerance were generally excluded from long term treatment.

Observations based on six recorded cases of attempted suicide through ingestion of moclobemide in doses ranging from 900 mg to 20 g, suggest that moclobemide is considerably less dangerous in overdosage than the tricyclic antidepressants and second generation antidepressants (Beaumont and Hetzel, 1992).

The main effects of moclobemide overdosage are severe drowsiness, nausea, hyporeflexia and disorientation; there are no significant cardiovascular complications or cardiotoxicity, convulsions, hepatotoxicity, respiratory failure or other life-threatening events at these doses. Treatment for overdosage included: fluid control, induction of vomiting, and gastric lavage. Recovery is uneventful, with cardiovascular and laboratory parameters normalising within one to five days. There appeared to be no residual complications.

2.16 DRUG INTERACTIONS

Most drug combinations, with the exception of those involving imipramine, clomipramine or tranylcypramine, appear to be relatively safe, provided that both drugs are gradually initiated together or the tricyclic antidepressant is commenced prior to the MAO inhibitor. Certain tricyclic antidepressants may protect patients receiving MAO inhibitor therapy from tyramine-induced hypertension by inhibiting tyramine uptake into the sympathetic nerve terminal (Kline et al., 1982), or by blocking α_1 adrenoceptors in vascular smooth muscle.

Single dose oral administration of desipramine (50 mg), reduced tyramine sensitivity in healthy volunteers pre-treated with moclobemide 150 mg/day (Korn et al., 1986). Amitriptyline (150 mg/day) and moclobemide 300 mg/day were well tolerated on concomitant administration, showing no evidence of any clinically significant pharmacodynamic interaction (Korn et al., 1986). Present evidence suggests, that, direct therapeutic changeover from moclobemide to a tricyclic or tetracyclic antidepressant can be safely

performed in depressed patients without the need for an intervening washout period.

Co-administration of moclobemide 600 mg/day and metroprolol to hypertensive patients slightly enhanced the latter's blood pressure lowering effects but caused no symptomatic postural hypotension (Zimmer et al., 1990). This finding as well as the lack of any clinically significant pharmacodynamic interaction between moclobemide 600 mg/day and nifedipine or hydrochlorathiazide in these patients (Amrein et al., 1992), suggests that moclobemide can be safely administered with antihypertensive agents.

The pharmacokinetics of moclobemide are modified significantly by cimetidine, and inhibitor of the hepatic mocrosomal cytochrome P450 system. Pretreatment of healthy volunteers with cimetidine 1000 mg/day for two weeks resulted in increases in the Cmax (39 percent), terminal elimination half-life (35 percent) and AUC (120 percent) values of a single oral dose of moclobemide 100 mg (Schoerlin et al., 1991; Zimmer et al., 1990). Irreversible hydrazine MAO inhibitors behave as non-specific enzyme inhibitors active against microsomal cytochrome P450 (Tollefson, 1983), it is not clear whether moclobemide shares a similar action.

Moclobemide shows no clinically relevant interaction with digoxin at therapeutic doses, benzodiazepines, alcohol, oral contraceptives, ibuprofen, glibenclamide, phenprocoumon, lithium, carbamazepine or neuroleptics (Amrein et al., 1992; Zimmer et al., 1990). Serotinergic syndrome of

hyperthermia, tremor, sedation and myoclonus has been described with administration of the early generation MAO inhibitors and the serotonin reuptake inhibitors (Marley and Wozniak, 1983). No such interaction has been reported between moclobemide and fluvoxamine, and animal data suggests a low liability for interaction between moclobemide and fluoxitine or clomipramine (Amrein et al., 1992).

Severe drug interactions between irreversible MAO inhibitors and opioids have been reported in the literature (Hill et al., 1992) and fatalities have been attributed to the combination of pethidine (meperidine) and dextromethorphan with MAO inhibitors, an effect apparently related to the inhibitory action of these opioids on neuronal serotonin reuptake (Stack et al., 1988). The combination of pethidine or dextromethorphan and moclobemide should therefore be avoided.

2.17 DOSAGE AND ADMINISTRATION

Moclobemide can be administered at a full therapeutic dose of 300 to 450 mg/day, administered in two or three divided doses, from the outset of treatment. Subsequent dosage increases to a maximum of 600 mg/day, may be performed from week two of treatment. Moclobemide may be reduced to 20 percent of initial treatment phase, in long term therapy. In patients who are receiving inhibitors of cytochrome P450, for example cimetadine, moclobemide should be administered at the lowest therapeutic dose (150 mg/day).

It is necessary to take moclobemide immediately after a meal, to minimise any possible risk of hypertensive responses to dietary tyramine. Whilst dietary restriction is unnecessary, consumption of large amounts of tyramine-rich food (for example 750 mg of mature or overripe cheese) should be avoided with any one meal, particularly in inpatients with hypertension or cerebrovascular disease. The combined use of moclobemide and the opioids pethidine (meperidine) and dextromethorphan is contraindicated.

2.18 PLACE OF MOCLOBEMIDE IN THERAPY

Practical consideration guiding the choice of appropriate antidepressant include: the drug's spectrum of activity and overall antidepressant efficacy, the latency of onset of therapeutic response, the adverse effect profile, and safety in overdose. Currently available antidepressants do not differ greatly from one to another in terms of their efficacy in major depression or speed of onset of antidepressant action, but they do vary appreciably with respect to nature of adverse effect profiles and toxicity in overdose; and these latter two factors therefore assume importance in determining therapeutic options.

The emergence of moclobemide; a competitive and selective inhibitor of MAO-A, provides a possible solution to the drawbacks which have restricted the use of earlier generation, irreversible, non-selective MAO inhibitors, viz. a perceived lack of efficacy in endogenous depression (Davidson et al., 1978; Paykel and White, 1989) coupled with the risk of potentially fatal interactions with dietary tyramine and concomitant medication. In contrast to these earlier MAO inhibitors with their claimed specificity of therapeutic efficacy in atypical depression, moclobemide appears to have a broad spectrum of

antidepressant activity, being effective in endogenous depression (uni and bipolar), neurotic depression and dysthymic disorder, and demonstrates therapeutic equivalence to the tricyclic antidepressants clomipramine and imipramine in placebo-controlled studies. The reversible nature of moclobemide's interaction with MAO-A permits good therapeutic control and, if necessary, abrupt discontinuation of therapy (for example prior to surgery) without the risk of carry-over effects. Also, a switch to alternative antidepressant drug therapy can also be made without the need for an intervening drug-free interval. If used appropriately moclobemide confers negligible risk of tyramine-induced hypertension, thereby obviating the need for the strict dietary precautions required with the earlier generation MAO inhibitors.

Patient compliance is further favoured by the drug's relative absence of anticholinergic side effects, symptomatic postural hypotension and weight gain more commonly associated with the tricyclic antidepressants and irreversible MAO inhibitors. The favourable tolerability profile in turn facilitates rapid upward dosage titration and permits full dosage administration from the outset of treatment. At present there is insufficient evidence to comment on the drug's potential for recreational abuse; and there is no evidence, to suggest that moclobemide confers either psychological or physical dependence. The risk for triggering hypomania or mania in susceptible (for example bipolar) patients must be considered, given the propensity of the irreversible nonselective MAO inhibitors and tricyclic antidepressants to evoke this response.

Moclobemide is likely to make an important contribution to the treatment of depressive disorders, on account of its demonstrated efficacy against clinical features of psychomotor retardation, blunted affect, apathy and depressed mood, as well as its good tolerability and safety characteristics. Moclobemide's lack of behavioural toxicity holds promise for its use in the ambulant patient, whilst its diminished risk of hypertensive crisis, low potential for anticholinergic effects and drug interaction, safety on overdose and beneficial effect on the cognitive impairment (reduced vigilance, attention and memory) associated with ageing would appear to confer therapeutic advantages in the elderly and those with concurrent physical illness. Further potential indications for the use of moclobemide include tricyclic-resistant depression, atypical depression, mixed anxiety and depression, and panic disorder.

CHAPTER THREE

3. MATERIAL AND METHODS

3.1 RATIONALE

Double-blind, controlled studies in Europe and South America have indicated that moclobemide is better tolerated and as effective as standard tricyclic antidepressants in patients with major depressive episodes. In these studies, moclobemide has been administered in daily dosages ranging between 300 mg and 600 mg, administered in three divided doses. The data relating to a twice a day dosage schedule is limited. The study, is therefore designed to assess the efficacy and tolerability of moclobemide administered twice daily in comparison with three times a day, in a total daily dosage of 300 mg and 450 mg.

3.2 OBJECTIVES OF THE STUDY

3.2.1 Primary Objective

To assess the comparative efficacy of moclobemide administered in three different dosage regimens viz. 100 mg three times a day (t.d.s.) vs. 150 mg three times a day (t.d.s.) vs. 150 mg twice a day (b.d.).

3.2.2 Secondary Objective

To compare the incidence of adverse reactions reported by patient being treated with moclobemide at the abovementioned dosage schedules.

3.3 EXPERIMENTAL DESIGN AND CONTROL METHODS

3.3.1 Overall Design and Control Methods

This is a randomised, double-blind multicentre, parallel group study to assess the comparative tolerability and efficacy of oral moclobemide administered in three different dosage regimens, in out-patients suffering from a new episode of depression.

The overall Study Plan including a schedule of assessments is attached as Appendix I.

This study forms one arm of multicentre trial. A total of 33 patients were included in our sample.

3.4 SUBJECT SELECTION CRITERIA

3.4.1 Population Base

Patients were recruited and treated as out-patients by our research team.

3.4.2 Inclusion Criteria

- Male or female
- Aged between 18 and 65 years inclusive
- Who satisfy the diagnostic criteria for a major depressive episode (DSM III-R) (Appendix II)
- With a total score on the 21 Item Hamilton Depression rating Scale (HDRS) of at least 17 (Appendix III)
- Able to comply with the requirements of the study protocol
- Witnessed oral or written consent given

3.4.3 Exclusion Criteria

Patients:

- Who are women of childbearing potential not actively avoiding pregnancy, or who are pregnant or lactating.
- Whom the investigator considers to have a clear suicide risk (scoring three or more on item three of the HDRS).
- With mood-incongruent delusions or hallucinations.
- With confusional states or cognitive impairment that is not due to the depression.
- Whose depressive symptoms are manifestations of some other psychiatric illness, for example schizophrenia, an obsessional or phobic state, or drug addiction (including alcohol) or patients with organic brain lesions.
- In whom it can be established that an organic factor initiated and maintained the disturbance. Patients whose disturbance is a normal reaction to the recent loss of a loved one (uncomplicated bereavement).
- Who have taken any investigational drug within the last four weeks.
- Who have been taking monoamine oxidase inhibitors in the past two weeks.
- Who have been taking other marketed antidepressants within the last seven days.
- Who have received ECT for the present depressive episode.
- Who are dependent on licit or illicit drugs.
- Who are being treated with cimetidine. However, if patients are switched to ranitidine, they may be eligible.

- With any significant organic disease which could put the patient at risk or obscure the effects of treatment (for example recent myocardial infarction, conduction defects, liver or renal disease, diabetes mellitus, prostatic hypertrophy) (Appendix IV).
- With a history of epilepsy.
- Requiring lithium treatment.
- Previous episode of mania.
- Known hypersensitivity to moclobemide or benzamide derivatives.

3.4.4 Concomitant Medication and Treatment

ECT and all psychotropic drugs (including antiepileptics, barbiturates and phenothiazine derivatives), with the exception of nocturnal hypnotics (for example a benzodiazepine or cloral hydrate) are prohibited during this study. No other antidepressant agent may be administered to a patient during this investigation.

Throughout the study doctors should be discouraged from prescribing hypnotics for the patient, however, if this is unavoidable benzodiazepines or chloral hydrate is recommended as the preferred medication. The use and dosage of the concomitant medication must be documented in the case reports forms (CRFs).

Patients who are receiving other, non-psychotropic treatment, may continue to do so provided that it has been stabilised for at least four weeks.

If at any follow-up visit, the patient presents with, or complains of, adverse events, symptomatic additional treatment can be administered if deemed necessary by the investigator. However, concomitant medication should be kept to a minimum and the use and dosage of all medications must be documented in the case report forms.

3.5 ASSIGNMENT TO TREATMENT GROUPS

A computer generated randomisation list was prepared by the product manufacturers, and drug supplies were prepacked according to this list. Eligible patients were randomised into three treatment groups.

When all entry criteria were satisfied, the lowest available number of an unused medication pack was given to the patient. Thus, the first patient entering the study was allocated the lowest available randomisation number for the centre, and each subsequent patient received the next number in sequential ascending order. The allocated number was the patient's number for the entire duration of the study, and was recorded whenever required on study documentation.

Sealed, numbered code-break envelopes were provided containing details of each patient's treatment. These could only be opened in case of emergency (see 3.11).

3.6 TRIAL MEDICATION

3.6.1 Rationale for Dosage Selection

Moclobemide has been assessed at daily dosages of 300 mg and 450 mg, administered in three divided doses. However, the data relating the efficacy and tolerability of moclobemide administered on a twice a day basis is limited.

3.6.2 Formulation and Packaging

3.6.2.1 Moclobemide Placebo

The manufacturers supplied moclobemide capsules 100 mg, 150 mg and matching placebo capsules.

Each patient's capsules (moclobemide or placebo as determined by the random allocation schedule) would be supplied in weekly packs (according to the dosage schedule in section 3.6.4) labelled with the study number, patient number, study week, expiry date and dosage instructions by the manufacturer. The centre name and patient initials were added by the research team.

3.6.3 Blinding

Investigators were provided with a set of numbered sealed envelopes which were retained by them throughout the study.

These envelopes contained the identity of the drug dispensed in the individual medication packs, and could be opened only in the case of immediately reportable adverse events (see Appendix IX for definitions) when knowledge of the test substance and dosage is needed to manage a patient's

condition. These envelopes were returned to the trial monitor at the conclusion of the study. Envelopes were checked to ensure the seals have not been broken unless warranted by the occurrence of the conditions mentioned above.

A duplicate copy of the randomisation code was kept by Roche which will only be opened in case of the conditions mentioned above.

3.6.4 Administration and Dosage

Study medication was administered orally three times a day, and patients were instructed to take their medication after meals, that is after breakfast, after lunch and after dinner.

Each patient was provided with a pack for every week of treatment. Patients were provided with one week's extra medication to allow tolerance for failure to attend an appointed date. The pack contained 21 capsules which were taken by the patient at that time on that day according to the following schedule.

Table 3: Tablets per week per patient

Treatment Weeks	Moclobemide (MCB) 100 mg 3 x day Group A			Moclobemide (MCB) 150 mg 3 x day Group B			Moclobemide (MCB) 150 mg 2 x day Group C		
	Morn	Noon	Eve	Morn	Noon	Eve	Morn	Noon	Eve
0 - 6	MCB 100 mg	MCB 100 mg	MCB 100 mg	MCB 150 mg	MCB 150 mg	MCB 150 mg	MCB 150 mg	P1	MCB 150 mg

NB: P1 = Placebo capsule

3.6.5 Accountability of Drug Supplies

All drugs supplied to the research team were fully accounted for.

A Drug Dispensing Log for each patient was kept current and contained the following information:

- the identification of the patient;
- the date when the drug was dispensed; and
- the date when any unused trial medication was returned by the patient.

The inventory was available for inspection by the Clinical Trials Co-ordinator.

Patients were instructed to return all unused drug supplies, including partially used or empty packs, to the investigator at the end of the study for eventual collection by the manufacturer's Clinical Trials Monitor.

3.6.6 Continuation Supplies

Moclobemide was supplied on a named patient basis at the end of the study; if it was deemed necessary.

3.7 SCHEDULE OF ASSESSMENTS

Assessment

Evaluation

Table 4: Overall Study Plan

	Day 0	*Day 3*	*Day 7 (End Wk. 1)*	*Day 14 (End Wk. 2)*	*Day 21 (End Wk. 3)*	*Day 28 (End Wk. 4)*	*Day 42 (End Wk. 6)*
Patient Demography	X						
DSM III-R	X						
HDRS	X	X	X	X	X	X	X
Pregnancy Test	X						
Concomitant diseases, Medication	X						
Information/consent	X						
Confirm fulfillment of inclusion/exclusion criteria	X						
Random allocation	X						
HARS	X	X	X	X	X	X	X
ZUNG	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X
Sleep questionnaire	X			X		X	X
Vital signs	X	X	X	X	X	X	X
Baseline symptoms	X						
Laboratory tests	X						
Adverse events		X	X	X	X	X	X
Additional medications	X	X	X	X	X	X	X
Global assessments (at study end or premature withdrawal)							X

The above information is included in the Overall Study Plan which is attached as Appendix I and also enclosed in the Case Report Form.

3.7.1 Timing of Assessments

Assessments of efficacy and safety were performed by the research team after three days and after one, two, three, four and six weeks of treatment.

3.8 SCREENING PROCEDURES FOR STUDY ENTRY

3.8.1 Initial Screening

The primary inclusion criterion into this study was the diagnosis of a major depressive episode as defined by the DSM III-R.

In addition patients were required to have a minimum baseline score > 17 on the 21-item HDRS. Patients who satisfied these criteria, as well as the other inclusion and exclusion criteria described in sections 3.4.2 and 3.4.3 were enrolled in the trial. Therapy initiated upon inclusion (no-run-in-period). Values recorded upon inclusion constituted baseline values.

Part of the pre-study screen was a pregnancy test. Patients were excluded if the result was positive.

Patients were issued with an Appointment Card to remind them of their next appointment (Appendix V).

3.8.2 Baseline Assessment

The following patient details were recorded on entry into the study:

Patient's:

- initials
- sex
- race
- date of birth
- weight

Details of concomitant diseases and any concomitant medication were recorded in the case report form.

Patients were informed of the study requirements to ensure a willingness to comply. Informed written or witnessed oral consent was obtained.

Efficacy and safety assessments were performed as detailed in the next sections (3.9 and 3.10).

3.9 EFFICACY PARAMETERS

3.9.1 Hamilton Depression Rating Scale (HDRS)

At each assessment the total score on the HDRS consisting of the sum of 21 items was determined by the same investigator whenever possible for each patient throughout the study. If medication was prescribed throughout the study for night-time sedation and additional score of one was added to the total HDRS to compensate for the insomnia factor. Because of the diurnal rhythm of mood in endogenous depression, the scale was administered at the same time of day at each visit, so far as possible.

3.9.2 Zung Self-Rating Scale for Depression (ZUNG)

At each assessment (including baseline), the total score on the ZUNG (Appendix VI) consisting of the sum of 20 items was determined.

Hamilton Anxiety Rating Scale (HARS)

At each assessment, the total score on the HARS (see Appendix VII) was determined by the same investigator whenever possible for each patient throughout the study. The investigator did not consult previous scores before administering the scale to the patient.

Sleep Questionnaire

At baseline assessment and every two weeks thereafter, the patient was asked to complete a sleep questionnaire as per Appendix XIV.

Clinical Global Impression (CGI)

At each assessment a CGI (see Appendix VIII) was to be completed according to the patient's condition.

Global Assessment

At the final Week Six assessment (or, if applicable, on the day of withdrawal), both the investigator and the patient made a final overall assessment of efficacy and general tolerability to the treatment, according to the following four-point scale:

1	=	excellent	2	=	good
3	=	moderate	4	=	poor

3.10 SAFETY PARAMETERS

3.10.1 Vital Signs

At each assessment (including baseline), the following "vital signs" were recorded:

- pulse rate (sitting and standing);
- blood pressure (sitting and standing);
- body weight.

Blood pressure and pulse rate were measured after sitting for at least five minutes and also immediately after standing.

Any clinically significant change in vital signs was reported on the case report form as an adverse event, and relationship to the treatment should be assessed (see Appendix IX).

Laboratory tests (see Safety Data) were performed at baseline ad at study end Day 42.

3.10.2 Adverse Events

On day zero patients will be asked if they experience any symptoms from a check list (Appendix XIII) to assess baseline symptoms.

On days three, seven, fourteen, twenty one, twenty eight and forty two assessments, patients were asked the question, "Has the treatment upset you in any way?"

If the answer was "yes" full details of the nature, date of onset, duration, severity, and relationship to treatment were recorded on the relevant pages of the case report form.

An adverse event is any change from the patient's baseline condition, including any clinical or laboratory test value abnormality which occurred during the course of a clinical study after treatment had started, whether considered related to treatment or not. "Treatment" includes all investigational agents administered during the course of the study.

Clinical adverse events were identified as serious or not, and graded on the following three-point scale:

Mild

The symptom did not hinder the subject's normal functioning level, that is his level of pretreatment. An annoyance to the subject.

Moderate

The symptom produces some degree of impairment to functioning but is not hazardous to health. Uncomfortable and/or embarrassing to the subject.

Severe

The symptom is a definite hazard to well being. Significant impairment of functioning or incapacitation.

Relationship of the adverse event to the treatment was assessed according to the guidelines in Appendix IX.

3.10.3 Immediately Reportable Events

Any clinical adverse event or abnormal laboratory test value that is serious (including death or overdose) occurring during the course of the study, irrespective of the treatment received by the patient, was reported within one working day of occurrence to the Manufacturer's Clinical Trials Officer.

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution, with respect to human clinical well-being. This includes any experience which:

- is fatal or life-threatening;
- is permanently disabling, that is incapacitating or interfering with the ability to resume usual life patterns;
- necessitates inpatient hospitalisation or prolongation of hospitalisation;
- is a cancer;
- is an overdose.

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome, even if toxic effects were not observed.

A death occurring during the study or within four weeks after stopping the treatment, whether considered treatment related or not, must be reported.

Such preliminary reports were followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

3.10.4 Treatment and Follow-Up of Adverse Events

The investigator was solely responsible for the decision to withdraw a patient from the study and/or to administer symptomatic therapy because of an adverse event. If the adverse event persisted a further follow-up report was required detailing the patient's progress.

3.11 PREMATURE WITHDRAWAL OF SUBJECTS FROM STUDY

In accordance with the Declaration of Helsinki (see Appendix XII) patients had the right to withdraw from the study at any time, for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure (after a prescribed procedure, protocol violations (for example not meeting protocol entry criteria or failing to adhere to protocol requirements), cure, administration reasons or other reasons.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable, therefore unnecessary withdrawal of patients was avoided. If a patient decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. A

complete final evaluation at the time of the patient's withdrawal was made with an explanation of why the patient was withdrawing from the study. If the reason for removal of a patient from the study was an adverse event or an abnormal laboratory test result, the principal specific event or test was also recorded on the Case Report Form. In the event of any emergency when the patient's condition required knowledge of the test medication dispensed the sealed envelope could be opened to determine the nature of the test medication dispensed. (Any broken code must be clearly justified and explained in the case report forms.)

3.12 REPLACEMENT POLICY FOR SUBJECTS WITHDRAWN FROM STUDY

Patients who were removed from the study due to an inadequate response after a minimum of three weeks treatment of the study medication were considered medication failures and were not replaced, however, their data was included in the final analysis. Withdrawal at a patient's own request for either lack of personal perceived improvement (= "medication failure") or because of personal perceived amelioration (= "success") constituted a valuable end point providing the patients had been treated for three weeks, and such patients were not replaced.

Patients who failed to take their medication properly, who were not co-operative, who became seriously ill during the study, or who did not finish the observation periods specified in the protocol for a number of non-drug related reasons were withdrawn from the study. When treatment was terminated prior

to day 21 these patients were replaced. The data was not included in the efficacy analysis but in the safety analysis.

3.13 CRITERIA FOR EXCLUSION OF SUBJECTS FROM ANALYSIS

The following conditions required the exclusion of a patient from the analysis of efficacy:

- violation of inclusion or exclusion criteria if it can influence the evaluation of efficacy, for example previous therapy;
- non-compliance to treatment regimes, less than 80 percent medication taken and a period of more than 24 hours without treatment..

3.14 ETHICAL ASPECTS

3.14.1 Declaration of Helsinki

The investigator ensured this study was conducted according to the "Declaration of Helsinki", the text of which is attached as Appendix XII.

3.14.2 Informed Consent

It was the responsibility of the investigator to obtain either informed verbal consent or informed written consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study (written consent was the preferred method when possible). Consent was witnessed. For patients not qualified to give legal consent, written consent was obtained from the legal parent or guardian. The investigator also explained that the patients were completely free to refuse to enter the study or to withdraw from it at any time.

3.14.3 Ethics Committee Approval

The protocol for this study was approved by the P and T as well as the M.C.C. Committees.

3.15 WARNING AND PRECAUTIONS

3.15.1 Hypertensive Crisis

Although hypertensive crises are a classical complication during treatment with MAOIs, their likelihood appears to be very low with moclobemide. Thus, no particular dietary precaution was necessary. Patients were however instructed to take their medication after meals. If a hypertensive crisis were to occur, it was treated with oral nifedipine (10 to 20 mg).

3.15.2 Other Warnings

If surgery was necessary, the aneasthetist was informed that the patient was being treated with moclobemide.

3.15.3 Overdose

Accidental or intentional overdoses are a non-negligible risk in the treatment of depressed patients with antidepressants including MAO-inhibitors.

Symptoms and signs of overdose with classical MAO-inhibitors may include drowsiness, dizziness, faintness, hyperactivity, agitation, severe headache, opisthotonus, convulsions, tachyarrhythmia, hyper-or hypotension, hyperprexia. Cases of death and coma have even been registered.

Experience of overdose with moclobemide in man is limited. Signs which have been observed are increasing agitation, aggressiveness and behavioural changes. Treatment of overdose should be aimed primarily at maintenance of the vital functions.

3.16 STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

The investigator maintained adequate records to enable the conduct of the study to be fully documented.

For each patient enrolled a CRF (case report form) was completed and signed by the principal investigator or co-investigator. This also applied to those patients who failed to complete the study. If a patient withdrew from the study, the reason was noted on the CRF. If a patient was withdrawn from the study because of a limiting adverse event, reasonable efforts were made to clearly document the outcome.

All forms were filled out using a black ball-point pen, and were legible. Errors were crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator.

3.17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator assured that patient's anonymity was maintained. On CRFs or other documents submitted to the sponsor, patients were not identified by their names, but by an identification code. The investigator kept a separate log of patients' codes, names and addresses. Documents, for example

patient's written consent forms, were maintained by the investigator in strict confidence.

3.18 DURATION OF STUDY

The duration of the study was approximately 18 months.

3.19 SIGNATURES

I/we agree to the conditions relating to this study as set out in this protocol and fully understand that any changes (not associated with the procedures necessary for the well being of the patients) instituted by the investigator(s) without previous discussion with appropriate sponsor's personnel (Clinical Trial Coordinator of Medical Advisor) would constitute a violation of the protocol.

I/we will assure that the drugs supplied by the sponsor will be used only as described in this protocol; if any other use is desired, written permission must be obtained from the sponsor.

Signature	Date	
_____	_____	Investigator
_____	_____	Clinical Trial Monitor
_____	_____	Medical Advisor

CHAPTER FOUR

4. RESULTS

The study population consisted of adult outpatients diagnosed as having a major depressive episode according to DSM III-R criteria, who had scores of 17 or more on the 21-item Hamilton Depression Rating Scale (HAM-D). Exclusion criteria included schizophrenia, bipolar mood disorder, organic brain disorders, mood incongruent psychotic features and dementia (other than the pseudo-dementia caused by depression). Also excluded were those patients with a clear suicide risk, substance dependence or abuse, obsessive and phobic disorders.

Concomitant psychotropic medicine, other than a single nocturnal hypnotic was not allowed.

Antidepressant efficacy was primarily assessed through change from baseline to end point, in the total (HAM-D) score of Hamilton Depression Rating Scale. The HAM-D was administered at each follow up visit. Responders were defined as patients who had a total score of ten or less endpoint, or a score of 50 percent or less than that of baseline score (see table 5). With respect to the individual items of the HAM-D, responders were defined as patients with a score of zero at end point. Zung Self-Rating Scores and a clinical global impression (CGI) of severity of illness and antidepressant efficacy of treatment was recorded. Responders were defined as patients who had a score of "minimally ill" or "not ill" on the CGI of severity and "marked improvement" or "complete remission" on the CGI of efficacy.

Tolerability was defined as a good or excellent response to treatment on the clinical global assessment of tolerance (CGAT). Patients who received at least three weeks of treatment and who complied with the inclusion and exclusion criteria only, were included in the trial.

Table 5: Treatment response rates on the Hamilton Depression Rating Scale

Treatment Group	100 mg t.d.s.	150 mg t.d.s.	150 mg b.d.
n	11	10	10
Responders*	6	5	7
Response rate	54,5%	50%	70%
Efficacy rate			
150 mg t.i.d./100 mg t.i.d. and 150 mg b.i.d./100 mg t.d.s.		0,91	1,29
150 mg b.i.d./150 mg t.d.s.			1,4

Responders: patients with a total score of 10 or less at endpoiont, or a score of 50% or less of the baseline score.

Thirty three adult outpatients were enrolled on the study. Two patients were excluded for being on more than one benzodiazepine at a particular time during the study. Of the thirty one patients included in the trial, five patients dropped out. Two patients required hospitalisation as their condition was deteriorating. One patient was non-compliant. One patient became increasingly hyperactive and one patient required a change of medication (n = 31). The small sample size resulted in a type II statistical error.

Selection was done on a double-blind basis, and patients were randomly allocated into three treatment groups, viz. groups 1, 2 and 3 (see table 6). Groups were comparable with respect to baseline characteristics of age, sex, weight and mean baseline scores for both the Hamilton and Zung rating

scales (see figures 4 and 5). The N-Pariway procedure was used to analyse the scores of patients on the Hamilton Rating Scale. At day zero, the *p* value obtained was 0,8991, this implies that there was no difference between patients chosen to join the trial. Also, there was no significant difference between the choice of patients in the individual groups they were allocated to. The experiment is therefore deemed valid, and there is no bias choice of patients allocated to Groups 1, 2 or 3. The same procedure was used to determine the Zung Scores on day nought. The *p* value obtained was 0,128.

Table 6: Demographic data and baseline scores (intention to treat analysis)

Treatment Group	**Group 1 100 mg t.d.s.**		**Group 2 150 mg t.d.s.**		**Group 3 150 mg. b.d.**	
N	11		10		10	
F	8		8		5	
M	3		2		5	
	Mean	Range	Mean	Range	Mean	Range
Age (years)	46.57	21.1-60.05	39.25	26.5-53.59	35.21	21.93-45
	72.45	41.8-87.9	67.45	47-77.4	71.52	49-98
Mean Baseline Score						
HAM-D	25.2	18-29	24	19-28	26	18-3
ZUNG	29.36	17-41	24,125	7-43	36	24-4

This is thought not to be of significance, but it implies that there was a larger difference between patient's scores on the HAM-D at day zero.

Group 1 received 100 mg t.d.s. (n = 11), Group 2 received 150 mg t.d.s. (n = 10) and Group 3 received 150 mg b.d. of moclobemide respectively (n = =10). There were three dropouts from Group 1, two dropouts from Group 2 and no dropouts from Group 3.

4.1 Efficacy Results

The data was analysed using the N-Pariway, the Univariate, the Kruskal-Wallis and the General Linear Models Procedures. No clinically relevant differences between treatment groups could be demonstrated with respect to: the mean change in total scores of Groups 1, 2 and 3 on the HAM-D or Zung Scales, from baseline to endpoint (see figures 4 and 5).

The dosages of drugs used, were found to be equally effective in that the overall Hamilton and Zung Scores did drop between days one and forty two (see figures 6 and 7). Both Hamilton and Zung scores for the seven clinic visits were analysed using the N-Pariway procedure. The HAM-D scores revealed that there was no statistically significant difference between the groups on day 42 (p = 0,9662). The same was true for the Zung scores, where the same p value was 0,9733. This implies that on a test day by test day comparison, the results of the three different groups were compared and there appears to be no statistically significant differences between the dosage groups. This was confirmed by the General Linear Models Procedure, as similar results were obtained.

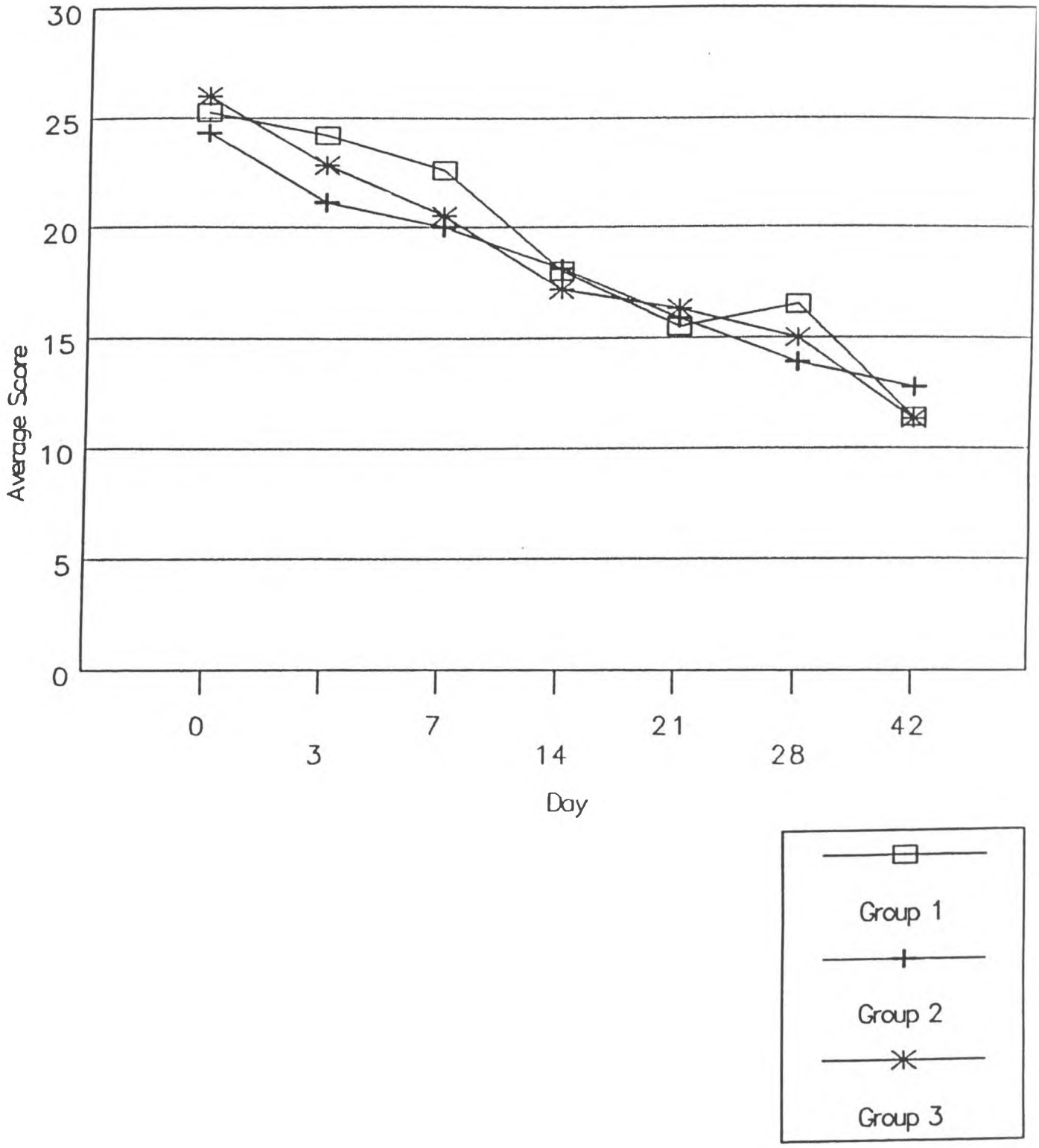


Figure 4: **Average Hamilton score groups 1 to 3**

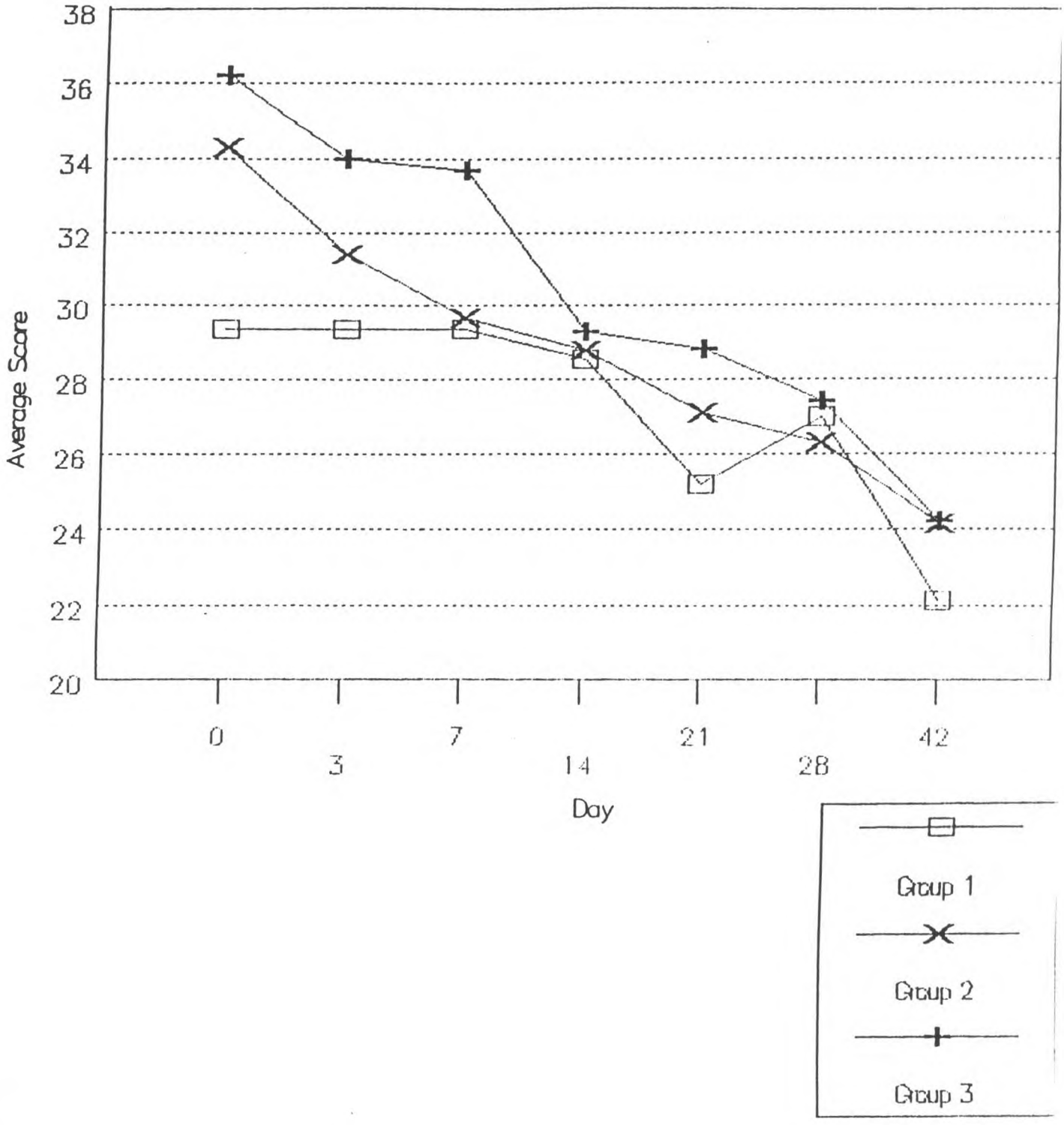


Figure 5: **Average ZUNG scores groups 1 to 3**

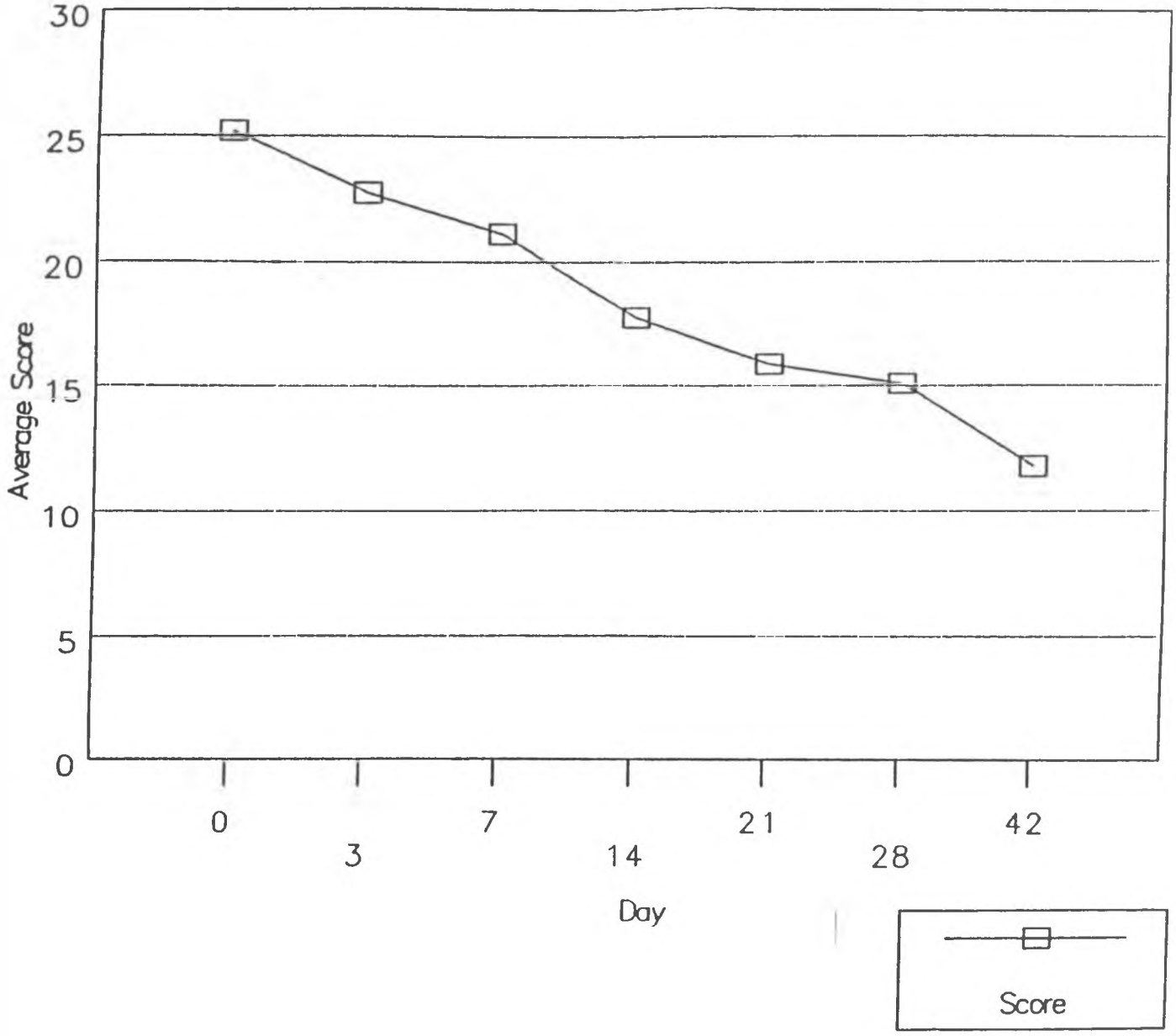


Figure 6: **Average Hamilton score - all groups combined**

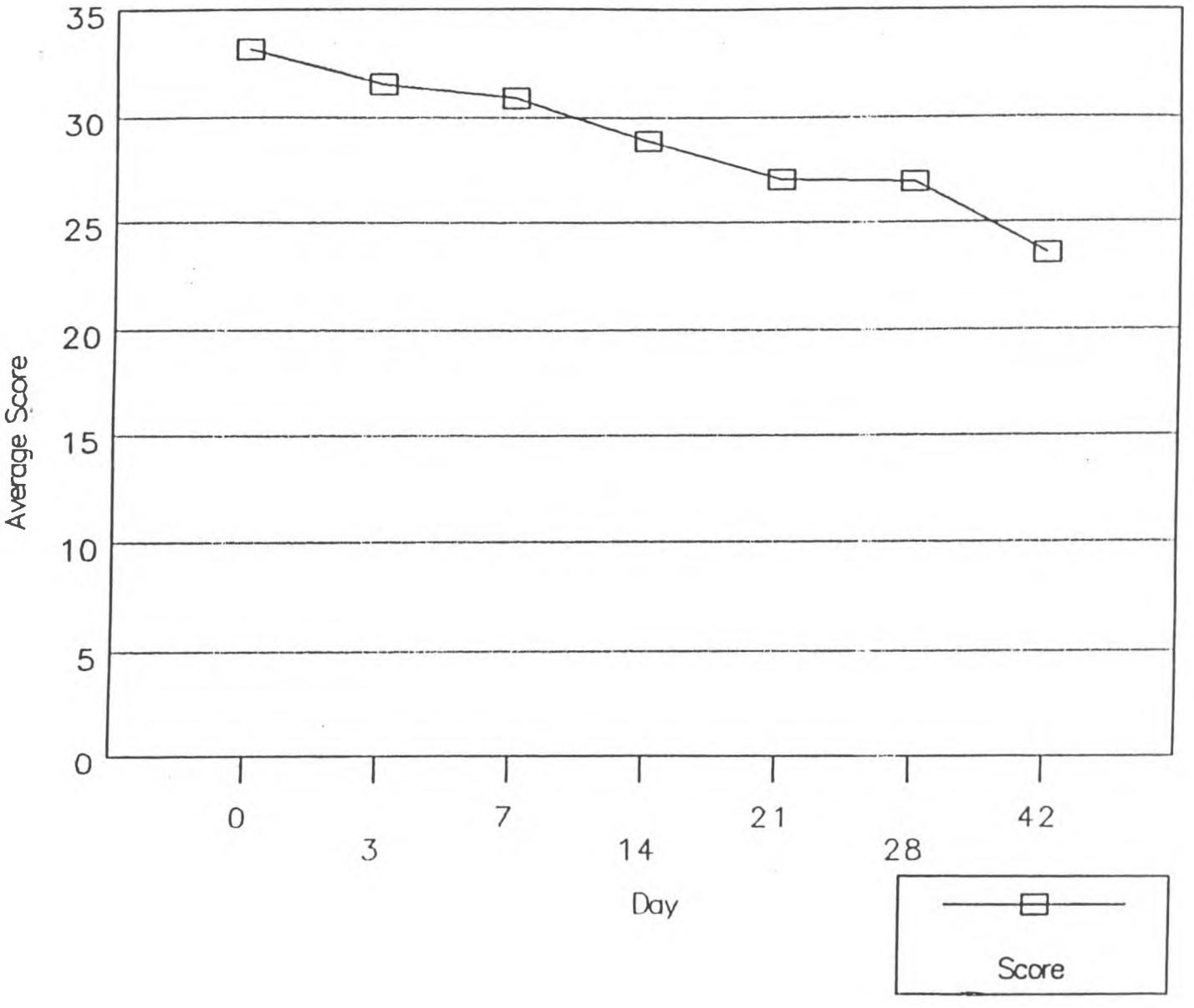


Figure 7: **Average ZUNG score - all groups combined**

Core features on the HAM-D scale were analysed individually, viz. guilt, suicide, work and activities, somatic features and loss of weight. Overall there were no significant differences between the Groups 1, 2 and 3 on the Hamilton Rating Scores. Neither was there a difference between the groups measured feature for feature on the Zung Rating Scores.

4.2 ANALYSIS OF CORE FEATURES ON THE HAM-D

4.2.1 Guilt - Item 2 on the HDRS (figure 8)

Patients were found to be less guilty on day 42 as compared to day 0, according to figure 8. The mean score for Group 2 was no guilt on day two. This suggests that patients on 150 mg three times per day, were overall less guilty than patients belonging to other groups. There was no significant difference between the groups at day 0 ($p = 0,443$) and at day 42 ($p = 0,042$), this implies that there is a significant difference between the groups, however, this figure probably occurred by chance due to the large number of comparisons made.

Despite the fact that the study was not designed to determine the efficacy of treatment, there was an improvement with a linear trend during the 42 days of the study. No control, however, was done. This has been confirmed in studies done by Cassachia et al. (1984) and Botte (1990), where placebo controlled trials indicate that about twice as many patients receiving moclobemide showed a marked improvement during a four week period, as compared to patients receiving placebo.

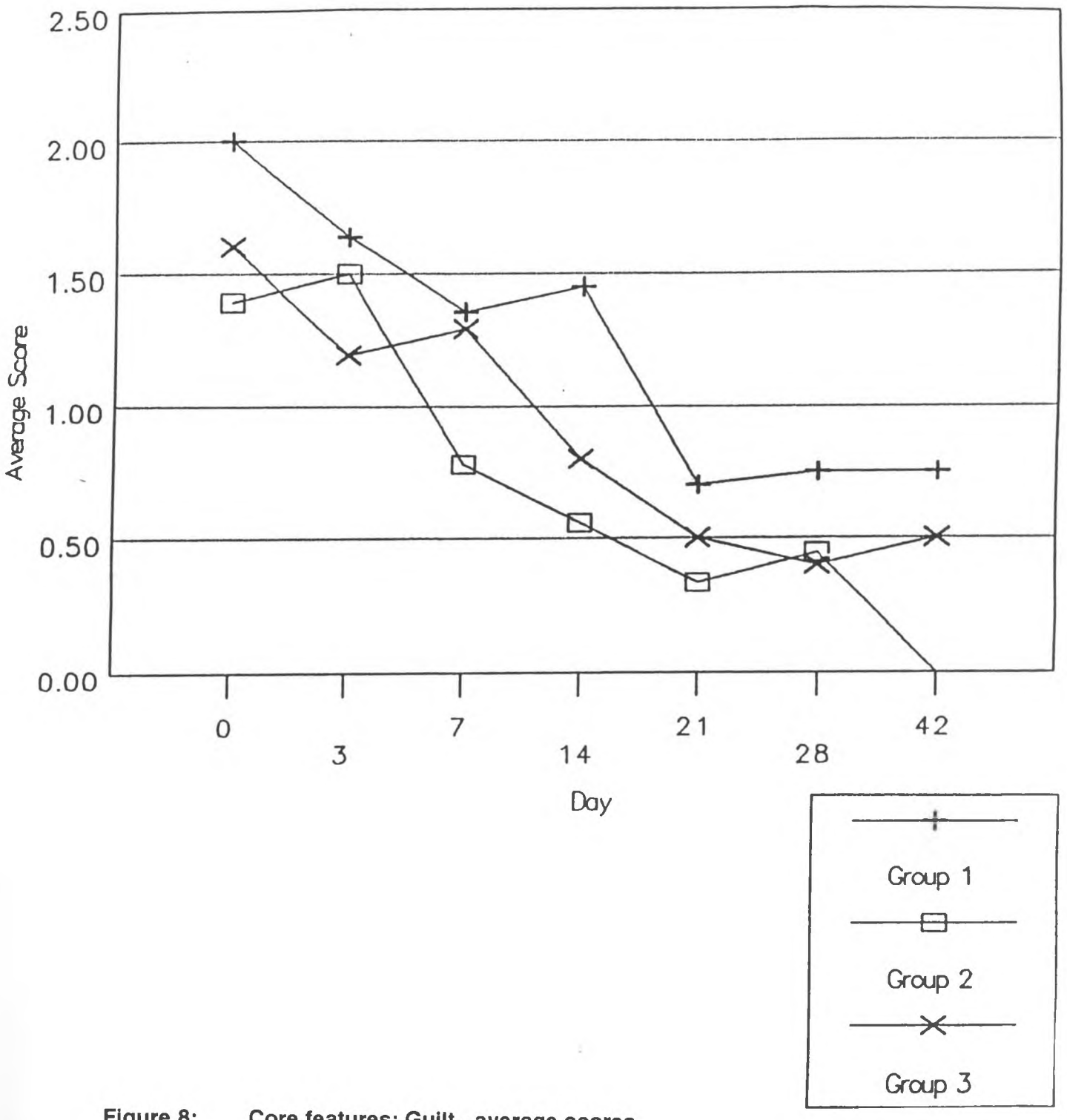


Figure 8: **Core features: Guilt - average scores**

4.2.2 Suicide - Item 3 on the HDRS (figure 9)

There was an overall decrease in the core item suicide. The difference in figures over the 42 day period was not found to be statistically significant. Group 2, however, had an average score for suicide of zero. This implies that patients on 150 mg t.d.s. (three times per day), did better than the other groups as far as this item is concerned.

Overall, on day zero, 93.5 percent of patients had suicidal ideation as compared to 51 percent of patients on day 42. Therefore there was a 42.5 percent decline in suicidal ideation over the 42 day period.

4.2.3 Work and Activities - Item 7 on HDRS (figure 10)

There was an overall trend for a decrease in impairment of work and activities, on the HDRS. The trend was for a linear decrease in scores for all three groups. No statistical difference between the groups was found.

4.2.4 Somatic Symptoms - Item 13 on the HDRS (figure 11)

As with previous core items mentioned, there was a linear trend towards a decline in somatic symptoms on the HDRS. The *p* value obtained at day zero was 0.366; whilst that for day 42 was 0.406. No statistical difference between the groups was found.

4.2.5 Weight Loss - Item 16 on the HDRS (figure 12)

No clear differences could be demonstrated between treatment groups with respect to weight loss or gain on the HDRS.

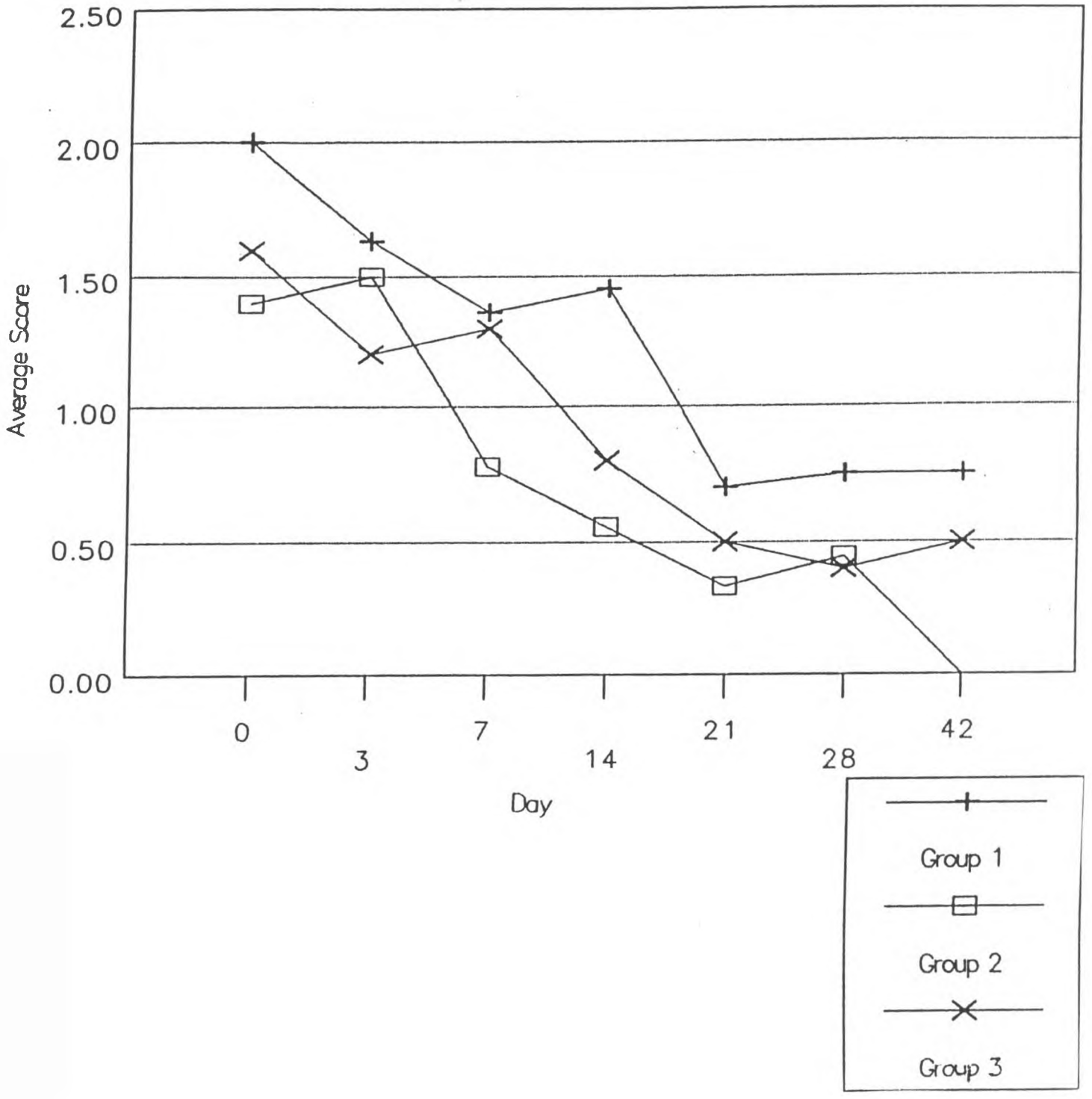


Figure 9: **Core features: Suicide - average scores**

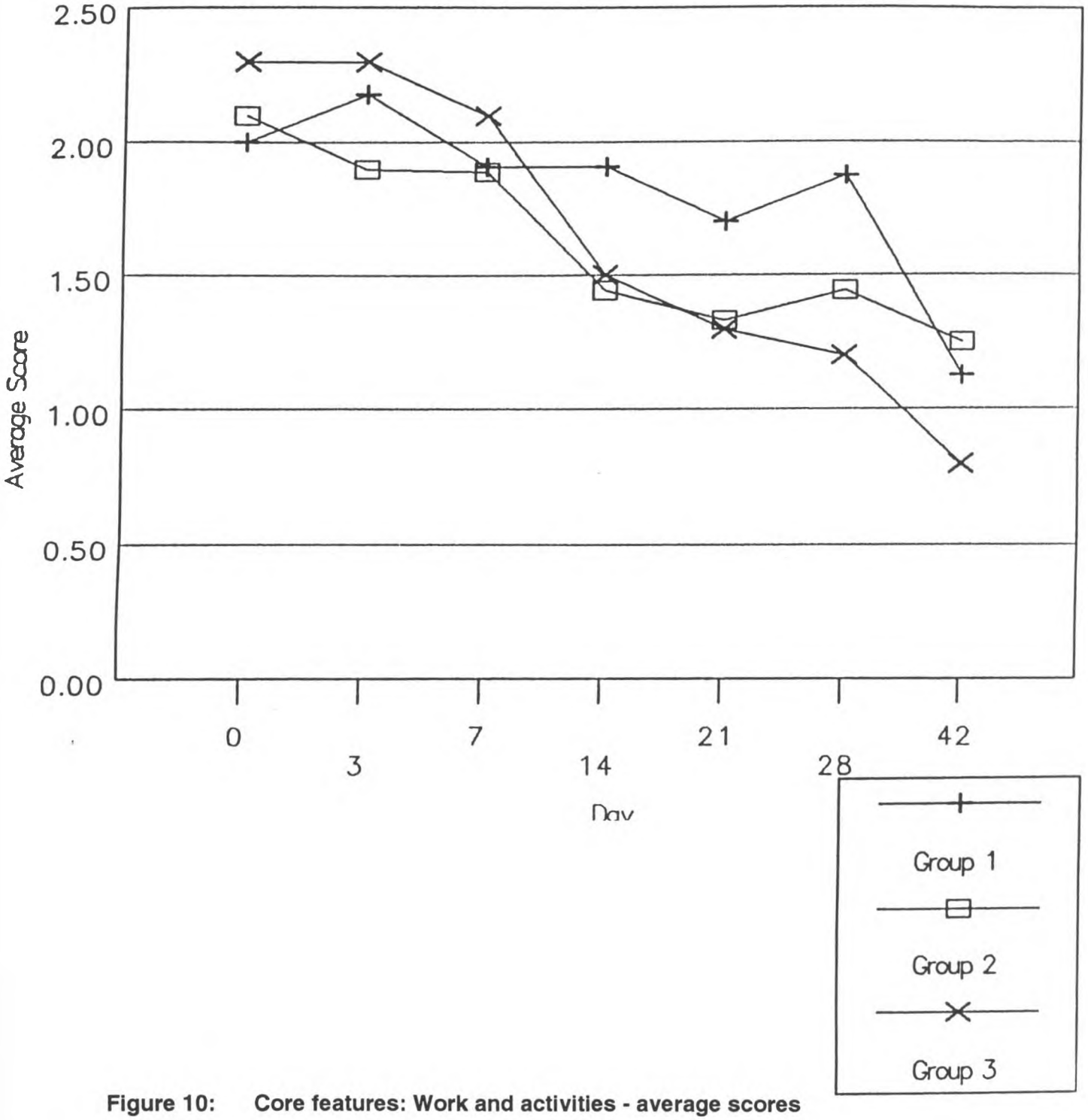


Figure 10: Core features: Work and activities - average scores

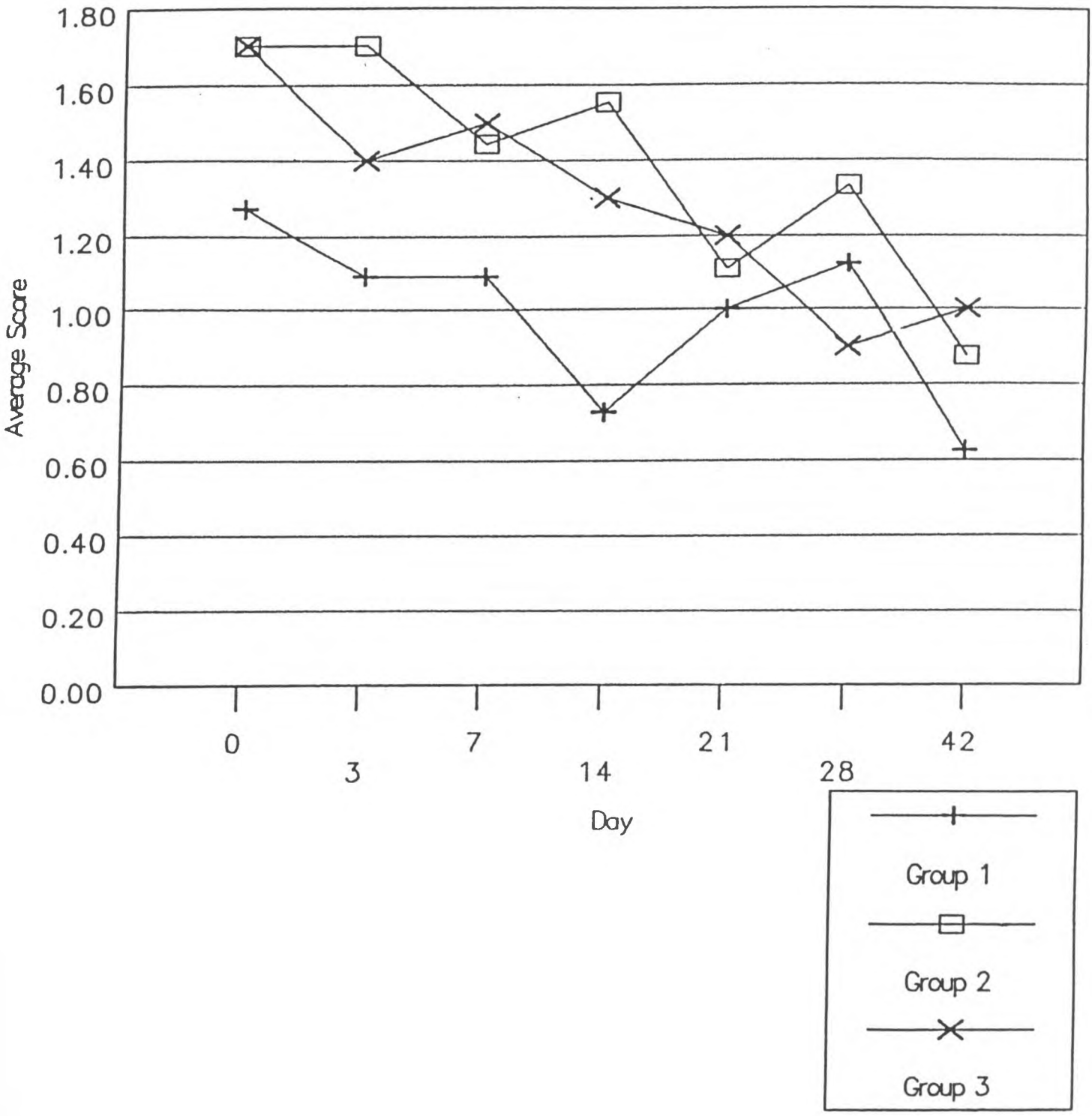


Figure 11: Core features: Somatic symptoms - average scores

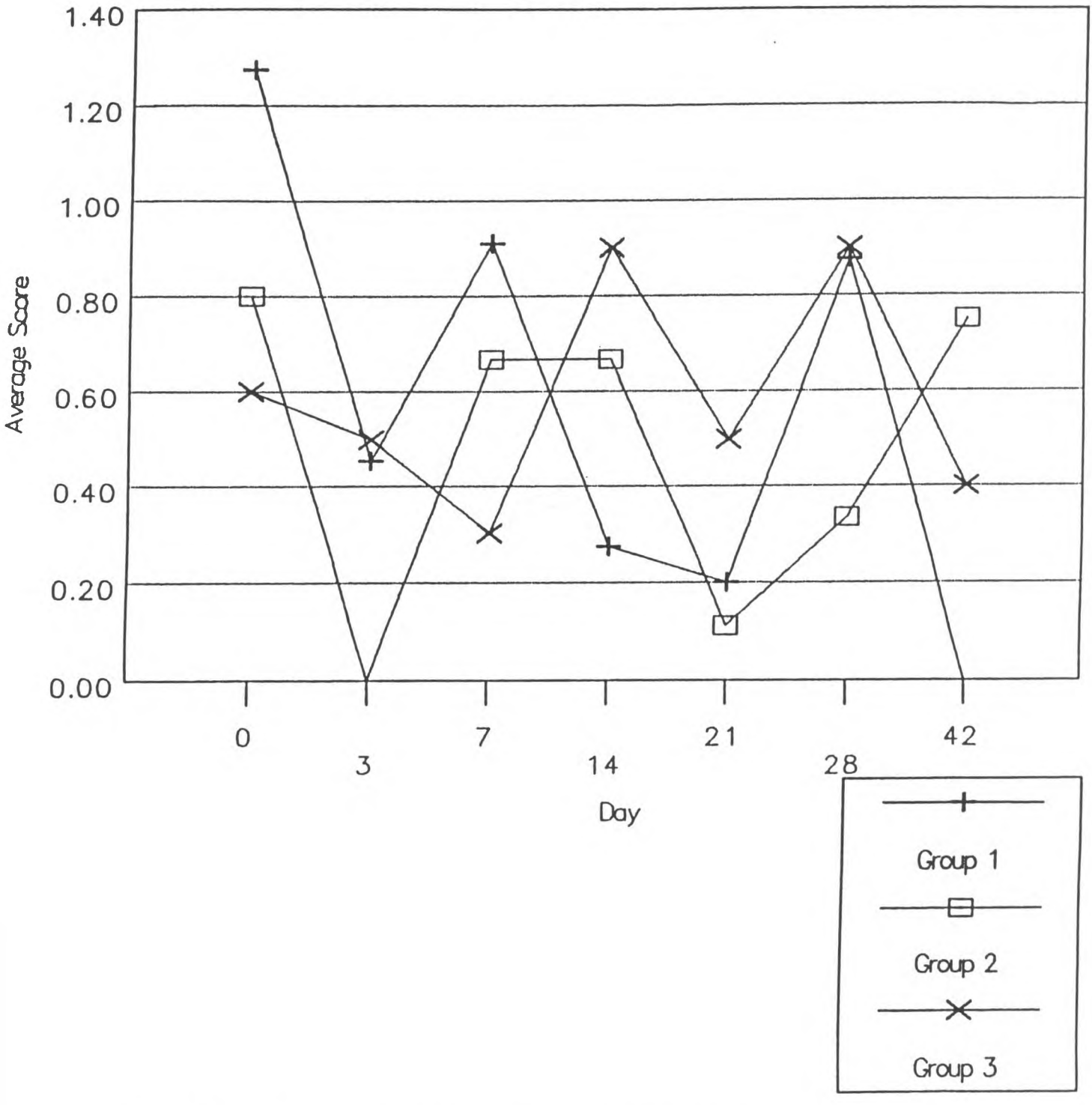


Figure 12: Core features: Loss of weight - average scores

4.3 ANXIETY/AGITATION SUBSCALE OF THE HDRS (figure 13)

There was a rate of 54.54 percent on 100 mg of moclobemide three times per day (t.d.s.) compared to a 50 percent response in Group 3, that is 150 mg twice a day (b.d.). The response rate in Group 2, that is 150 mg three times a day (t.d.s.) was 40 percent.

Patients in Groups 1 and 2 had an average score on the Anxiety/Agitation subscale of 18.6 as compared to Group 3, where the patients had an average score of 16.4. No patients dropped out of Group 3. Could this be that patients in this group were less agitated or anxious? Perhaps the 150 mg t.d.s. dosage had more effect on Anxiety/Agitation! Figure 13 shows a graph tracing of the anxiety scores for groups 1, 2 and 3 over the 42 day period of the trial. There appears to be linear decrease in the average anxiety/agitation scores over this period (see table 7).

Table 7: Treatment response rates on the anxiety/agitation subscale of the Hamilton Depression Rating Scale (HDRS)

Treatment Group	100 mg t.d.s.	150 mg t.d.s.	150 mg b.d.
n	11	10	10
Responders	6	4	5
Response rate	54.54%	40%	50%
Efficacy ratio			
150 mg tds/100 mg tds and 150 mg bd/100 mg tds		0.74	0.92
150 mg bd/150 mg/tds			1.25

Responders: Patients with a total score of 10 or less at end point, or a score of 50% or less of the baseline score

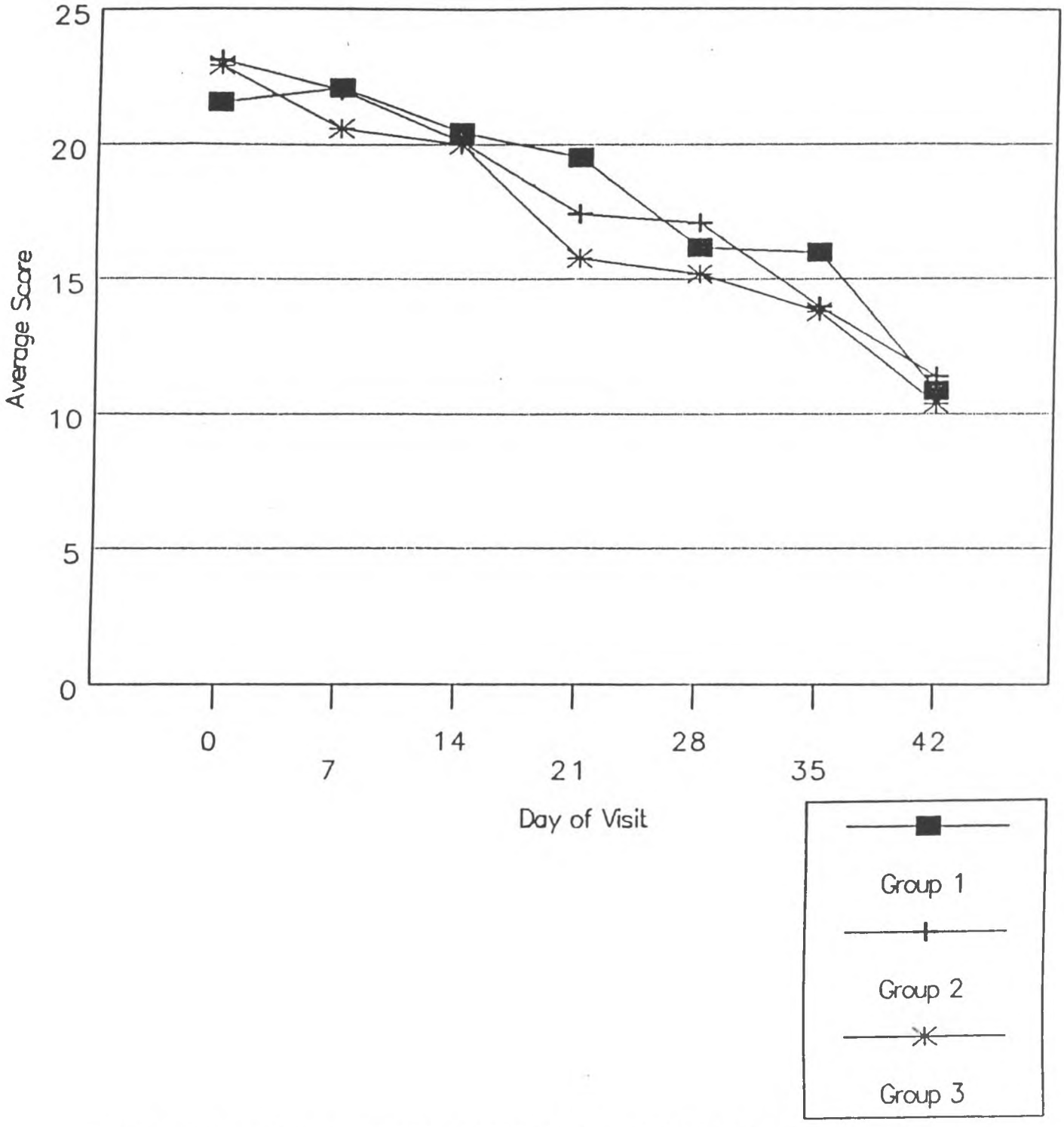


Figure 13: Average anxiety/agitation scores (HAM-D subscale)

4.4 TOLERABILITY AND SAFETY

There were no marked differences between the treatment groups, with respect to the type and frequency of adverse events. Side effects were uncommon. At most one patient in each group suffered from one side effect. The exception to this was in Group 1, where four patients had insomnia and three patients suffered from agitation. The Chi-square test was used to determine the statistical significance of these figures, viz. insomnia and agitation, in these particular patients in Group 1, and no statistical significance could be attached to any of these figures (see table 8). Overall 19 out of 31 patients suffered from at least one adverse effect - this amounts to an incidence of 61.2 percent of adverse effects. The most commonly occurring were insomnia and agitation, occurring with a frequency of 61.2 percent.

The incidence of adverse effects in group 1 was 25.8 percent, Group 2 was 16.12 percent and Group 3 was 19.35 percent. Tolerability was rated as good or excellent in 90.3 percent of the study population. The response rates for the treatment groups are listed in table 9. Blood pressure and pulse rates remained constant in all groups throughout the treatment period. Overall there was a trend for insomnia to initially get worse in all three treatment groups for the three individual Hamilton items on insomnia, viz. item 4, 5 and 6 on the HDRS (that is, early, mid and terminal insomnia). However, at endpoint there is an improvement in insomnia overall (see figures 14, 15, 16 and 17).

Table 8: Adverse effects by group

ADVERSE EVENT	GROUP 1	GROUP 2	GROUP 3
Insomnia	4	0	1
Agitation	3	1	1
Nausea	1	0	2
Headache	1	0	1
Loose stools	1	1	0
Anxiety	0	0	1
Postural hypotension	0	0	1
Hair loss	0	1	0
Palpitations	1	0	0
Bitter taste	0	1	0
Muscle cramps	0	0	1
Hypomania	0	1	0
Prickly sensation	1	0	0
Bloatedness	1	0	0

In terms of actual treatment response rates, all dosages of medication were efficacious (see table 9). In terms of actual measurement of tolerance to the drug (using CGAT scores) all groups appeared to tolerate the drug well. In Group 1, a 90,9 percent tolerance rate was measured; Groups 2 and 3 had a 90 percent tolerance rate. Group 1 therefore showed a slightly higher response rate, but this was not statistically significant. Overall there was a 90.3 percent response rate in all groups (see figure 20).

Table 9: Treatment response rates (percentage of patients)

TREATMENT GROUP	100 MG TDS	150 MG TDS	150 MG BD	ALL PATIENTS
N	11	10	10	31
CGI: Disease severity	54.5%	50%	90%	64.8%
CGI: Treatment efficacy	54.5%	50%	82%	61.5%
CGI: Tolerability	90.9%	90%	90%	90.3%

CGI - Clinical Global Impression

Overall 61.5 percent of patients found the drug to be effective (see table 9 and figure 19). Group 1 had a 54.5 percent efficacy rate, Group 2 had a 50 percent efficacy rate and Group 3 an 80 percent efficacy rate. This data suggests, that Group 3 had the most effective dose.

Table 9 shows that overall patients had a decrease in severity of illness by 64.8 percent. Group 3 had a 90 percent decrease in severity of illness; Groups 1 and 2 followed with response rates of 54.5 percent and 50 percent respectively. According to figure 18, there appeared to be a linear trend towards the decreases of severity of illness in all groups.

Blood pressure, both supine and standing were constant in all groups through the period. There were no hypertensive or hypotensive crises.

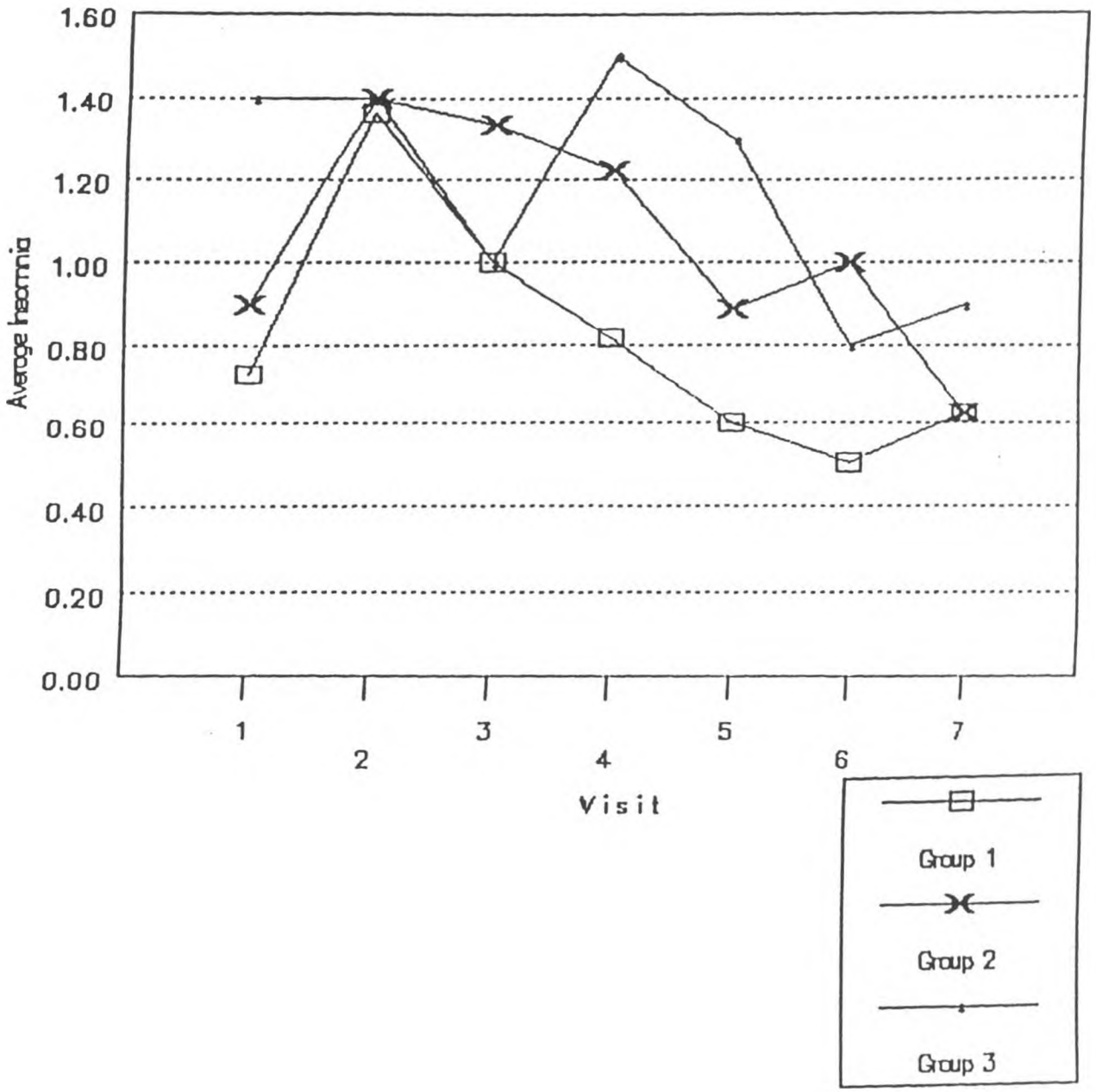


Figure 14: **Average middle insomnia - groups 1, 2 and 3**

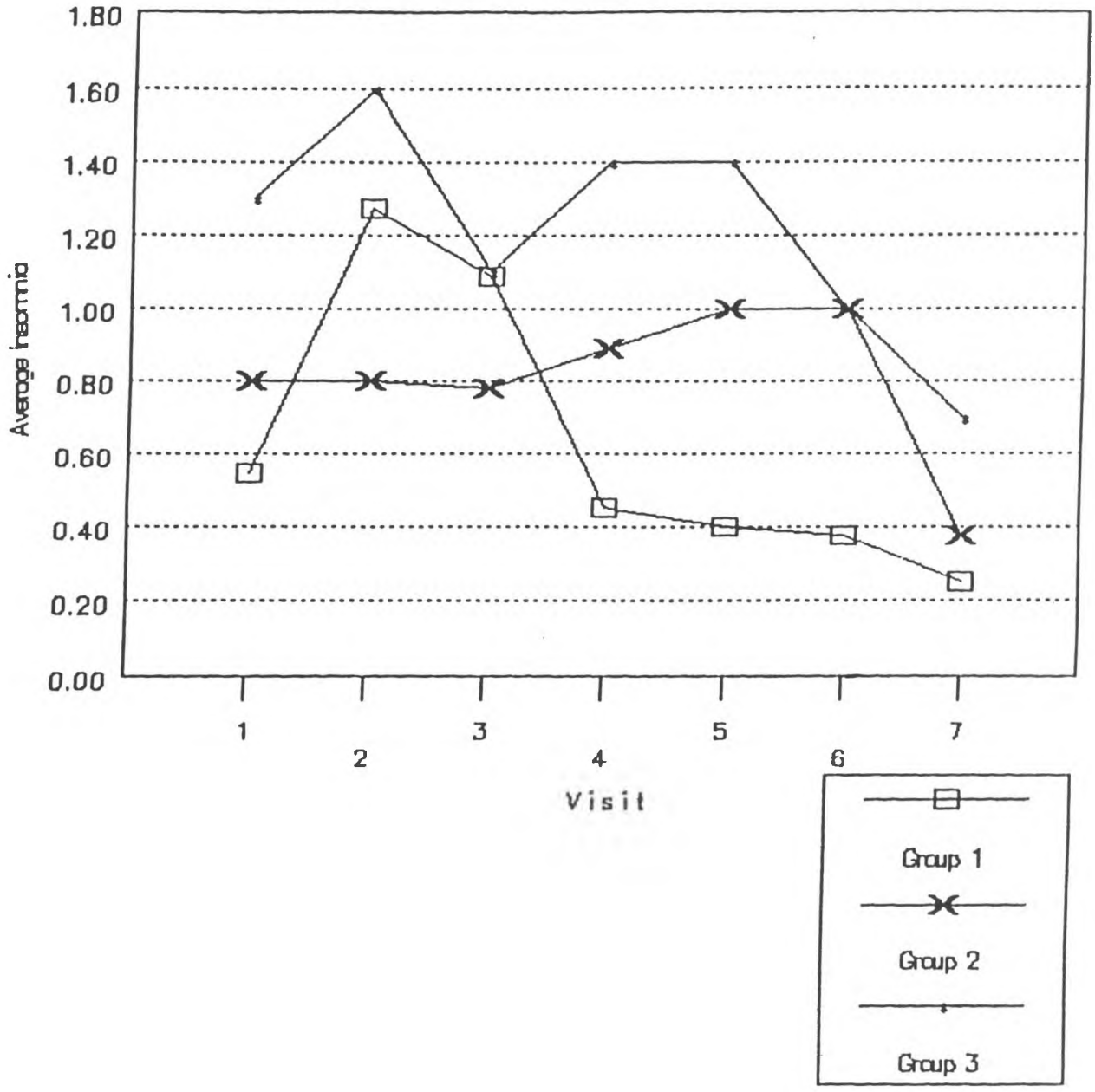


Figure 15: Average early insomnia - groups 1, 2 and 3

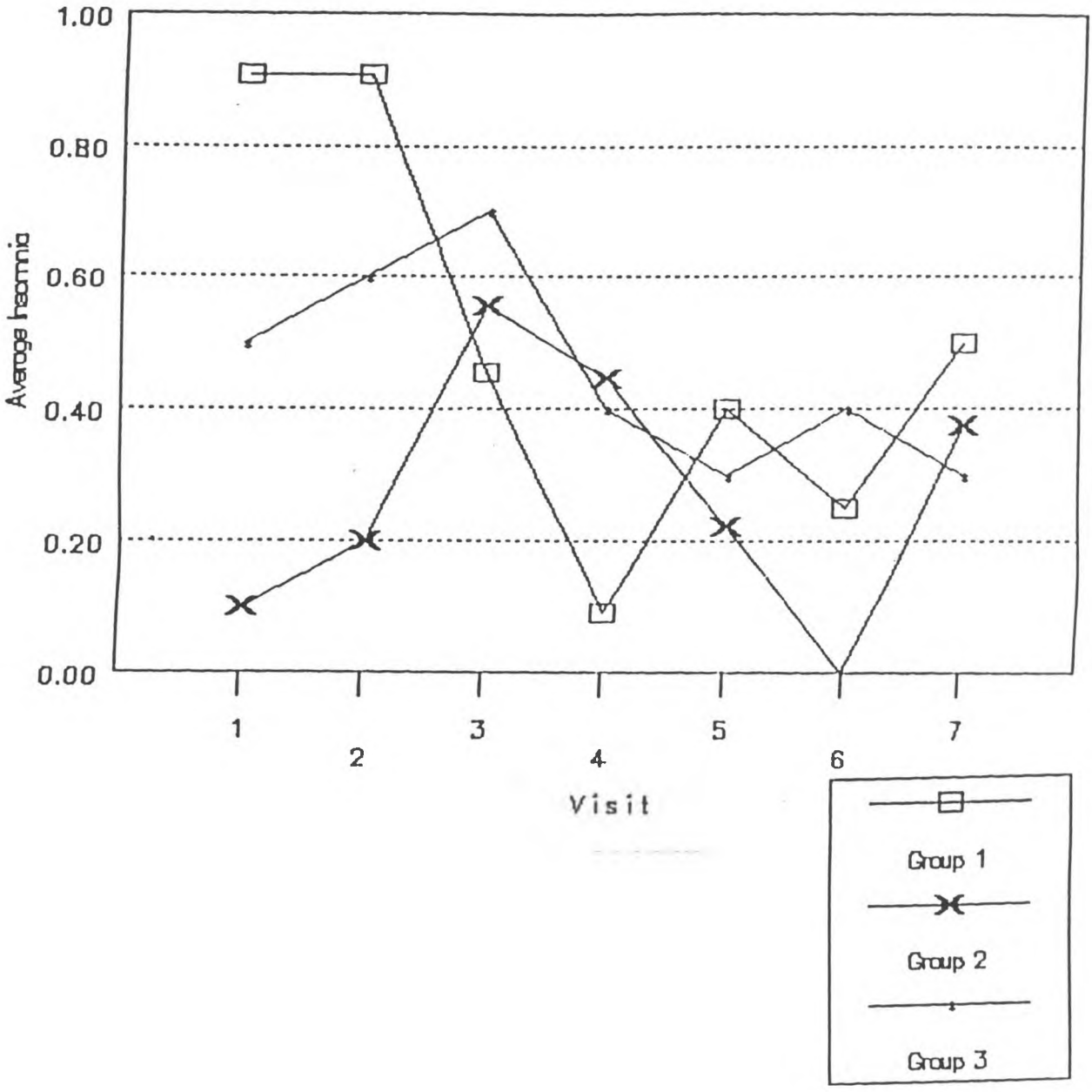


Figure 16: **Average late insomnia - groups 1, 2 and 3**

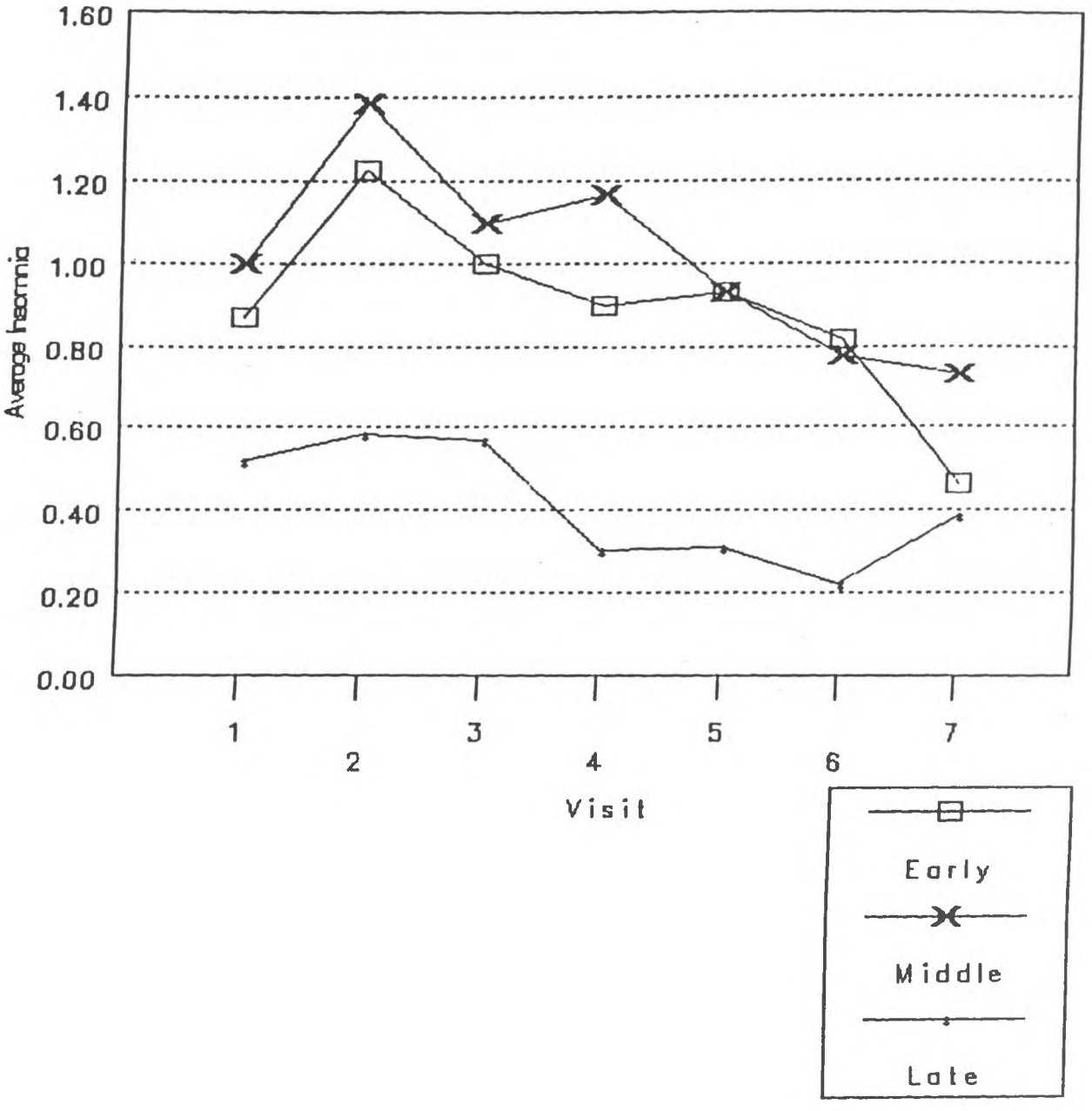


Figure 17: Average insomnia - all groups combined

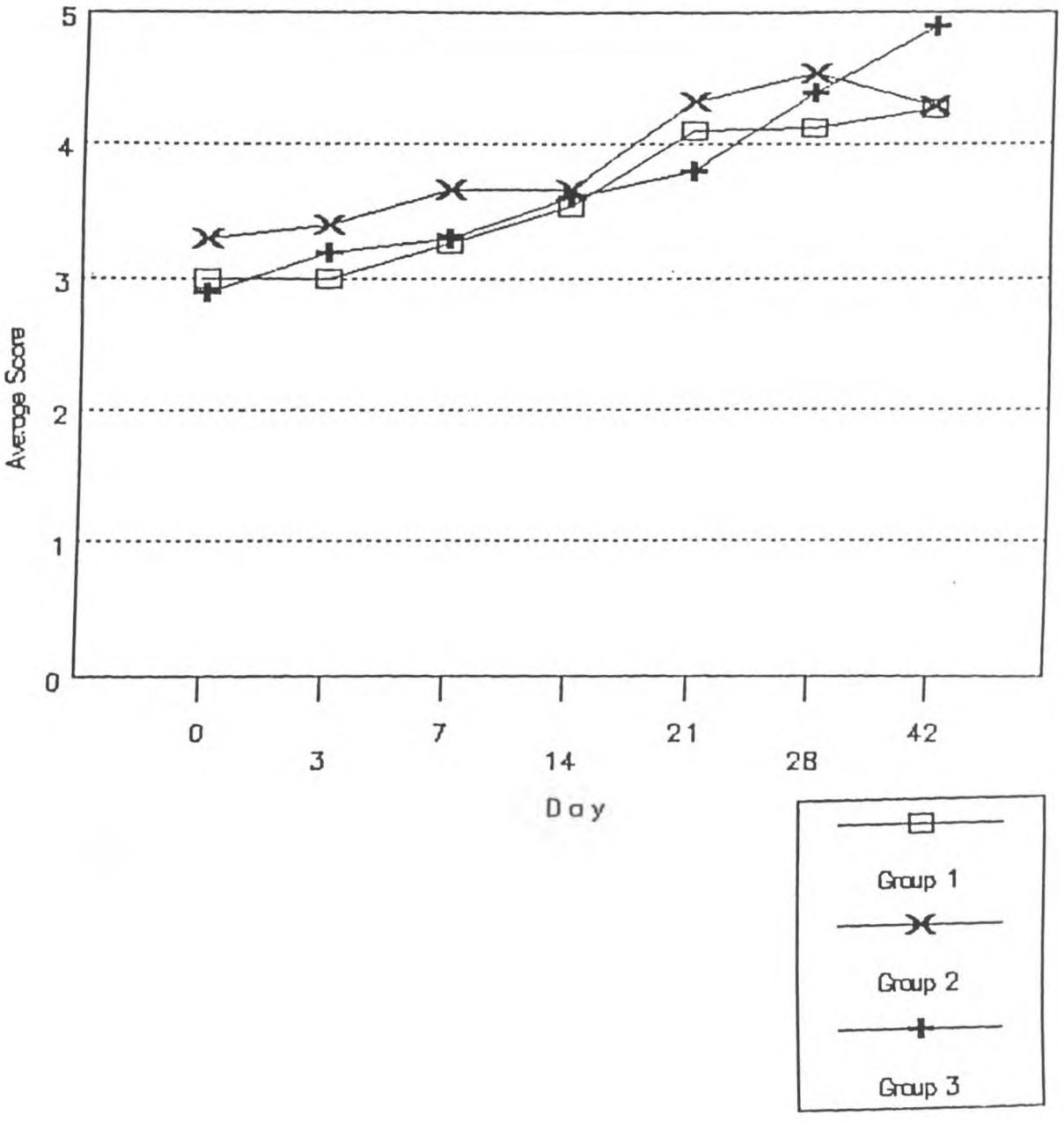


Figure 18: Clinical global assessment - illness

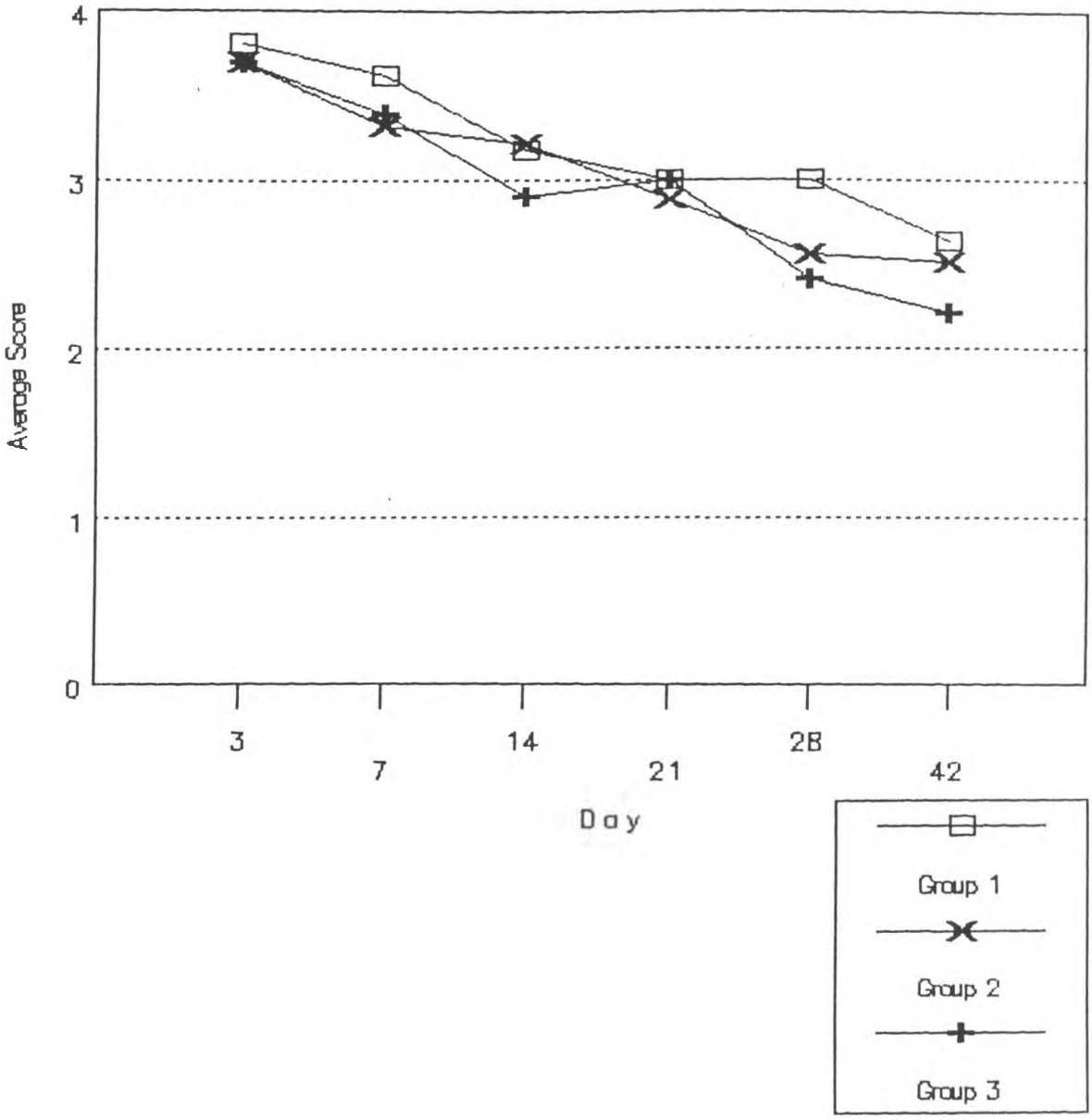


Figure 19: Clinical global assessment - efficacy

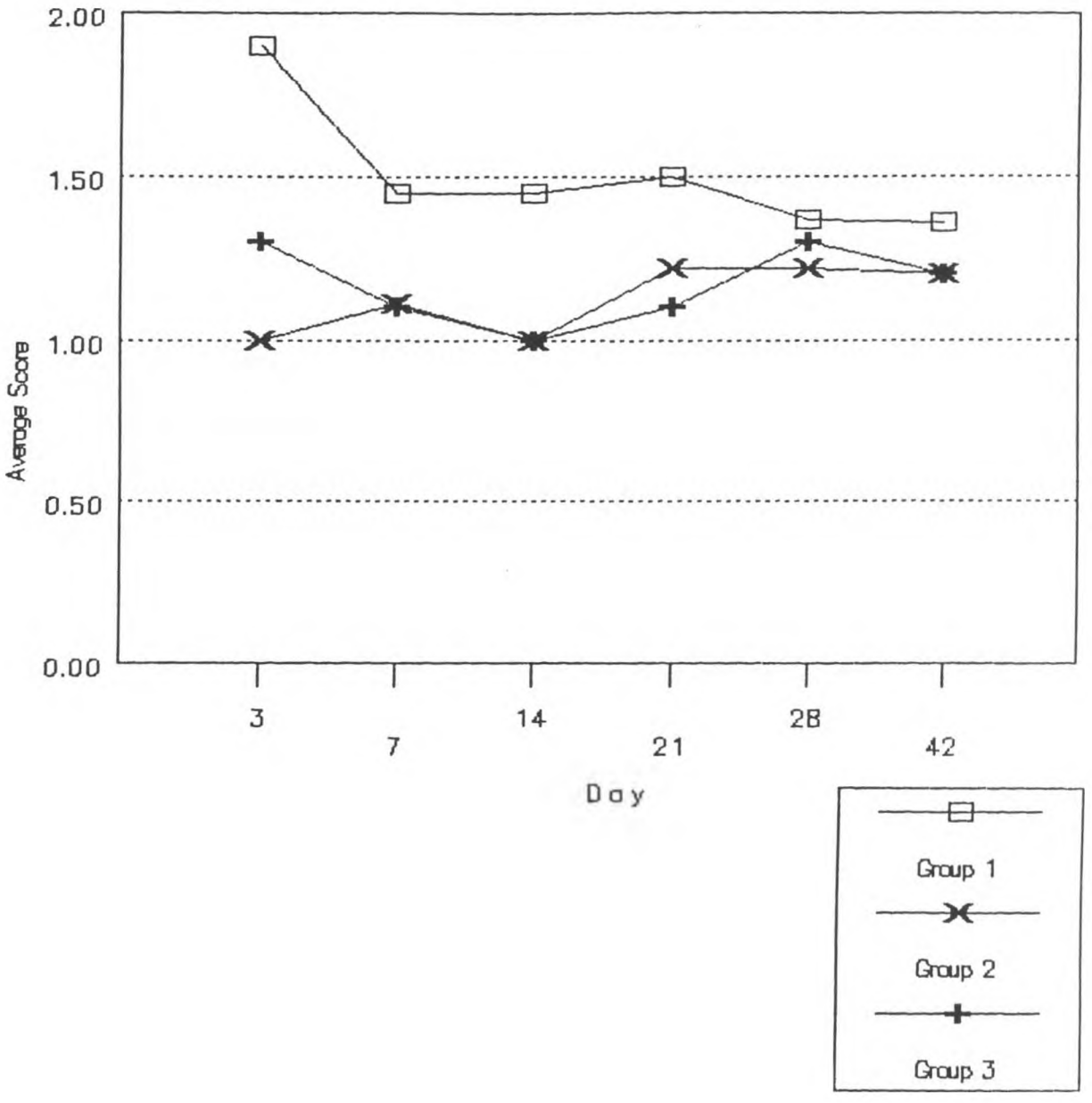


Figure 20: **Clinical global assessment - tolerance**

CHAPTER FIVE

5.1 DISCUSSION

All three dosage regimens were effective in that there was a linear decrease in the overall Zung and HAM-D scores over the 42 day study period, but the differences in these scores were not statistially significant (p values were 0,9733 and 0,9662 respectively). Patients belonging to Group 3 (dosage of 150 mg b.d.) found the drug to be more effective, and there was more of a marked decline in the severity of the diseases compared to the two other groups. It is more effective (82 percent response) than the 100 mg t.d.s. dosage (54.5 percent response), and more effective than the 150 mg t.d.s. dosage (50 percent response). Whilst the total daily dosage is less than Group 2, (150 mg t.d.s.), the twice daily dosage schedule is more convenient and for this reason, one can expect better compliance compared to the three times a day dosage regimen (see table 9). This is confirmed by an analysis of the treatment response rates on the HAM-D scores (table 5), where there is a response rate of 70 percent in group 3, as compared to 54,5 percent in group 1 and 50 percent in group 2.

The incidence and types of adverse events reported by patients correspond to those reported in other studies (Chen et al., 1993). Insomnia and agitation were the most commonly reported adverse events (16.12 percent incidence). It is difficult to distinguish the secondary insomnia (a side effect of the medication) from the primary insomnia (one of the neurovegetative features of depression). No patients left the trial due to insomnia. Generally speaking, moclobemide administration leads to a decrease in insomnia (early, middle

and late) in all three dosage regimens. The incidence of early morning waking, tended to be lower than the incidence of both early and middle insomnias (see figure 17).

As is true for patients with major depressive disorders, a proportion of the trial patients had comorbid anxiety symptoms or anxiety disorders. This study confirmed previous reports by Angst et al. (1992) that moclobemide is an effective drug in treating the comorbid symptoms of anxiety and agitation in depressed patients. Figure 13 shows that there appeared to be a linear trends towards a decrease in the average anxiety/agitation over the study period in all three treatment groups. There was, however, a difference in the response rates between the three groups. patients on 150 mg twice a day had a 40 percent responses rate; as compared to patients on 100 mg and 150 three times a day whose response rates were in the 50 percent ranges. Could it be that the more frequent administration resulted in the patient feeling less anxious? Does more frequent dosing result in more of a placebo effect?

No successful suicides were reported on moclobemide alone; and large overdoses of the drug have been reported to have mild transient sequaelae (Hetzel, 1992). There was a parasuicide on this trial, where an unknown mixture of drugs were used without sequelae. Overall, there was a decrease in suicidal ideation over the 42 day period; and patients in Group 2 (150 mg b.d.) tended to score lowest on this item. Overall there was a reduction of 42,5 percent in suicidality over the treatment period (see figure 9).

Antidepressant therapy often results in fluctuations in weight. Consequently compliance is often a problem due to this side effect. This study has indicated, that moclobemide has no particular effect on weight, be it weight gain or weight loss. Moclobemide is, therefore, an important drug to consider in patients where weight fluctuations are not acceptable; as it enhances compliance.

This study has demonstrated that moclobemide in all three dosage schedules was extremely well tolerated; and was an effective drug to use in the treatment of major depressive disorders. There were, however, no statistically significant differences between the different dosage regimins.

Appendix I: Overall Study Plan

	Day 0	*Day 3*	*Day 7 (End Wk. 1)*	*Day 14 (End Wk. 2)*	*Day 21 (End Wk. 3)*	*Day 28 (End Wk. 4)*	*Day 42 (End Wk. 6)*
Patient Demography	X						
DSM III-R	X						
HDRS	X	X	X	X	X	X	X
Pregnancy Test	X						
Concomitant diseases, Medication	X						
Information/consent	X						
Confirm fulfillment of inclusion/exclusion criteria	X						
Random allocation	X						
HARS	X	X	X	X	X	X	X
ZUNG	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X
Sleep questionnaire	X			X		X	X
Vital signs	X	X	X	X	X	X	X
Baseline symptoms	X						
Laboratory tests	X						
Adverse events		X	X	X	X	X	X
Additional medications	X	X	X	X	X	X	X
Global assessments (at study end or premature withdrawal)							X

NB.

1. The investigator must check for any death occurring within four weeks of stopping medication.

2. All assessments prescribed for end of week 6 (Day 42) must be completed in the event of premature withdrawal of a patient from the study.

Appendix II: Diagnostic Criteria for a Major Depressive Episode (DSM III-R)

Major Depressive Episode

A. At lest five of the following symptoms have been present during the same two week period and represents a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations).

1. Depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated either by subjective account or observation by others

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others) or apathy most of the time

3. Significant weight loss or weight gain when not dieting (for example, more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day (in children, consider failure to make expected weight gains).

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B.

1. It cannot be established that an organic factor initiated and maintained the disturbance

2. The disturbance is not a normal reaction to the loss of a loved one (Uncomplicated Bereavement)

Note: Morbid preoccupation with worthlessness, suicidal ideation, marked function impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major Depression.

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e. before the mood symptoms developed or after they have remitted)

D Not superimposed or Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder.

Appendix III : 21-Item Hamilton Depression Rating Scale (HDRS)

1.	DEPRESSED MOOD	0.	Absent
		1.	These feeling states indicated only on questioning
		2.	These feeling states spontaneously reported verbally
		3.	Communicates feeling states non-verbally i.e. through facial expression, posture, voice and tendency to weep.
		4.	Patients report VIRTUALLY ONLY these feeling states in his spontaneous verbal and non verbal communication
2.	FEELINGS OF GUILT	0.	Absent
		1.	Self-reproach, feels he has let people down
		2.	Ideas of guilt or rumination over past errors or sinful deeds
		3.	Present illness is a punishment Delusions of guilt
		4.	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3.	SUICIDE	0.	Absent
		1.	Feels life is not worth living
		2.	Wishes he were dead or any thoughts of possible death to self
		3.	Suicide ideas or gesture
		4.	Attempts of suicide (any serious attempt rates)
4.	INSOMNIA EARLY	0.	No difficulty falling asleep
		1.	Complains of occasional difficulty falling asleep i.e. more than half an hour
		2.	Complains of nightly difficulty falling asleep
5.	INSOMNIA MIDDLE	0.	No difficulty
		1.	Patient complains of being restless and disturbed during the night
		2.	Waking during the night - any getting out of bed rates 2 (except for purposes of voiding).
6.	INSOMNIA LATE	0.	No difficulty
		1.	Waking in early hours of the morning but goes back to sleep
		2.	Unable to fall asleep again if he gets out of bed

7.	WORK AND ACTIVITIES	0.	No difficulty
		1.	Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
		2.	Loss of interest in activity, hobbies or work - either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
		3.	Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
		4.	Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted
8.	RETARDATION	0.	Normal speech and thought
		1.	Slight retardation at interview
		2.	Obvious retardation at interview
		3.	Interview difficult
		4.	Complete stupor
9.	AGITATION	0	None
		1.	Fidgetiness
		2.	"Playing with" hands, hair, etc.
		3.	Moving about, can't sit still
		4.	Hand wringing, nail biting, hair pulling biting of lips
10.	ANXIETY PSYCHIC	0.	No difficulty
		1.	Subjective tension and irritability
		2.	Worrying about minor matters
		3.	Apprehensive attitude in face or speech
		4.	Fears expressed without questioning
11.	ANXIETY SOMATIC	Physiological concomitants of anxiety, such as: gastrointestinal: dry mouth, wind, indigestion, diarrhoea, cramps, belching. Cardiovascular: palpitations, headaches. Respiratory: hyperventilation, sighing. Urinary: frequency. Sweating.	
		0.	Absent
		1.	Mild
		2.	Moderate
		3.	Severe
		4.	Incapacitation

12.	SOMATIC SYMPTOMS GASTROINTESTINAL	0.	None
		1.	Loss of appetite but eating without staff encouragement. Heavy feeling in abdomen.
		2.	Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for G.I. symptoms.
13.	SOMATIC SYMPTOMS GENERAL	0.	None
		1.	Heaviness in limbs, back or head, Backaches, headaches, muscle aches. Loss of energy and fatiguability
		2.	Any clear cut symptom rates
14.	GENITAL SYMPTOMS	Such as: loss of libido, menstrual disturbance.	
		0.	Absent
		1.	Mild
		2.	Severe
15.	HYPOCHONDRIASIS	0.	Not present
		1.	Self absorption (bodily)
		2.	Preoccupation with health
		3.	Frequent complaints, request for help, etc.
		4.	Hypochondrial delusions
16.	LOSS OF WEIGHT	(Rate either 'A' or 'B')	
		A.	WHEN RATING BY HISTORY:
		0.	No weight loss
		1.	Probable weight loss associated with present illness
		2.	Definite (according to patient) weight loss
		B.	ON WEEKLY RATINGS BY WARD PSYCHIATRIST WHEN ACTUAL WEIGHT CHANGES ARE MEASURED
		0.	Less than half kg weight loss in week
		1.	Greater than half kg weight loss in week
		2.	Greater than 1 kg weight loss in week
17.	INSIGHT	0.	Acknowledges being depressed and ill
		1.	Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
		2.	Denies being ill at all.

18.	DIURNAL VARIATIONS	a)	Note whether symptoms are worse in morning or evening, mark none if no variations.
		0.	None
		1.	Symptoms worse in the morning
		2.	Symptoms worse in the evening
		b)	If there are variations, please rate severity, mark none if no variations.
		0.	None
		1.	Mild
		2.	Severe
19.	DEPERSONALISATION & DEREALISATION	Such feelings of unreality, nihilistic ideas.	
		0.	Absent
		1.	Mild
		2.	Moderate
		3.	Severe
		4.	Incapacitating
20.	PARANOID SYMPTOMS	0.	None
		1.	Suspicious
		2.	Ideas of Reference
		3.	Delusions of reference and persecution
21.	OBSESSIONAL AND COMPULSIVE SYMPTOMS	0.	Absent
		1.	Mild
		2.	Severe

Appendix IV: Definition of Significant Organic Disease

For the purposes of this study severe uncontrolled organic disease is defined as a disease which by current medical standard constitutes an important threat to the life or the normal functioning of the individual. Examples of severe and uncontrolled diseases in this sense are: cancer, florid tuberculosis, decompensated congestive heart failure, severe hypertension (systolic BP above 180 mm/Hg; diastolic BP above 100 mm/Hg), epileptic seizures. Examples of diseases which do not constitute severe uncontrolled diseases are: benign tumours which may be surgically treated at any time; a history of tuberculosis which has been successfully treated; treated hypertension with blood pressure values below the above-mentioned limits; a history of epileptic seizures which have been managed successfully with antiepileptic drugs; slight known laboratory anomalies. It is understood that it is a purely clinical decision whether in an individual patient a disease is classified as severe and uncontrolled.

Appendix V: Appointment Card

PLEASE REMEMBER TO BRING YOUR EMPTY/UNUSED BLISTER PACKS WITH YOU TO YOUR NEXT APPOINTMENT

YOUR NEXT APPOINTMENT IS:
DATE TIME

Day 3
Week 1
Week 2
Week 3
Week 4
Week 6

PATIENT NOTE:

You are taking antidepressant therapy as part of a clinical trial. If you experience any problems concerning this treatment contact your Psychiatrist.

Very Important

1. If you need to see a doctor, other than your Psychiatrist, show him this card. If he requires further information this can be obtained from:

   Mrs H Klerck
   Roche Products (Pty) Limited
   Tel. No. (011) 974-5335.

2. If you cannot keep an appointment, contact your Psychiatrist as soon as possible.

Appendix VI: Zung Self-Rating Scale for Depression

Initials .....

Age ..... Sex ..... Date .....

Tick Appropriate Box

	None OR a little of the time	Some of the time	Good part of the time	Most OR all of the time
1. I feel down-hearted, blue and sad				
2. Morning is when I feel best				
3. I have crying spells or feel like it				
4. I have trouble sleeping through the night				
5. I eat as much as I used to				
6. I still enjoy sex				
7. I notice that I am losing weight				
8. I have trouble with constipation				
9. My heart beats faster than usual				
10. I get tired for no reason				
11. My mind is as clear as it used to be				
12. I find it easy to do the things I used to				
13. I am restless and can't keep still				
14. I feel hopeful about the future				
15. I am more irritable than usual				
16. I find it easy to make decisions				
17. I feel that I am useful and needed				
18. My life is pretty full				
19. I feel that others would be better off if I were dead				
20. I still enjoy the things I used to				

Appendix VII: Hamilton Anxiety Rating Scale (HARS)

For each item select the "cue" which best characterises the patient.

0 = Not present
1 = Mild
2 = Moderate
3 = Severe
4 = Very severe

1.	ANXIOUS MOOD	Worries, anticipation of the worst, fearful anticipation, irritability
2.	TENSION	Feelings of tension, fatiguability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax
3.	FEARS	Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.
4.	INSOMNIA	Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.
5.	INTELLECTUAL (cognitive)	Difficulty in concentration, poor memory.
6.	DEPRESSED MOOD	Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.
7.	SOMATIC (muscular)	Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.
8.	SOMATIC (sensory)	Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

			0 = Not present 1 = Mild 2 = Moderate 3 = Severe 4 = Very severe
9.	CARDIOVASCULAR	Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.	
10.	RESPIRATORY	Pressure or constriction in chest, choking feelings, sighing, dyspnea.	
11.	GASTROINTESTINAL SYMPTOMS	Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.	
12.	GENITOURINARY	Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.	
13.	AUTONOMIC SYMPTOMS	Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.	
14.	BEHAVIOUR AT INTERVIEW	Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos.	

Appendix VIII: Clinical Global Impression (CGI)

1. DEGREE OF GLOBAL PSYCHOPATHOLOGY
How ill is this patient now, compared to your experience with other depressed outpatients?

Circle:
1. Not ill
2. Very mild
3. Mild
4. Moderate
5. Moderate - Severe
6. Severe
7. Extremely Severe

---

2. HOW MUCH HAS PATIENT CHANGED SINCE STUDY ONSET?

Circle:

	a) In doctor's opinion	b) In patient's opinion
Very much better	1	1
Much better	2	2
A little better	3	3
No change	4	4
A little worse	5	5
Much worse	6	6
Very much worse	7	7

Appendix IX: Categories for Determining Relationship of Adverse Events to Test Drug

Unrelated
This category is applicable to those adverse events which, after careful medical consideration at the time of evaluation, are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under REMOTE, POSSIBLE or PROBABLE.

Remote (must be first two)
In general, this category is applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged to be remotely related to the test drug. An adverse event may be considered remote if, or when, for example:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It does not follow a known response pattern to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

Possible (must have first two)
This category applies to those adverse events in which, after careful medical consideration at the time they are evaluated, the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It follows a known response pattern to the suspected drug.

Probable (must have first three)
This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are considered, with a high

degree of certainty, to be related to the test drug. An adverse event may be considered probable if, for example:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug yet drug-relatedness clearly exists, for example (1) bone-marrow, (2) fixed drug eruptions, and (3) tardive dyskinesias.
4. It follows a known pattern of response to the suspected drug.

Appendix X: Patient Information Leaflet Moclobemide Study - RO IIS-109T

You have been asked whether you would like to take part in a clinical study to look at the effectiveness of a new drug, moclobemide, in relieving depression. The information given in this leaflet will be explained by your psychiatrist. You may keep the leaflet to refer to.

Although there are many antidepressant drugs already available, none are perfect. Moclobemide is currently being used in many countries overseas, and the evidence suggests that the unwanted side effects sometimes seen with other antidepressants are reduced with this new drug.

In this study we will be comparing moclobemide at different dosage levels and time intervals (treatment regimens). If you take part, you will be given one of these treatment regimens to take for 6 weeks. Neither the psychiatrist nor you will know which treatment regimen you are receiving (although it will be possible to find out should the need arise). You will receive regular health checks throughout the study. Your psychiatrist will ask to see you again after 3 days and then at the end of weeks 1, 2, 3, 4 and 6.

Moclobemide has undergone many tests to ensure that it is safe and approval to conduct this study has been given by an independent ethical committee. However, as is normally the case with new drugs, you should not take part in the study if:

- you are or may be pregnant
- there is any risk that you may become pregnant during the trial (if you use contraception, check with your psychiatrist that this will be adequate)
- you are a nursing mother

If you would like to take part in the study you will be asked to sign a written consent form and all information will be used in strict confidence. If, on the other hand, you decide not to take part, or if you decide to withdraw from the trial at any time, you will be offered another treatment and your care will not suffer in any way. Your psychiatrist will provide you with any further information that you need to make your choice.

If you have decided to take part then please read the following carefully:

* Take all the medicine as directed on the pack: ONE CAPSULE just after breakfast, ONE CAPSULE just after lunch, and ONE CAPSULE after your evening meal as specified by your doctor. Do not stop taking the medicine just because you start to feel better.

* Bring the medicine pack and any capsules that are left with you each time you visit your doctor.

* Keep the medicine pack in a cool, dry place and OUT OF REACH OF CHILDREN. Do not give your medicine to others.

* You are advised that the effects of alcohol may be potentiated during the treatment period. This is a standard precaution with most antidepressant medicine.

* It is all right to take paracetamol if you have a headache or a cold, but it is best to avoid codeine.

* Inform your doctor of any unusual symptoms that occur while you are taking the treatment. Some patients have previously noticed mild symptoms, such as dry mouth, headaches, constipation, dizziness, sleep disturbance and nausea.

PLEASE REMEMBER TO RING ALL YOUR TABLETS, CAPSULES OR MEDICINES EACH TIME YOU SEE THE DOCTOR.

Appendix XI: Patient Consent Form

I _____ (PRINT NAME) hereby consent to take part in this study.

I confirm that the purpose of the study and the effects of the drug have been explained to me and that I have received the Patient Information Leaflet.

I am aware that I will be required to visit the doctor after 3 days and then at the end of weeks 1, 2, 3, 4 and 6.

I understand that I may withdraw from the study at any time and that this will not prejudice my treatment in any way.

_____ _____

Patient's signature Date

_____ _____

Doctor's signature Date

Appendix XII: Declaration of Helsinki

THE WORLD MEDICAL ASSOCIATION, INC

28, AVENUE DES ALPES - 01210 FERNEY-VOLTAIRE-FRANCE

Telephone (50) 40 75 75

Cable address: WOMEDAS, Ferney-Voltaire

DECLARATION OF HELSINKI

Recommendations guiding physicians

in biomedical research involving human subjects

Adopted by the 18th world Medical Assembly,

Helsinki, Finland, June 1964,

amended by the 29th, World Medical Assembly,

Tokyo, Japan, October 1975

and

the 25th World Medical Assembly,

Venice, Italy, October 1983

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient". The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under reviews in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

1. Basic Principles

1.1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

1.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

1.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically

competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

1.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

1.5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

1.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

1.7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigations if the hazards are found to outweigh the potential benefits.

1.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

1.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

1.10 When obtaining informed consent for the research project, the physician should be particularly cautions if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigations and who is completely independent of this official relationship.

1.11 In case of legal incompetence, informed consent should be obtained form the legal guardian in accordance with national legislation. where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the

minor's consent must be obtained in addition to the consent of the minor's legal guardian.

1.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

2. Medical Research Combined with Professional Care (Clinical Research)

2.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

2.3 In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

2.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

2.5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1.2).

2.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

3. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

3.1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

3.2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3.3 The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

3.4 In research on man, the interests of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix XIII: Check List

BASELINE SYMPTOMS:
Ask the patient "Do you presently experience any of the following symptoms?"

ADVERSE EVENTS
Ask the patient "Has the treatment upset you in any way?"

	Y/N	Frequency 1. Rarely 2. Occasionally 3. Frequently	Severity 1. Mild 2. Moderate 2. Severe	Relation to treatment 1. Unrelated 2. Remote 3. Possible 4. Probable
HEADACHE	☐	☐	☐	☐
TREMOR	☐	☐	☐	☐
DRY MOUTH	☐	☐	☐	☐
DIZZINESS	☐	☐	☐	☐
SEDATION	☐	☐	☐	☐
AGITATION	☐	☐	☐	☐
NAUSEA	☐	☐	☐	☐
VOMITING	☐	☐	☐	☐
CHANGE OF BOWEL HABIT	☐	☐	☐	☐
SLEEP DISTURBANCES	☐	☐	☐	☐
VISUAL DISTURBANCES	☐	☐	☐	☐
SWEATING	☐	☐	☐	☐
PALPITATIONS	☐	☐	☐	☐
MICTURITION DIFFICULTY	☐	☐	☐	☐
OTHER (SPECIFY)	☐	☐	☐	☐

Appendix XIV: Sleep Questionnaire

Today's date: day.month.year ☐☐☐☐☐☐

Directions:

In the following you are asked how you slept in the past two weeks.
Please tick those answers that seem to be the most appropriate for you!
Move from one question to the next without interruption and do not omit any questions!
Please fill out immediately on waking up in the morning.

1.	Did you go to bed at a regular hour in the past two weeks?	never 1	sometimes 2 / very often 3
2.	At what time did you usually put the light out to go to sleep in the past two weeks?	hours	minutes
3.	On average how long did it take you to fall asleep in the past two weeks after putting out the light?	Less than 5 minutes 5 to 10 minutes 10 to 20 minutes 20 to 30 minutes 30 minutes to 1 hour More than 1 hour	1 2 3 4 5 6
4.	If you could not fall asleep immediately what do you think was the cause? (More than one answer possible)	* personal problems problems at work * noise in the room or outside * events of the day on my mind * I had to go to the toilet * my thoughts were going round and round * I was very tense * strange surroundings * others: _____	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
5.	Did you have a nap at any time during the past two weeks?	no at the weekends almost every day	1 2 3

6.	Did you experience, as you were falling asleep, any muscle twitching in your arms or legs in the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
7.	Have you experienced in the past two weeks a stabbing pain in your chest or an aching pain in your left arm during the night?	never seldom sometimes often very often 1 2 3 4 5
8.	Did you wake up during the night at time during the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
9.	If you woke up during the night, at any time, what do you think was the cause? (more than on answer possible)	personal problems/problems at work 1 noise in the room or outside 2 I had to go to the toilet 3 I had had a dream 4 I had not gone into a deep sleep 5 Others: _____ 6
10.	If you woke up during the night, at any time, did you have difficulties in going back to sleep?	never seldom sometimes often very often 1 2 3 4 5
11.	Over the past two weeks could you remember your dreams when you woke up?	never seldom sometimes often very often 1 2 3 4 5
12.	Were you aware of sweating during the night in the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
13.	Did you get up at a regular time in the mornings in the past two weeks?	never sometimes very often 1 2 3
14.	At what time on workdays did you usually get up in the past two weeks?	☐☐ hours ☐☐min
15.	In the past two weeks did you fall asleep immediately when you decided to go to sleep and switched out the light?	never seldom sometimes often very often 1 2 3 4 5

16.	Have you suffered from a headache in the morning during the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
17.	Do your night-time dreams come to mind during the day?	never seldom sometimes often very often 1 2 3 4 5
18.	Have you drunk alcohol beverages (beer, wine, spirits, etc.) after your evening meal in the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
19.	In the past two weeks have you woken too early in the morning, i.e. long before you have to get up?	never seldom sometimes often very often 1 2 3 4 5
20.	Have you smoked a lot recently, i.e. more than 5 cigarettes, 2 cigars, 2 pipes a day?	no, not at all 1 yes, on some days 2 yes, every day 3
21.	Have you taken sleeping pills recently?	never seldom sometimes often very often 1 2 3 4 5
22.	If yes, which drugs?	_____ _____
23.	Was work very exhausting for you in the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
24.	Where there any important changes recently in your personal life which put you under stress? (more than one answer possible)	no, none ☐ yes, in relation to my partner ☐ yes, job-related changes that had an effect on my personal life ☐ yes, within the family ☐ yes, in relation to my health ☐
25.	Did you need some time until you really got going in the mornings during the past two weeks?	never seldom sometimes often very often 1 2 3 4 5
26	Can you usually sleep well in strange surroundings	never sometimes very often 1 2 3

Directions: On this page you will find a few expressions to describe how you felt in the mornings and evenings recently and how you slept during the night. After every expression please tick the box which is most appropriate for you. Please move quickly from one to the next without omissions!

		never	seldom	sometimes	often	very often
27.	How was your sleep over the past two weeks?					
	deep	1	2	3	4	5
	fitful	1	2	3	4	5
	relaxed	1	2	3	4	5
	restless	1	2	3	4	5
	good	1	2	3	4	5
	untroubled	1	2	3	4	5
	long	1	2	3	4	5
28.	How did you feel before going to bed in the past two weeks?					
	drowsy	1	2	3	4	5
	exhausted	1	2	3	4	5
	in need of sleep	1	2	3	4	5
	composed	1	2	3	4	5
	calm	1	2	3	4	5
	tired	1	2	3	4	5
	relaxed	1	2	3	4	5
29.	How did you feel in the mornings in the past two weeks?					
	composed	1	2	3	4	5
	drowsy	1	2	3	4	5
	energetic	1	2	3	4	5
	rested	1	2	3	4	5
	ready to act	1	2	3	4	5
	relaxed	1	2	3	4	5
	clumsy	1	2	3	4	5

PLEASE CHECK WHETHER YOU HAVE ANSWERED ALL QUESTIONS!

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