RITANSERIN IN DEPRESSIVES: DYSTHYNIC TYPE AND ADJUSTMENT DISORDER WITH DEPRESSED MOOD (DEPRESSIVE NEUROSIS) - A DOUBLE BLIND PLACEBO CONTROLLED DOSE RANGE FINDING STUDY

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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.

Johannesburg, March 1991

DEDICATION

To my children, Rudolph and Monja, who showed understanding, far beyond their years, throughout my studies

DECLARATION

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

References which I have used, have been duly acknowledged.

SIGNED: H Bellew

25th day of March 1991

I DECLARE THAT THIS WORK HAS BEEN APPROVED BY THE COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS ON 31 OCTOBER 1988.
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ABSTRACT

In the first part of the dissertation a literature survey is done, looking at

1. An overview of dysthymic disorder.
2. An overview of serotonin and its involvement in psychiatric disorders.
3. An overview of Ritanserin, a potent centrally acting serotonin ($5HT_2$) antagonist.

In the second part the methodology and results of a dose range finding study are discussed. The aim of the study was to compare the clinical efficacy of 2,5 mg; 5 mg and 10 mg Ritanserin daily in a placebo controlled way, in patients suffering from dysthymic disorder or adjustment disorder with depression, to obtain information about the minimum effective dose of Ritanserin.

Although the results showed no statistically significant difference in the response in the different groups, there were certain factors that could have influenced this negative outcome.

PART I : OVERVIEW OF DYSTHYMIA

CHAPTER ONE

1. DEFINITION AND CRITERIA

1.1 Introduction

Dysthymia is a very common disorder and many people suffer from it, without knowing that it is a disorder. Even as far back as 1512, Michelangelo wrote to his father: "I lead a miserable existence.....I live wearied by stupendous labours and beset by a thousand anxieties. And thus I have lived for some fifteen years and never an hour's happiness have I had".

Dysthymia literally means ill humoured. The patients have a temperamental inclination to melancholy and they are gloomy, introverted, brooding, over conscientious, incapable of fun and pre-occupied with personal inadequacy (Kraepelin 1921, Akiskal 1983).

Dysthymia lies on the border between the normal and the pathological. Hamilton (1990) mentions that authors have different viewpoints on dysthymia, for instance:

a) a reaction to continuous stress,
b) a mild form of depressive illness,
c) a depressive variety of prodromal phases of depressive illness,
d) an incomplete recovery from acute illness,
e) a particular type of personality.

1.2 Definition

Defining dysthymia has been a major problem in studying it, since the terminology has been changed so often over the years. Goldberg and Bridges (1990) put it very well when they said: "Dysthymic disorder is a new plastic box for some rather old wine".

1.2.1 Depressive temperament

This term was in vogue at the beginning of the century, but Cassano *et al.* 1989 mentions the criteria in Table 1.

1.2.2 Neurotic depression

This term was used at the same time as depressive temperament in a time of great changes in the classification of depression before and after world war one. Kraepelin and Bleuer used these terms at a time when psychiatrists were moving away from asylums to general hospitals and community practices (Bronisch and Klerman 1988). The same authors mention **Matussek's criteria** for neurotic depression:

a) reactivity to the outside world;
b) normal sadness;
c) hypochondriasis;
d) open aggression;
e) insidious onset of depression;
f) long duration;
g) neurotic personality.

Table 1 Hyperthermic and depressive temperaments

Frequency (%) of traits observed in the two temperamental types	
Hyperthermic temperament	
Irratable, cheerful, overoptimistic, or exuberant	100
Warm, people seeking or extroverted	100
Overtalkative	94,5
Vigorous, full of plans, improvident, rushing off with restless impulse	90,9
Naive, overconfident, self-assured, boastful, bombastic, or grandiose	81,8
Overinvolved and meddlesome	50,9
Uninhibited, stimulus-seeking, or promiscuous	32,7
Depressive temperament	
Brooding and given to worry	96,1
Conscientious or self-disciplining	90,8
Quiet, passive and indecisive	84,2
Self-critical, self-reproaching and self-derogatory	82,9
Gloomy, pessimistic, humourless or incapable of fun	76,2
Pre-occupied with inadequcy, failure and negative events to the point of morbid enjoyment of one's failure	73,7
Sceptical hypercritical or complaining	69,7

The criteria for neurotic depression according to Zimmerman *et al.* (1987) are:

a) personality disturbance;
b) psychosocial stress;
c) onset before the age of forty
d) blaming others for their depression
e) non-serious suicide attempts
f) marital separation and/or divorce.

DSM II (American Psychiatric Association, 1968) and ICD 9 (World Health Organisation, 1978) still had neurotic depression as a category.

1.2.3 Hysteroid dysphoria

This concept was introduced by Liebowitz and Klein (1979) and they described a lifelong pattern of:

a) fluctuating reactive mood;
b) somatization;
c) fatigue
d) lack of typical vegatative features
e) more common in females;
f) hyposomnia and initial insomnia;
g) worsening at night
h) increased appetite

i) extreme sensitivity to rejection in interpersonal situations;

j) emotional responses that are intense, immediate and exaggerated.

1.2.4 Characterological depression

This term was coined by Akiskal *et al.* (1980) to describe chronic dysphoria without signs of melancholia. It usually has an insidious onset in childhood or adolescence. Often the trait (personality) and state (depression) are so interwoven, that it is difficult to separate life style from illness. It is however, important to be aware of the fact that it is not only a character problem, but that there is an affective component too, which responds to thymoleptic drugs (Akiskal *et al.* 1980, Klein *et al.* 1980).

1.2.5 Dysthymia

This term was first mentioned in DSM III (American Psychiatric Association, 1980) and in DSM IIIR (American Psychiatric Association, 1987) it was included as an affective disorder, rather than a personality disorder.

1.3 DSM IIIR Criteria for Dysthymia:

Table 2

Dysthymia has been subdivided by Klein *et al.* (1980) and Akiskal *et al.* (1980):

1.3.1 Subaffective dysthymia

The patients in this category have a predominantly affective presentation. They show anhedonia, guilt feelings, hypersomnia and psychomotor retardation. There are some subtle bipolar tendencies, for instance brief hypomanic switches on tricyclic antidepressant challenge.

The personality structure is that of the depressive temperament, as described in Table 1.

The patients usually have a positive family psychriatic history of unipolar and bipolar mood disorder.

There are shortened rapid eye movement (REM) latencies on electro-encephalogram - less than seventy minutes on consecutive nights.

The patients respond favourably to tricyclic antidepressants, Lithium, or both

Table 2 Diagnostic criteria for 300.40 Dysthymia

A. Depressed mood (or can be irritable mood in children and adolescents) for most of the day, more days than not, as indicated either by subjective account or observation by others, for at least two years (one year for children and adolescents)

B. Presence, while depressed, of at least two of the following:

(1) poor appetite or overeating
(2) insomnia or hypersomnia
(3) low energy or fatigue
(4) low self-esteem
(5) poor concentration or difficulty making decisions
(6) feelings of hopelessness

C. During a two-year period (one year for children and adolescents) of the disturbance, never without the symptoms in A for more than two months at a time.

D. No evidence of an unequivocal Major Depressive Episode during the first two years (one year for children and adolescents) of the disturbance

Note: There may have been a previous Major Depressive Episode, provided there was a full remission (no significant signs or symptoms for six months) before development of the Dysthermia. In addition, after these two years (one year in children or adolescents) of Dysthermia, there may be superimposed episodes of Major Depression, in which case both diagnoses are given.

E. Has never had a Manic Episode (p.217) or an unequivocal Hypomanic Episode (see p.217).

F. Not superimposed on a chronic psychotic disorder, such as Schizophrenia or Dalusional Disorder.

G. It cannot be established than an organic factor initiated and maintained the disturbance, e.g. prolonged administration of an antihypertensive medication.

Specify primary or secondary type:

Primary type: the mood disturbance is not related to a pre-existing, chronic, non-mood, Axis I or Axis III disorder, e.g., Anorexia Nervosa, Somatization Disorder, a Psychoactive Substance Dependence Disorder, an Anxiety Disorder, or rheumatoid arthritis.

Secondary type: the mood disturbance is apparently related to a pre-existing, chronic, non-mood Axis I or Axis III disorder.

Specify early onset or late onset:

Early onset: onset of the disturbance before 21
Late onset: onset of the disturbance at age 21 or later.

1.3.2 Character spectrum disorder

These patients formed two-thirds of the group. They lacked melancholic features and showed a lifelong characterological instability. The personality structure showed dependent, histrionic and antisocial traits with poly drug and alcohol abuse.

The family psychiatric history was positive for alcoholism and personality disorders, but not mood disorders.

The REM latencies were normal, which showed that it was not in the affective range. The patients had a poor response to tricyclic antidepressants, mono-amine oxidase inhibitors and Lithium.

This dysphoric condition develops in the context of an early unstable family environment and it may represent a variant of histrionic-antisocial personality. This condition overlaps with the depression spectrum disease as described by Winokur (1979).

CHAPTER TWO

2. DIAGNOSIS

2.1. Dysphoria

Dysphoria is one of the major symptoms of dysthymia. Patients may call it sadness, irritability or a combination of the two. In every day life people often feel dysphoric as a normal affective response to daily life events, but the feeling is usually brief and does not lead to functional impairment or help seeking behaviour (Rush 1990).

2.1.1 Differential diagnosis of dysphoria

a) Dysthymia;
b) cyclothymia;
c) adjustment disorder with depression
d) grief or bereavement
e) major mood disorders
f) anxiety disorders
g) medical disorders

Table 3 gives a list of medical disorders associated with depression (A.J. Rush 1990).

Table 3 Medical Disorders Associated with Depression

Autoimmune disorders Systemic lupus, rheumatoid disease, sarcoidosis
Cancers Head, pancreas, gastrointestinal, lung, renal
Central nervous system diseases Parkinson's disease, degenerative dementias, normal-pressure hydrocephalus, subarachnoid haemorrages, Huntington's disease, reversible dementias, focal lesions (non-dominant), stroke, head trauma, temporal lobe epilepsy (?)
Disabling/deforming disorders All types
Endocrinopathies/metabolic disorders Hypothyroidism, hyperthyroidism, Addison's disease, Cushing's disease, pituitary tumours, diabetes, hyperparathyroidism, hypoglycemia (?), porphyria
Intoxications Lead, mercury, thallium, others (?)
Occult infections Genitourinary tract, liver etc.
Viral infections Influenza, viral pneumonia, mononucleosis, hepatitis, others.

h) drugs causing dysphoria or depression - Table 4 from A.J. Rush (1990).

Table 4 Drugs Associated with Major Depression or Dysthymia

Anticancer Vincristine, vinblastine
Antihypertensives Reserpine, methyldopa, propranolol, guanethidine, hydralazine, clonidine.
Antiinfectives Cycloserine
Antiparkinson agents Levodopa, amantadine, carbidopa
Corticosteroids
Hormones Estrogens, progesterone
Psychotropics Benzodiazepines (?), antipsychotics (?)

2.2. Clinical Presentation

The clinical presentation many differ due to may factors: Men may deny all symptoms to keep up their "macho" image. Older people usually present with more somatic complaints than younger patients. Chronic pain is a very common symptom, especially headaches, abdominal pain and chest pain. Socio-economically disadvantaged people may have more problems with impulse control, aggressivity or trouble with the law. The consequences of the chronic depression may often be the presenting complaint, for instance marital problems, occupational conflicts, suicide attempts, substance abuse (Rush 1990).

The patients present with the history of longstanding chronic low grade depression, often saying that they had been born depressed or had been depressed as long as they could remember. They may present in demanding and narcissistic ways, flaunting their suffering, saying that they are the most miserable creatures on earth. Akiskal quotes Schneider's remark that these patients feel they belong to the "aristocracy of suffering" (Askiskal *et al.* 1980). The patients may be considered to be manipulative or malingering because there is a relative absence of objectively ascertainable depressive features and the symptoms outnumber the signs. The depression is also not sharply demarcated from the sufferer's normal self.

Patients with intellectual inclinations may harp on themes of the outsider, religion, alienation, absurdities in the human condition, or they may be brooding over the miseries of the world (existential depression) Nemiah (1975) called this "Weltschmerz".

Primary care physicians see many dysthymic patients and are impressed by their somatic complaints until they find no abnormalities and then they label them hypochondriacal. After exclusion of underlying or contributary medical disease and repeated drug trials, some patients will remain symptomatic for various degrees of time. However, they are not refractory to treatment, because they do usually show at least some response, like symptom attenuation and improved functioning (Askiskal 1985). If they really are refractory to treatment, the chronic depression might be associated with occult malignancies, endocrine abnormalities or neurological disease.

Repeated treatment failure in dysthymia, may frustrate the clinician and the diagnosis may be changed to that of a personality disorder (Price 1978). The clinician may also tell the patient "to pull himself together". Because of the symptoms of anxiety and insomnia the clinician may prescribe anxiolytics or sedative hypnotics, thereby increasing the risk of substance abuse and dependence. Askiskal (1983) quotes Weissman and Klerman (1977) and Lipsitt (1970).

2.3. Dysthymia versus Major Depression

There is controversy over whether dysthymia and major depression represent distinct psychopathological disorders or are different phases of a single condition (Keller and Sessa 1990). Some people also see dysthymia as being part of the bipolar spectrum (Akiskal *et al.* 1989) Table 5.

Table 5 The bipolar spectrum

Episodic Bipolar schizoaffective Bipolar I Bipolar II Bipolar III
Intermittent or persistent Chronic mania Continuous cycling Protracted mixed state Cyclothymic disorder Hyperthymic disorder Irritable temperament Subaffective dysthymia

The inclusion of dysthymia in this spectrum is based on the bipolar family history in a substantial number of patients and the fact that some dysthymic patients, when given tricylic antidepressants, switch to mania.

Chronicity occurs in fifteen per cent of mood disorders according to Akiskal (1983). Major depressions may last two or three years, but most depressions remit spontaneously or have an episodic course. That implies that inadequate treatment is not a primary course of chronicity (Angst *et al.* 1979). An unremitting course over decades or even a lifetime, is often seen (Price 1978).

2.4 Pure Dysthymia

It is difficult to find patients with "pure" dysthymia, who have never suffered from major depression at any time. Akiskal (1981) found that they were only ten per cent in his study.

The National Institute of Mental Health research branch programme on the psychobiology of depression (Keller and Sessa 1990) found that they were only able to recruit nine patients with pure dysthymia at five collaborating medical centres over a period of eighteen months. Keller and Lavori (1984) were also unsuccessful at other public and private out patient settings.

2.5. Double Depression

This term was coined by Keller *et al.* (1983). It is the co-existence of acute episodes of major depression superimposed on a background of dysthymia.

In the National Institute of Mental Health study mentioned above, twenty five per cent of three hundred and sixteen patients with major depression had pre-existing chronic minor depression of at least two year's duration (Keller *et al.* 1983).

In the Epidemiologic Catchment Area (ECA) programme (Weissman *et al.* 1988) thirty nine per cent of patients with the diagnosis of dysthymia also met the critera for major depression.

Akiskal *et al.* (1978) suggested that minor depressions often form the substrate from which major mood disorders arise. They mention that in ninety per cent of dysthymics the course may be complicated by major mood disorders (Keller and Sessa 1990).

Keller and Shapiro (1982) say that the two year recovery rate from major depression in double depression is ninety seven per cent, whereas for major depression alone, it is seventy nine per cent. This suggests that it is easier to return to a state of chronic low grade depression than to a state of no depression.

Keller *et al.* (1983) mention that the longer a patient remains ill with underlying dysthymia after recovering from major depression, the greater is the chance of a relapse into a major depression.

2.6. Dysthymia as Residual Syndrome of Major Depression

Strictly speaking, according to the DSM IIIR criteria for dysthymia, the diagnosis of dysthymia can not be made if the patient suffered from an unequivocal major depressive episode during the first two years of the disturbance.

In practice, however, some patients may have residual dysphoric symptoms for months to years after a major depression (Cassano *et al.* 1983) and they may show "characterological" manifestations, like

a) a sense of resignation;

b) inhibited communication;

c) rigidity;

d) irritability;

e) emotional lability;

f) overdedication to work;

g) inability to enjoy leisure activities (De Lisio *et al.* 1986);

h) marital conflict in deadlock, where patients are unable to divorce to reconcile (Akiskal *et al.* 1981);

i) somatic manifestations involving vegetative or autonomic nervous system problems;

j) insomnia.

Insomnia associated with shortened REM latency, is a sign that the chronic phase is a genuine affective process (Akiskal 1982). The insomnia is often one of he main residual symptoms of chronic depression and it often does not respond to antidepressants. The insomnia may actually have been caused by the antidepressant's suppressant effect on REM sleep (Akiskal 1985).

Other post depressive symptoms that are often resistant to pharmacological interventions, are attitudes of passivity, dependence, resignation and pessimism. Because of this, patients develop serious interpersonal complications and personal handicaps. These problems often cause realistic unhappiness that complicates

the condition through demoralization (Klein 1974). Psychotherapy is important here to help with coping skills and to help the patients to choose environments and jobs best suited for their temperaments.

There are many factors that prevent recovery from primary major depression. Table 6 is taken from a paper by Akiskal (1985) and shows clearly the multifactorial origin for chronicity in depression.

2.7 Comorbidity

According to Bromisch *et al.* (1985) and Akiskal *et al.* (1978) the most frequent diagnoses that co-exist with dysthymia are: Panic disorder, anxiety, phobias, Briquet's syndrome, alcoholism and obsessive compulsive disorder.

Akiskal (1981) also claims that fifty per cent of so called "borderline" patients suffer from lifelong affective disorders.

Table 6 Comparison of chronic and episodic primary depressions on selected variables

	Chronic depression (N = 38)	Episodic depressions (N = 40)	P*
Demographic factors			
Mean age	50,8	47	ns
Female sex	76%	80%	ns
Proximate Stressors **			
Multiple deaths in family	21%	3%	.033
Disabled family member	21%	3%	.033
Superimposed medical illness	47%	10%	.001
Use of depressant antihypertensives	21%	3%	.033
Secondary sedativism	34%	17%	.043
Developmental Predisposition			
Loss of parents before age 15	21%	18%	ns
Family History			
Unipolar	42%	20%	<.05
Bipolar	5%	3%	ns
Psychiatric illness in both parents	16%	13%	ns
Personality			
„Unstable„ (histrionic-sociopathic traits)	21%	15%	ns
Depressive (Schneiderian criteria)	44%	28%	ns

2.8 Association with Anxiety

There is a great overlap between depression and anxiety and many people question the validity of separating them into different categories (Tyrer 1985).

When patients with mild psychiatric disorders present to general practioners, answer health questionnaires or are part of a random sample, one often sees mixtures of depressive and anxiety symptoms. Selvewright and Tyrer (1990) quote a study by Goldberg and Huxley (1980) where general practioners found that of eighty

eight patients, eighty two complained of anxiety and worry and seventy one complained of despondency and sadness. The complaints normally occurred together.

Kendell (1974) found that of patients with an initial diagnosis of "reactive depression" the diagnosis will be changed to that of an anxiety disorder in sixty per cent after five years.

Sashidharan *et al.* (1985) found that in a random sample of women with psychiatric disorders, the commonest symptoms could qualify for both a depressive disorder and a generalised anxiety disorder. There was a lack of specificity and many patients' diagnoses were changed over an eighteen month period.

Tyrer *et al.* (1988) did a study where they compared the characteristics of dysthymia, generalised anxiety disorder and panic disorder. They found that most of the demographic data were similar in the three groups. When looking at precipitating life events, significantly more patients with panic disorder had had no events, as compared to the other groups. The other differences were in the duration of the illness. The duration was the longest in dysthymia. This is of course built into the diagnostic criteria. Dysthymia has to have been present for more than two years, generalised anxiety disorder for six months and panic disorder for three weeks.

In another study quoted by Seivewright and Tyrer (1990) it is mentioned that ninety one per cent of patients with agoraphobia also met the criteria for a primary mood disorder.

Anxiety and depression normally cluster together in families. In a study by Leckmann *et al.* (1983) it was found that the rates of DSM III major depression and anxiety disorders or a combination of both, were all higher than would be expected in relatives of probands with combined depression and anxiety disorders.

CHAPTER THREE

3. OUTCOME OF DYSTHYMIA

3.1 Natural Course

This is often difficult to ascertain, because most data come from people who have looked for help, but many dysthymic patients never seek treatment. They may also be treated in non-medical or non-psychiatric settings, for instance by psychologists, church counsellors or social workers. They are often not treated with the appropriate medication when they seek help from general practioners.

Keller and Sessa (1990) mention studies by Gonzales *et al.* (1985) where the recovery rate for dysthymia was fourty three per cent and self report studies by Barrett (1984) where a thirty seven per cent rate of improvement was measured. The one year relapse rate is thirty three per cent according to Gonzales *et al.* (1985).

Rounsaville *et al.* (1980) and Keller *et al.* (1982) found that the average duration of chronic depression was 5.5 years (range two to twenty years).

Of patients with a major depression, ten to twenty per cent will have a chronic course (Murphy 1974). In the National Institute for Mental Health study, nineteen per cent remained chronically depressed for two years and ten per cent for five years. There was no association between outcome and the age of onset of dysthymia.

Akiskal (1978) did a follow up study in "neurotic depression" and found that after three or four years, the diagnoses had been changed to bipolar II in eighteen per cent, and unipolar depression in twenty two per cent. This was confirmed by Stone (1978) and Rihmer (1990).

In a seven year study of dysthymic patients, Bronisch *et al.* (1985) found that:

twelve per cent had committed suicide

forty four per cent had developed a major depression

four per cent had been diagnosed as bipolar mood disorder.

In a prospective study by Tyrer *et al.* (1988), they followed the course of dysthymia over a twelve month period. The results are as follows:

After four months:

Twenty six per cent still had dysthymia

Twenty one per cent improved and had no disorder

Fifty per cent had a new diagnosis - mostly major depression, panic disorder, generalised anxiety disorder, agoraphobia and social phobia.

After eight months:

Thirty three per cent had no disorder

Twenty two per cent still dysthymic

Twenty two per cent had major depression

Twenty two per cent had anxiety disorders

After twelve months:

Thirty nine per cent had improved

Forty per cent still had dysthymia

Fifty seven per cent had diagnoses of major depression or anxiety disorder.

3.2. Social Adjustment

Follow up studies quoted by Bromisch and Klerman (1988) show that dysthymic patients tend to relapse frequently and that they have at least moderate impairment in psychosocial functioning. Even when they become relatively asymptomatic, they are still at least as impaired in social and leisure activities as paitents with mild to moderate symptoms. The areas that are being looked at in the literature, are interpersonal difficulties (Cassano *et al.* 1990), marital problems (Merikangas *et al.* 1985) and work and leisure activities (De Lisio *et al.* 1986).

The patients pass through different phases:

3.2.1 At onset of depression

There is an alteration in work affect, which means the degree of liking and interest for one's job. Impaired leisure activity is also present at the onset. (De Lisio *et al.* 1986). At this stage the patient might still be functioning well at work, even though there is a change in the work affect.

3.2.2 During dysthymia/depression

There is a signifiant maladjustment in all spheres. The patients feel uneasy at work and they may have disagreements with co-workers. They feel inadequate and have personal anguish. They have difficulty maintaining stable relationships, there are problems with intimate relationships and sexuality and they often have marital problems. There is a reduced capacity to use and enjoy leisure time and to manage financial matters. Functions that depend on traditional roles in the family or at work, for instance, parenting and self care, may remain relatively intact (De Lisio *et al.* 1986).

Social adjustment problems seem to be specific for depressive illness, especially in areas that require effort, motivation and anticipation of pleasure. These functions remain relatively intact in patients with anxiety disorders.

3.2.3 During recovery/follow up

The remission of the depression is associated with better social adjustment in work skills and relationships, as well as feeling of personal well being. Unfortunately this is not associated with a significantly greater improvement in social or leisure activities. The incapacity to enjoy leisure time specifically, is the most refractory area and may represent a trait marker during the dysthymic patient's lifetime (Cassano *et al.* 1990).

These residual symptoms may jeopardize the patient's re-integration into the environment (Murphy *et al.* 1974) and may even cause long term changes in the patient's personality (De Lisio *et al.* 1986).

Because most dysthymic patients are treated in out patient settings, one should do a careful evaluation of the psychosocial situation at home, to see patients in their daily lives, to identify the problems caused by the illness and to select the appropriate treatment.

Weissman *et al.* (1979) found that pharmacological treatment was effective in controlling the depression and preventing relapse. It was also effective in improving adjustment at work, but it was not effective in controlling maladjustment socially and in leisure activities.

Interpersonal psychotherapy is indicated to alleviate this problem, to help patients to re-adjust into various social roles, and domestic and interpersonal dynamics (Perugi *et al.* 1988).

Some authors (Goldberg and Bridges 1990) feel that no pharmacotherapy is indicated, but that patients simply need social help, relaxation therapy, exercise to restore sleep and reduced intake of alcohol, tobacco and drugs. They feel that it is especially important to have a social worker attached to the unit. This is confirmed by Cooper (1975) and Shepherd *et al.* (1979), although Corney (1981) feels that social worker intervention is only effective in double depression.

3.3 Outcome of Dysthymia in Old Age

Katona and Bell (1990) mention a one to fifty two year follow up study by Ciompi in Lausanne. He found that depressive symptoms became gradually less severe with increasing age. But even then the patients still had residual symptoms of general dissatisfaction, despair, mistrust, demanding behaviour, hypochondriasis, anxiety, reduced vitality, motivation and social contacts.

They found that the patients who did well, normally had good health, could still continue working and were living outside institutions.

Their life expectancy was however lower than that of controls - a 5,1 per cent reduction in males and a 7,6 per cent reduction in females.

The suicide rate was seven to eight times higher than that of the general population.

In a hospital study, Blessed and Wilson (1982) found that the dysthymic patients had considerable persisting mobidity. Most of them could not be discharged from hospital or they had to be re-admitted within two years.

CHAPTER FOUR

4. EPIDEMIOLOGY OF DYSTHYMIA

Much more is known about the epidemiology of major mood disorders, than of dysthymia. There is very little to be found in the world literature about the epidemiology of dysthymia.

4.1 Prevalence

The prevalence rates for dysthymia are quite high. The 1975 New Haven Survey (Weissman and Myers 1978) found the prevalence rate to be 4,5 per cent. Keller and Sessa (1990) quote the Epidemiologic Catchment Area programme where a life time prevalence rate for dysthymia was found to be 3,1 per cent and that for major depression 4,4 per cent. Von Korff *et al.* (1987) found a 3,7 per cent prevalence rate in Baltimore and Newman *et al.* (1989) found a 4,5 per cent rate in Alberta.

In primary care centres and in the community "prolonged disorders" with longstanding symptoms of both anxiety and depression are very commonly found (Goldberg and Bridges 1990). Regier *et al.* (1985) found that this type of disorder accounted for five out of six morbidity figures in a primary care setting in Wisconsin.

4.2. Other Epidemiological Issues

Murphy and Checkley (1990) studied dysthymia at the Emergency Clinic at the Maudsley Hospital and found some interesting data. However Akiskal (1990) warns that one should be careful when studying patients in an emergency clinic, since dysthymics are more readily seen in private practice.

Table 7 is taken from the study by Murphy and Checkley (1990) and gives a comparison of epidemiological issues in patiens with dysthymia and major mood disorders

From Table 7, it is clear that dysthymics had higher Hamilton anxiety rating scale scores than major depressives, they had an earlier onset of illness and an earlier onset of presentation. They had a greater number of previous overdoses and in childhood there was more separation from either parent before the age of fifteen years, especially through divorce. These patients also had a smaller number of legitimate children than major depressives. They found that if one took the criteria age of onset, Hamilton anxiety rating scale scores and the number of separations before the age of fifteen years, one could identify ninety six per cent of dysthymics.

The above study did not go into sex differences in detail. In collaborative research done between the Universities of Pisa and Tennessee, it was found that women were more likely to develop dysthymia (depressive temperament). Men were more likely to develop hyperthymic temperaments (Akiskal 1989). See also Table 1.

Table 7 Comparison of patients with dysthymia with those with major affective moods

	Dysthymia (n = 24)	Major affective episode (n = 20)	Statistical significance
Mean age at interview: years ± s.d.	31,4 (± 10,3)	39,9 (± 13,1)	t-test P<0,01
Mean age at onset : years ± s.d.	17,4 (± 7,2)	36,4 (± 12,9)	t-test P<0,001
% female	25%	50%	P = 0,12
Mean Hamilton depression score (± s.d.)	15,2 (± 4,8)	17,3 (± 4,3)	
Mean Hamilton anxiety score (± s.d.)	14,1 (± 7,0)	8,8 (± 4,8)	t-test P = 0,006
Past affective illness[1]	85%	45%	Fisher's P = 0,004
Past overdoses	37%	5%	Fisher's P = 0,01
Past admissions to psychiatric hospital	24%	10%	NS
DSM-III criteria for personality disorder	33%	25%	NS
Mean no. of legitimate children	0,39 (± 0,78)	1,15 (± 1,57)	NS
Parents separated by divorce	54%	5%	P<0,001
No. of experiences of separation before age 15:			
0	33%	85%	x^2 = 12,6
1	46%	15%	d.f = 2
3	21%	0%	P = 0,002
Family history of			
alcoholism only	20%	5%	NS
affective disorder only	12%	50%	Fisher's P = 0,009
affective disorder and alcoholism*	24%	15%	NS
affective disorder and other	12%	0%	NS

* Fisher's exact test (2-tail) for presence alcoholism alone or in combination with other psychiatric disorder, P = 0,11

1. DSM-III criteria

Other interesting findings in the literature are that many dysthymics are professional people (physicians and lawyers) (Akiskal 1990) and that there was a significant variation in both dysthymia and major depression in spring and autumn (Eastwood and Stiasny 1978).

4.3. Epidemiology of Dysthymia in Old Age

4.3.1 Introduction

According to Katona and Bell (1990) dysphoria in the elderly is very common and can be very disabling. There are however, many factors that make it difficult to study the condition in the elderly:

(a) Hospital and old aged home samples are highly selected and unrepresentative, whereas community based studies are the best, but they are not always practical.

(b) When choosing instruments to detect dysphoria, one must keep in mind that elderly people might have difficulty reading, understanding or responding to questionnaires.

(c) The clinical presentation is often very different from that of dysphoria in younger people. They display more somatic symptoms and sleep disturbances, rather than dysphoria. Copeland *et al.* (1986) included a separate somatic symptom rating scale into his diagnostic schedule for this purpose.

(d) One must be careful to make the distinction between depression or dysphoria and dementia, not only to be able to treat them correctly, but also to prevent demented patients from contaminating one's depressive sample (Katona and Aldridge 1985, Bulbena and Berrios 1986).

(e) Defining dysphoria in the elderly may also be a problem. Gillis and Zabow (1982) did a study where they used the following criteria for dysphoria: A score of less than fifteen on the Life Satisfaction Index of Neugarten and a score of less than fifteen on the Hamilton Depression Rating Scale. They noted that this group resembled Akiskal's character spectrum dysthymia (Akiskal 1983).

4.3.2 Prevalence of dysthymia in old age

This differs depending on which group is studied and what method is used (Katona and Bell 1990).

(a) Rating scale studies

The prevalence ranges between seven per cent and thirteen point seven per cent (Kivela *et al.* 1986, Morgan *et al.* 1987, Ben-Arie *et al.* 1987). Rating scale studies often show high scores in the elderly because of fatigue, poor sleep and increased physical illness associated with ageing.

(b) Diagnosis system studies

The prevalence seems to change from country to country, as seen in Table 8.

Table 8

Study	Country/ city	Prevalence
Blazer & Williams (1980)	North Carolina	14,7%
Kay *et al.* (1985)	Tasmania	14,2%
Copeland *et al.* (1987)	New York	16,2%
	London	19,5% depression
		5,3% dysthymia
Hasegawa (1985)	Japan	1-2%

(c) Old Aged Homes

Gillis and Zabow (1982) found that in elderly people living in old aged homes in Cape Town, 16,6 per cent had dysthymia and ten per cent had at least moderate depression.

Copeland *et al.* (1986) studied inhabitants of old aged homes in Camden, London, and found that thirty eight per cent had significant depressive symptoms.

(d) General practioners attenders

MacDonald (1986) found that 30,6% of his elderly attenders suffered from depression.

4.3.3 Sex

Although it is quite clear that major depression is commoner in elderly females than males, it is less clear in dysthymia.

Two studies found a higher incidence in females in a ratio of two to one (Kay *et al.* 1964, Bergman 1971) but Myers *et al.* (1984) found a non-significant higher prevalence in females and Blazer and Williams (1980) found no significant difference.

4.3.4 Age

Blazer and Williams (1980) found that dysthymia was more frequent in the sixty five to seventy four age group and Kay *et al.* (1985) found that the prevalence was even higher after eighty years.

4.3.5 Marital status

Blazer and Williams (1980) found that dysthymia was non-significantly commoner in the widowed, the separated and the divorced.

4.3.6 Social factors

Elderly dysthymic patients show marked present social isolation and also reduced rates of social contact in the past (Gillis and Zabow 1982). There is also a tendency for dysthymics to be poorer than controls (Blazer and Williams 1980). The relationship between recent loss and dysthymia is not as clear as it is with major depression.

4.3.7 Physical health

It is well known that elderly dysthymic patients often somatize as part of their dysthymic syndrome, but Gillis and Zabow (1982) showed that there was an actual increase in current physical illness and handicaps in dysphoric patients of twenty eight per cent, compared to a ten per cent increase in controls.

Many of the medications the elderly patients are using for their medical problems, may also cause or worsen thier dysphoria.

CHAPTER FIVE

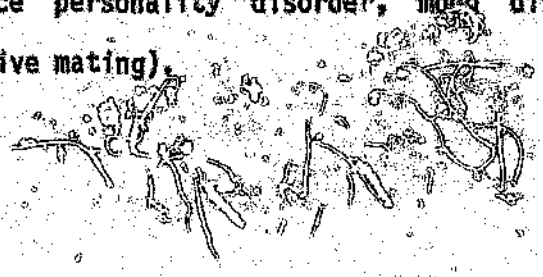
5. AETIOLOGY

5.1 Early Childhood Experiences

Disturbed child rearing is often found in patients who later develop dysthymia (Parker *et al.* 1987). Loss of significant objects in childhood or adolescence may predispose children to develop dysthymia (Birtchnell 1970) and in fact any life events with a significant individual impact, may have the same effect (Paykel *et al.* 1969).

Perris (1966) found that unipolar depressives who had had major losses in childhood, developed their illness ten years earlier than other depressives. There is also a tendency to have a higher incidence of suicide attempts with this kind of background history.

Children that grow up in a family where one parent has a primary mood disorder, have two disadvantages. There is an increased genetic vulnerability, but there are also issues like separation through parental illness, suicide, divorce and exposure to a bad marriage. The other parent may also have a psychiatric problem for instance personality disorder, mood disorder or alcoholism (assortative mating).



But all the studies don't agree. Akiskal (1978) found that early losses were more associated with unstable characterological traits, like immaturity, hostile dependency, manipulation, impulsivity and substance abuse, rather than mood disorders. All these traits may make the patients more vulnerable to marital discord and other stressors. The clinical expression may also be influenced and modified and the coping skills may be impaired because of these unstable traits.

Lloyd (1980) found that a history of childhood loss was absent in two-thirds of adult depressives, an argument against a clear association between the two.

5.2 Personality

5.2.1 Theories

The relationship between personality and dysthymia is a very confusing one. According to Hirschfeld (1990) there are four theories:

(a) Personalty predisposes to dysthymia

This means that the personaltiy features precede the onset of dysthymia. These pre-existing longstanding personality patterns are usually maladaptive with high neuroticism scores (Garside *et al*, 1970, Charney *et al*, 1984). Because of introversion, lack of social skills and dependency (Hirschfeld *et al*, 1983),

these patients may contribute to the life siuations that bring about their chronic depression. Because their self esteem depends or approval, attention, reassurance and love from others, they easily become depressed when there is a lack of these factors.

This is also in line with the cognitive behavioural therapy theory of Beck, where the basic cognitive schema developed in early life, predispose one to depression later.

Another very interesting finding in the personalities of patients who develop dysthymia, especially the subaffective dysthymic subgroup, is that they frequently display polyglottism. That is the good ability to learn foreign languages by internal rather than external motivation (Rihmer 1982). Polyglottism is also associated with cyclothymic patients and patients with bipolar mood disorders.

(b) The same genetic spectrum

This theory states that personality features and dysthymia may not have the same aetiology, but are associated with each other because of their joint heritability due to some third factor. This is a difficult field to study.

Klein *et al.* (1988) found that early onset dysthymia may be genetically related to major depression. But Torgersen (1984) did not find increased concordance for dysthymia in identical twins in Norway. However, in twins who are discordant for bipolar illness, the "unaffected" twin often shows cyclothymic or dysthymic tendencies (Bertlesen *et al.* 1977).

According to Akiskal *et al.* (1977) and Akiskal (1983), dysthymia may be a precursor of a more serious mood disorder. In this temperamental structure, the genetic potential for mood disorder is subclinically active at all times and can easily be triggered into clinical illness by environmental characteristics (Akiskal *et al.* 1983). This means that they may lie on the same genetic spectrum.

(c) Dysthymia is a personality disorder

In this case the personality features are part of dysthymia itself and are indistinghuishable from it. In the past many authors spoke of dysthymics as having a depressive character. If dysthymia is a personality disorder, the research that is done on the efficacy of thymoleptic drugs in dysthymia, may lead to very interesting possibilities in the pharmacological treatment of personality disorders.

(d) The complication theory

In this theory it is hypothesized that one's personality features are changed by dysthymia. One can understand that living for more than two years (and often for a whole life time) with low self esteem, low energy, general pessimism, insomnia and being miserable may change one's general outlook and influence the personality structure adversely.

5.2.2 Personality structure in dysthymia

Hirschfeld (1990) mentions a prospective collaborative National Institute for Mental Health study where nine hundred and fifty five patients and two thousand two hundred and eighty four first degree relatives were tested. The results showed that dysthymics had extremely abnormal personalities. They had low levels of emotional strength, they broke down under stress, they were moody, fearful, shy, introverted and they avoided social interactions. The personalities of dysthymics were significantly more disturbed than those of patients with major depression.

Roy *et al.* (1985) found that of eleven dysthymic patients, nine had associated personality disorders: four with borderline, two with schizoid, one with histrionic, one with compulsive and one with dependent personality disorder.

5.2.3 Personality, dysthymia and the elderly

Blazer and Williams (1980) found that there was an increased incidence of alcohol and analgesic abuse and a perceived need for "treatment for nerves" in elderly dysthymic patients. They also had a decreased life satisfaction with periodic grief due to physical, social and economic difficulties encountered by ageing people in the community

Gillis and Zabow (1982) found that elderly dysthymics had life-long manifestations of undue dependency, poor coping skills and inadequacy in interpersonal relationships. These patients became, as the authors put it "increasingly like themselves".

5.3 Stressors

It is generally believed that stressors can aggrevate chronic depression. Akiskal (1985) however, feels that stressors often result from depressive prodromata (Lloyd 1980). Dysphoric mood and associated vegetative and psychomotor disturbances, as well as passive aggressive behaviours may alienate significant others and cause difficulties at work or school. This may lead to lack of social support.

Environmental circumstances may play a part in the precipitation of the initial episode and maybe the timing of subsequent depressions. These include psychosocial, biological and seasonal factors (Akiskal 1986) (Cassano *et al.* 1990).

All mood disorders are likely to be associated with cognitive change. Therefore patients are likely to selectively recall one or two negative events, trying to explain their dysphoria. The events may not even have been experienced as negative at the time, but are now seen as such in a person with a negative outlook because of the dysphoria (Rush 1990).

5.4 Heredofamilial Factors

Akiskal (1989) starts his article with a Memphis Slim song:

"My mama had them
Her mama had them
Now I've got them too.

I've got something
Something you just don't learn in school
You'll never find them in no books
You just got to inherit the blues.

When I'm sad and lonely
Even when I am happy too
All of a sudden
I find myself singing the blues
That's why I know I was born with them."

Akiskal mentions that Slim was talking metaphorically not just about the blues as a clinical entity, but about the blues as a frame of mind, a form of music and blues as a talent. He also mentions that the poet had remarkable insight into depression in the nineteen sixties when many psychiatrists did not even believe in the familial-hereditary factors in mood disorders.

Family risk is not synonymous with genetic risk. Patients who have a first degree biological relative with a mood disorder are at increased risk of developing depression. If a person has one affected parent (single mating), the risk is tripled and if both parents are affected (dual mating), the risk is at least tenfold (Gershon *et al.* 1982).

Heredity may play a major role in the pathogenesis of mood disorder, but familial factors seem to modify the actual clinical expression of the disorder (Akiskal 1986).

5.5 Genetics

In their review article Bronisch and Klerman (1988) quote Shapiro (1970), who found that in "non-endogenous depression" the monozygotic:dizygotic ratio was four to nil.

But Torgersen (1983) found no higher concordance of "neurotic depression" in monozygotic twins compared to dizygotic twins. The sample sizes were small, but it does look as if hereditary factors are not as important in dysthymia as in the other mood disorders.

Berglesen *et al.* (1977) found that, where monozygotic twins were discordant for bipolar mood disorder, the unaffected twin often showed cyclothymic or dysthymic tendencies.

Akiskal (1989) mentions that the genetic potential to develop affective episodes might be transmitted as subclinical temperamental dysregulation This may be in the form of dysthymia, hyperthymia or cyclothymia. These in turn might interact with other risk factors to bring about major mood disorders. It is interesting to note that one finds shortened REM latencies in dysthymic and hypomanic temperaments. This sleep neuro-physiological abnormality behaves like a trait marker of vulnerability and is not merely a non-specific stress reaction or a correlate of anxiety (Akiskal *et al.* 1984).

5.6 Biological

In the past, most of the work on dysthymia was done on a psychological level, but recent researchers have focused more on biological aetiologies. The areas that are being looked at that reflect the biological involvement, are:

(a) EEG changes
(b) Receptor binding studies
(c) Anatomic localization studies
(d) Neuro endocrine studies
(e) Serum tryptophan
(f) Cerobrospinal fluid and ventricular concentrations of five-hydroxy-indole-acetic acid (5HIAA)
(g) Blood platelet studies.

5.7 Conclusion

The predisposition to mood disorders is probably developed in childhood and life events and biological issues in adulthood may serve as triggering factors. The predisposing roles of heredity and early life experiences are mediated through personality variables which create the circumstances that precipitate episodes of mood disorders in adult life (Akiskal 1986).

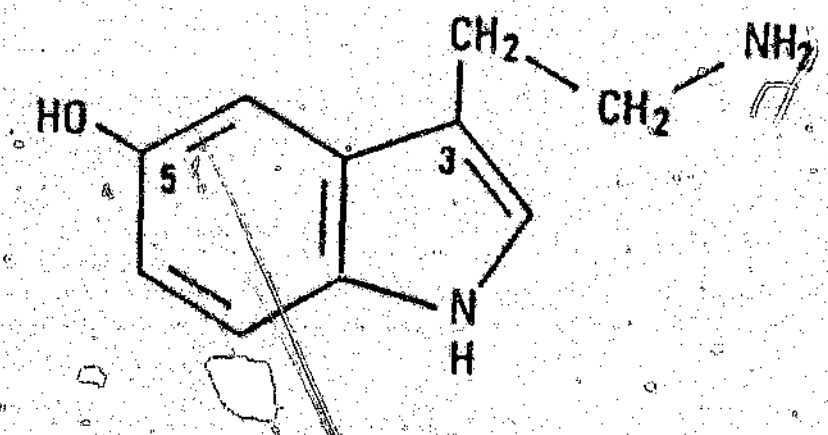
PART II : OVERVIEW OF SEROTONIN

CHAPTER SIX

6. SEROTONIN

6.1 Chemical Structure

Serotonin (5-hydroxytryptamine) (5HT) is one of the indoleamines having the following chemical structure (Figure 1)



6.2 Anatomic Localization

Serotonergic neurons project to many areas of the brain which play a major role in the modulation of behaviour, so on an anatomical base, it makes serotonin a good candidate to be involved in depressive psychopathology.

Serotonin was first detected in the brain with bio-essay techniques in 1954, by its vasoconstrictive effects. This was not a very sensitive technique, and by 1957 it was detected using spectrophotofluorometry. However, the big breakthrough

came in 1962, when Swedish researchers developed a histochemical method to visualise the biogenic amines. Molliver (1987) explained the technique: Freeze dried brain tissue was exposed to humid formaldehyde vapour, which reacted with the biogenic amines, converting them to fluorescent derivatives (beta carbolines) which emit yellow fluoresence when stimulated by ultraviolet light. This made the molecules visible under the light microscope and one could now localize serotonin neuronal cell bodies and axonal processes.

The serotonin cell bodies were restricted to the midline of the brainstem, mostly within the raphé nuclei. In 1964 nine groups of serotonergic cell bodies were described, but since then it has been clear that there are many other projections to other parts of the brain.

With newer anatomic methods, looking at the anterograde axonal transport of tritiated amono acids, it was found that tritiated serotonin accumulated directly through the high affinity uptake pump of the axon terminals. By immunocytochemical methods using an antibody directed against serotonin, one could also detect serotonin intracellularly (Figure 2).

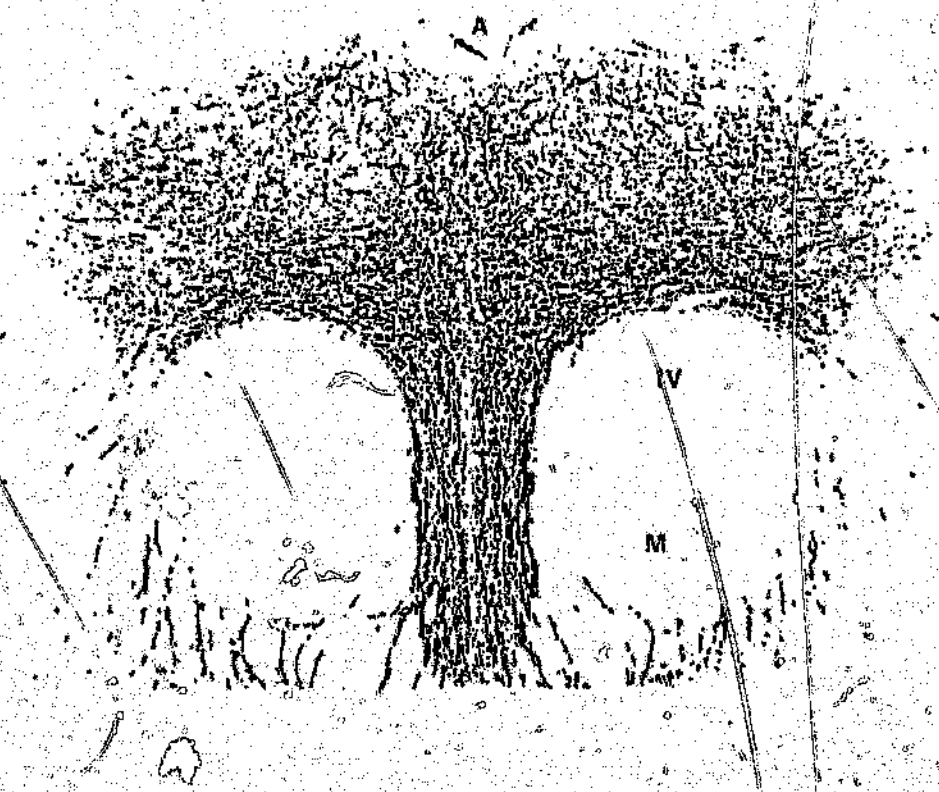


Figure 2 Serotonergic neurons in the primate midbrain demonstrated by immunocytochemistry. Note the highly differentiated arrangement of 5HT neurons in the dorsal raphé nucleus just below the cerebral aqueduct. Compared with rat, the primate dorsal raphé shows a more intricate anatomic organization and the cells are more widely spaced. The dorsal and median raphé nuclei give rise to a highly differentiated and topographically organized projection to cerebral cortex in the primate. Micrograph courtesy of Mary Ann Wilson, Johns Hopkins University. (Abbreviations: A = aqueduct, M = MLF, IV = trochlear nucleus.)

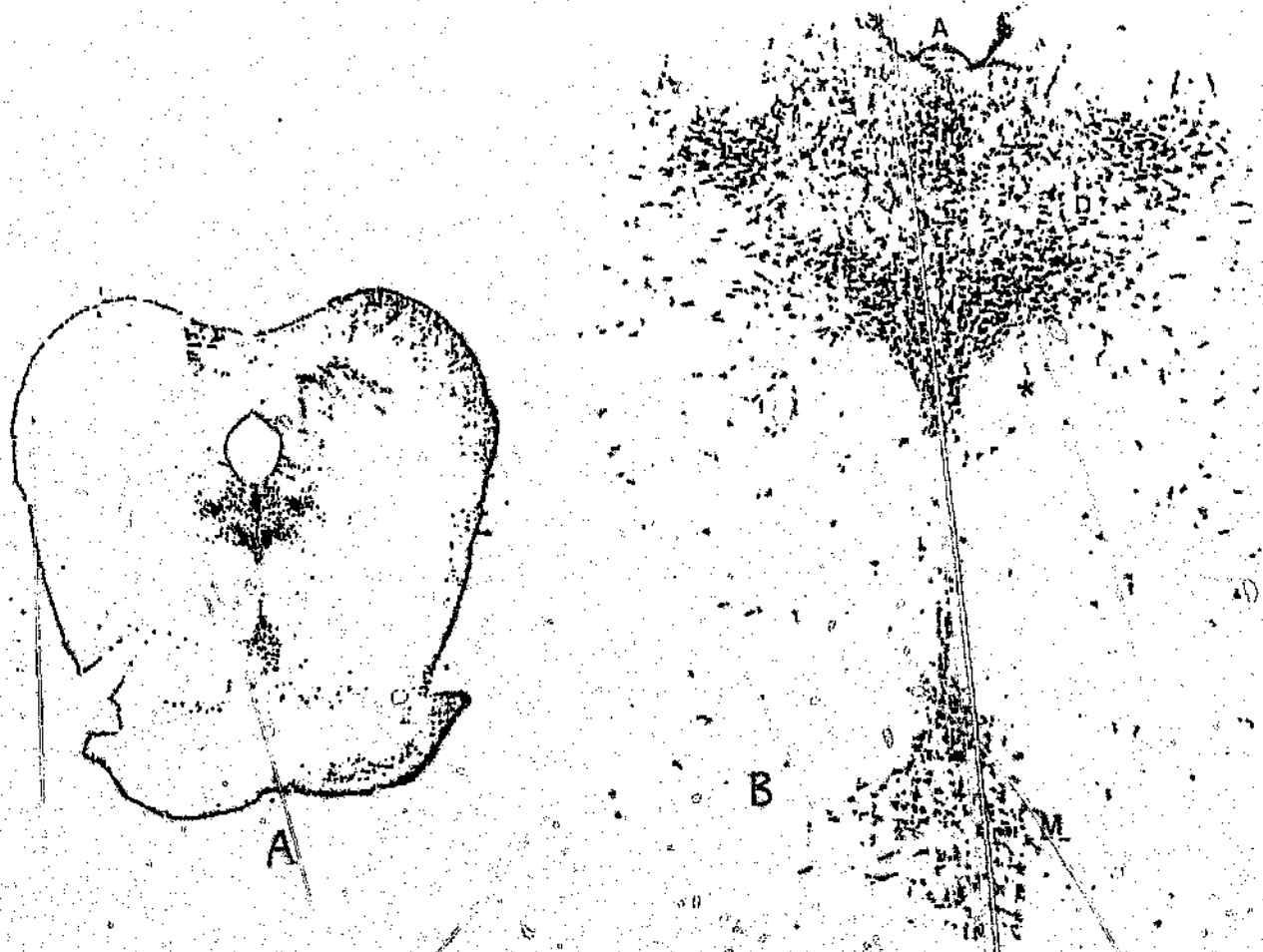


Figure 3 Serotonergic cell bodies in the midbrain raphé nuclei demonstrated by 5HT immunocytochemistry. A. Low magnification survey view of transverse section through the rat midbrain. The three raphé cell groups shown here in the midbrain give rise to widespread serotonergic projections to cerebral cortex and other parts of the forebrain. B. Higher magnification micrograph showing 5HT neurons in dorsal and median raphé nuclei. The dorsal raphé nucleus (B7) lies in the central gray matter just beneath the cerebral aqueduct. In the transverse plane, the dorsal raphé can be further subdivided into a ventromedial cell cluster between and just above the MLF's, a smaller dorsomedial groups just below the aqueduct, and large bilateral cell groups, the lateral wings. The principal cortical serotonin innervation arises from the ventromedial zone of the dorsal raphé. The median raphé nucleus (B7) lies in the central core of the midbrain, below the MLF. In addition to a modest projection to neocortex, the median raphé projects heavily to hippocampus, septum, and hypothalamus. The B9 cell group lies in the ventrolateral midbrain along the fibres of the medial lemniscus. Figure courtesy of Laura Mamounas, Johns Hopkins University. (Abbreviations: D = dorsal raphé, M = median raphé, A = aqueduct, * = MLF [medial longitudinal fasciculus]).

Molliver (1987) found that there were two anatomically and functionally distinct serotonergic projections to the cortex. The dorsal raphé neurons are very fine and very vulnerable to some neurotoxic amphetamines that cause elevated mood. The median raphé axons have large varicosities and are not sensitive to mood elevating drugs. The neurons in the dorsal raphé play a major role in the control of mood.

6.3 Serotonin Receptors

Our ability to distinguish different receptor subtypes has been expanded markedly by new techniques, for instance mollecular biology, radioligand binding, electrophysiology and biochemistry.

There are three main classes of serotonin (5HT) receptors.

$5HT_1$: a, b and d

$5HT_2$: 1c, 2a and 2b

$5HT_3$

Each subtype potentially provides a target that can be manipulated pharmacologically to change the function of serotonin to achieve a specific clinical effect (Gonzales-Heydrich and Peroutka 1990).

6.3.1 $5HT_1$ receptors

These are located on the serotonin neurons and have an inhibitory effect on serotonin release, thereby monitoring the extracellular serotonin concentration.

(a) $5HT_{1A}$ receptor

Autoradiographic studies have shown that the highest concentrations of these receptors are found in the dentate gyrus, the hippocampus and the raphé nuclei.

Electrophysiologic studies show that the serotonin auto-receptor, located on the serotonergic cell bodies in the dorsal raphé nuclei, might be a $5HT_{1A}$ receptor site. This auto-receptor might partially mediate the inhibitory effect of serotonin on its own release (Conn and Sanders-Bush 1987).

(b) $5HT_{1B}$ receptor

This receptor has only been demonstrated in rat and mouse brains, but not in humans.

(c) $5HT_{1D}$ receptor

This receptor seems to function as the serotonin auto receptor.

6.3.2 $5HT_2$ receptors

These are exclusively post synaptic receptors, which don't modify serotonin release. They do not become supersensitive or proliferate after chronic treatment with antagonists. This prolonged subsensitivity which was described by Leysen *et al.* (1986) is quite mysterious and the mechanism behind it, it not known.

(a) $5HT_{1C}$ receptor

This receptor is classified here, because it is similar to the $5HT_2$ receptor. It is found in the choroid plexus, in high densities, as well as in the hypothalamus, hippocampus, basal ganglia and spinal cord. It is not yet clear what the clinical significance of this receptor is.

(b) $5HT_{2A}$ and B receptors

These sites have been labelled using Spiperone, Mianserin, Kitanserin and Mesulergine.

The subtypes were distinguished on the basis of binding of the radio-active derivative of the hallucinogen 4-bromo-2,5-dimethoxy-amphetamine and on the competition binding curves of serotonin versus ^3H Kitanserin (Gonzales-Heydrich and Peroutka 1990). They also mentioned that a c-DNA encoding a functional serotonin two ($5HT_2$) receptor had been isolated using probes generated from the $5HT_{1C}$ receptor c-DNA. This c-DNA is fifty one per cent homologous with the $5HT_{1C}$ receptor c-DNA.

Many authors do not distinguish between the A and B sites.

6.3.3 $5HT_3$ receptors

Very little is known about these receptors in humans.

In rats these receptors seem to be concentrated in cortical areas like the entorhinal cortex and the area postrema. It seems as if there is some interaction between this receptor, dopamine and acetylcholine (Gonzales-Heydrich and Peroutka 1990)

6.3.4 Other putative serotonin receptors

(a) $5HT_{1p}$ receptor

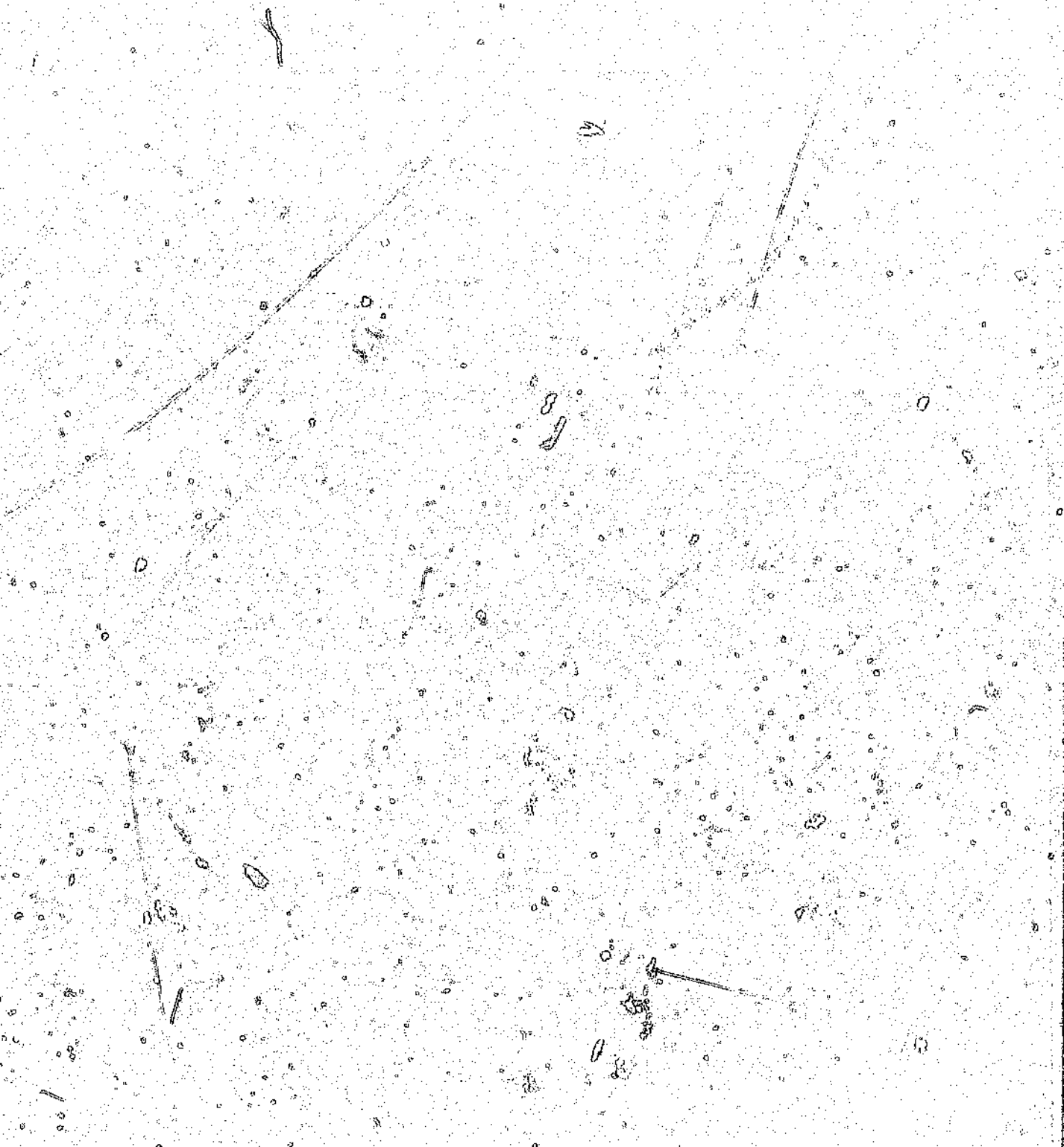
This receptor is found in gut membranes and is labelled by ^3H-5HT and its pharmacological profile is different from all other known serotonin receptors.

(b) $5HT_4$ receptor

This receptor is found in cell cultures of mouse embryo colliculi. Serotonin can stimulate c-AMP production in a dose dependent way via this receptor.

The clinical significance of these two receptors is not known (Gonzales-Heydrich and Peroutka 1990)

Obviously, much more research has to be done to determine the importance and the significance of each 5HT receptor subtype in the central nervous system. Only then, can new more selective drugs be developed to pharmacologically manipulate these sites to achieve specific clinical effects.



CHAPTER SEVEN

7. BIOCHEMICAL INVOLVEMENT OF 5HT IN PSYCHIATRIC AND OTHER DISORDERS

7.1 Introduction

Changes in 5HT neurotransmission are possibly involved in many psychiatric disorders like depression, dysthymia, anxiety, panic disorder, obsessive compulsive disorder, anorexia and bulimia nervosa, alcohol and other drug addictions, aggression, suicide, migraine, drug induced vomiting, psychosis, premenstrual syndrome, seasonal affective disorder, pain, sleep disorders and circadian rhythm disorders (Curzon 1988).

Montgomery and Fineberg (1989) tried to make associations between specific receptor subtypes and specific syndromes:

(a) $5HT_1$ receptors

These receptors seem to be involved in depression, anxiety, appetite, thermoregulation, migraine, memory and possibly obsessive compulsive disorder. Buspirone has been tested mainly at this site.

(b) $5HT_2$ receptors

These receptors are mainly involved in depression, anxiety, dysthymia, migraine and the negative features of schizophrenia. Ritanserin has mainly been tested at this site.

(c) $5HT_3$ receptors

These receptors are involved in anxiety, memory impairment and dementia, addictions, schizophrenia and the treatment of nausea associated with chemotherapy or whole body irradiation in patients with cancer.

7.2 5HT and Depression

7.2.1 Introduction

Even psycho analytically orientated psychiatrists agree that depression is a biochemical condition requiring medication. Akiskal (1990) quotes Cooper (1986) who said "There is a group of chronically depressed and anxious patients, whose mood regulation is vastly changed by antidepressant medication. The entry of these new molecules into their metabolism, alters, tending to normalize the way they see the world. It controls their utter helplessness of being at the mercy of moods that sweep over them without apparent rhyme or reason".

Amongst the many theories of depression, most data favour the serotonin deficiency theory (Coccaro *et al.* 1989, Goodwin *et al.* 1973).

In animals, depression is seen as learned helplessness or behavioural despair, or as failure of adaptive or protective responses to stress. This is associated with decreased serotonin release, which supports the serotonin deficiency theory.

Deakin (1990) quotes studies done on rats, where they were subjected to two hours of immobilisation. This caused them to be less active and to defaecate more in an open field twenty four hours later. With repeated daily immobilisation, though, they became tolerant to the stress and showed no abnormal behaviour. These rats showed enhanced behavioural stereotypes in response to drugs that acted on the $5HT_1$ receptor. Therefore it seems as if the $5HT_1$ receptor is involved in the adaptation to stress. It is interesting to note that the female rats showed less tolerance to repeated stress and did not develop enhanced behavioural responses to $5HT_1$ receptor antagonists. This might explain why women have a greater susceptibility to develop depression.

7.2.2 Causes of deficient 5HT

There are various potential causes of deficient serotonin, namely: (Meltzer *et al.* 1989).

(a) Limited precursor

(b) Changes in tryptophan hydroxylase action

(c) Abnormal release or re-uptake of serotonin at the synapse

(d) Functional deficit of serotonin relative to other neurotransmitters or neuromodulators.

(e) Abnormal receptors with subsensitivity of some of the subtypes

(f) Abnormal interaction between subtypes

(g) Abnormal second messenger systems

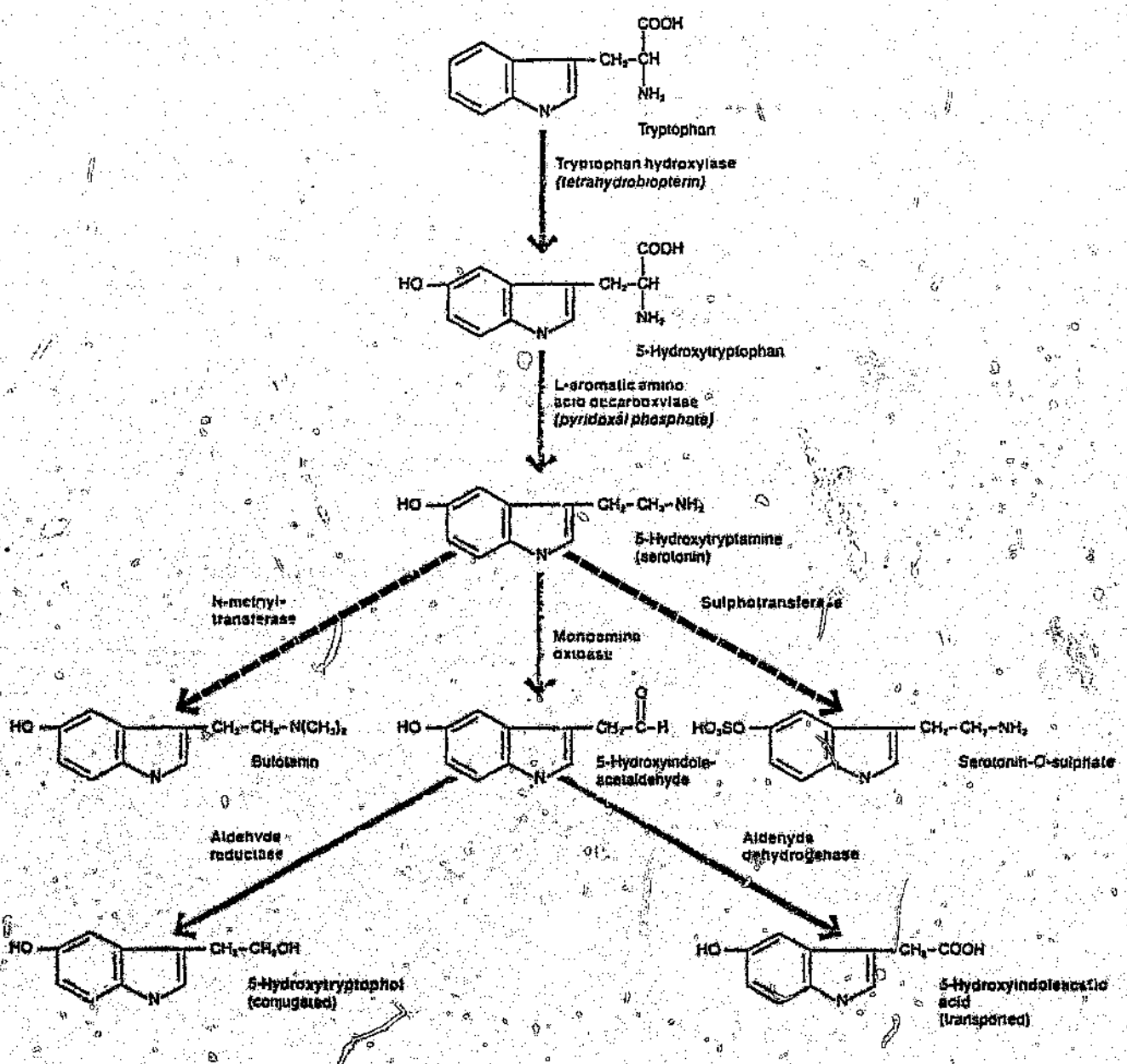


Figure 4 : Synthesis and breakdown of 5HT

7.2.3 Neuro endocrine studies

5HT pharmacological agents that are used in human neuro endocrine studies are the following (Price *et al.* 1990):

(a)	Precursors	-	L Tryptophan
		-	5-hydroxytryptophan
(b)	Releasers	-	fenfluramine
(c)	Re-uptake blockers	-	domipramine
(d)	Receptor agonists	-	metachlorophenylpiperazine
		-	MK 212
(e)	Receptor antagonists		
	Non-selective	-	methysergide
		-	cyproheptadine
		-	metergoline
	Selective	-	Ketanserin
		-	Ritanserin

(a) Plasma tryptophan

Most studies show that the plasma tryptophan is lower in depressed patients than in controls (Coppen and Wood 1978, De Myer *et al.* 1981), however, some studies showed no difference (Møller 1985).

The fasting plasma tryptophan levels are significantly lower in both depressed female patients and female controls. This may be a reason why females are more vulnerable to depression (Meltzer 1989). Some studies report an association between low tryptophan levels and post partum depression (Handley *et al.* 1980).

Meltzer *et al.* (1984) showed a positive correlation between the severity of the depression and the cortisol response to 5-hydroxy-tryptophan. They attributed this to an upregulation of the $5HT_2$ receptors, which is related to 5HT deficiency.

Another way of studying serotonergic function in depression, is by giving intravenous L tryptophan as a serotonin challenge agent. The rationale behind it is that L tryptophan administration will increase serotonin synthesis in the hypothalamus, which is where serotonin mediates the effect of serotonin on prolactin.

After intravenous L tryptophan administration, there is a clear increase in serum prolactin in healthy subjects. This is an indicator of 5HT function (Charney *et al.* 1982, Cowen *et al.* 1985, Winokur *et al.* 1986). There is also an increase in growth hormone in some cases, but it varies to such an extent, that it cannot be used as a reliable indicator of central 5HT function. The healthy subjects experience subjective mood changes to L tryptophan administration, saying that they feel drowsy, mellow or high.

There are authors who believe that the prolactin response to L tryptophan is not mediated by 5HT, but Charney *et al.* (1982) and Cowen *et al.* (1985) have found that there is attenuation of the response by non-selective 5HT antagonists like methysergide, cyproheptadine and metergoline. The phenomenon may be mediated primarily by the $5HT_1$ receptor though, because the selective $5HT_2$ antagonist, Ritanserin, causes no such attenuation or it may in fact even increase the response.

Heninger *et al.* (1984) found that non-melancholic depressives had a blunted prolactin response. This is an indication of altered serotonergic function (Meltzer *et al.* 1984, Coccaro *et al.* 1989) that is probably specific to depression and not merely a non-specific correlate of severe psychiatric illness. Patients with other psychiatric disorders who do not show this blunted effect, are patients with panic disorder (Charney *et al.* 1986), obsessive compulsive disorder (Charney *et al.* 1988) and schizophrenia (Price *et al.* 1990).

When depression is associated with significant weight loss, the prolactin response is increased. It is decreased when there is no significant weight loss. Cowen *et al.* 1987 and Goodwin *et al.* 1987 found that there was an increased prolactin response in healthy females who showed weight loss after dieting. This was not seen in males who were dieting and may once again explain why females are more likely to develop depression than males.

Another approach would be to study the clinical effects of tryptophan depletion. Shopsin *et al.* (1976) showed that parachlorophenylalanine inhibited the activity of tryptophan hydroxylase, thereby inhibiting 5HT synthesis (see figure 4). This was given to patients who had suffered from depression, but were now stable on antidepressants. Within seven to twenty-four hours after giving it, the depressive symptoms came back and the patients relapsed. (Delgado *et al.* 1990). These data are among the most convincing in support of the role of serotonin in thymoleptic drug action.

Gradual dietary tryptophan depletion can lead to a seventy five per cent reduction in plasma tryptophan levels, which causes subjective depression even in normal adults (Smith *et al.* 1987, Young *et al.* 1985, Delgado *et al.* 1990), although some authors say that it leads to mild impairment in attention and increased subjective reports of negative moood, but no clear clinical depression in healthy male subjects. What is even more exciting, is that when depressed patients who are maintained on an antidepressant, are given a low tryptophan diet, there is a depressive relapse within seven hours in sixty seven per cent of patients (Delgado *et al.* 1990).

Reserpine may also precipitate depression in vulnerable patients by lowering the synaptic concentrations of 5HT. Iproniazid may cause mood elevation in some people treated with Reserpine by inhibiting monoamine oxidase and elevating synaptic concentrations of brain 5HT (Byerley and Risch 1985).

From the above, it seems that a tonic serotonergic effect has to be present to maintain a normal mood. The mood may be altered by experimentally induced decreases or increases in 5HT function and this may even change the effects of antidepressant drugs.

(b) 5HIAA studies

Low concentrations of the main metabolite of serotonin, 5-hydroxyindoleacetic acid (5HIAA) are found in the cerebrospinal fluid of depressed patients as well as in autopsy studies of brains from suicide victims (Beskow *et al.* 1976, Åsberg *et al.* 1984, Korpiet *et al.* 1986).

The studies do however show contradictory results, with some studies not finding low concentrations of 5HIAA in depression (Gjerris *et al.* 1987, Koslow *et al.* 1983). But Byerley and Risch (1985) mention that one must be careful when interpreting lumbar cerebrospinal fluid data, since there is controversy over how much brain 5HT neurons and spinal cord 5HT neurons contribute to the lumbar cerebrospinal fluid 5HIAA concentrations.

It is possible that only a subgroup of depressed patients has reduced 5HT levels. Asberg *et al.* (1986) used gas chromatography/ mass spectrometry to measure 5HIAA and found that depressed patients had a bimodal distribution of cerebrospinal fluid 5HIAA concentrations, with only thirty per cent of severe major depressives showing the low levels.

Bridge *et al.* (1976) measured ventricular 5HIAA concentrations and found that severely depressed patients had very low concentrations.

Shaskan *et al.* (1980) showed that monozygotic twins had a higher concordance for low cerebrospinal fluid concentrations 5HIAA than dizygotic twins. This means that the regulation of serotonin metabolism may be genetically determined and 5HIAA concentration may be a genetic trait. The fact that 5HIAA values change little over time in individual subjects, also supports this theory. These authors also reported that psychologically healthy people with low cerebrospinal fluid 5HIAA concentrations were more

likely to have relatives with depression, than the controls. Of course, if cerebrospinal fluid 5HIAA values are genetic traits and if low values predispose to depression and suicide, prospective studies in young patients at risk, would be important.

Plasma 5HIAA levels correlate negatively with the severity of the depression and symptoms like guilt, insomnia, worthlessness, hopelessness and suicide (Meltzer 1989).

Urinary 5HIAA levels vary from day to day and cannot be correlated with cerebrospinal fluid 5HIAA levels (Bertilsson *et al.* 1982).

Platelet monoamine oxidase activity may be a reflection of some aspect of the central serotonin system, but it does not correlate well with cerebrospinal fluid 5HIAA levels (Åsberg *et al.* 1986).

(c) Blood platelet studies

Platelets are often used as a model of the serotonergic nerve terminal. Studies show that depressed patients have decreased numbers of 5HT uptake sites in the platelets (Meltzer *et al.* 1981, Healy *et al.* 1986).

There are also significantly fewer platelet ^{3}H-imipramine binding sites in depressed patients. This phenomenon seems to be region specific: Gross-Isseroff *et al.* (1989) found increases in the hippocampus, but decreases in the post central cortical gyrus, insular cortex and claustrum. Imipramine binding is a presynaptic serotonergic marker.

A $5HT_2$-like receptor in platelets, that is comparable to those of brain $5HT_2$ receptors, has been described. Biegon *et al.* (1987) have shown that depressed patients have more than twice the concentration of $5HT_2$ receptors in platelets. They have also shown that the number of sites returned to normal after four weeks of antidepressant therapy. This is important, because Arora and Meltzer (1989) found increased numbers of these binding sites in the frontal cortex of suicide victims. One might be able to use the $5HT_2$-like receptor in the platelets to measure suicide risk.

7.3 5HT and Suicide

7.3.1 Introduction

When a clinician only studies the psychosocial factors associated with suicide, it can cause problems, because one needs a more definite measurement to predict suicide risk. In 1976 Åsberg *et al.* said "Low cerebrospinal fluid 5HIAA may be a biochemical suicide predictor".

Most authors agree that there is an abnormality in the 5HT system in patients who commit suicide, especially if it is a violent suicide (Coccaro *et al.* 1989). In most studies in suicide victims, only fifty per cent had a diagnosis of major depression. Other diagnoses included alcohol abuse, adjustment disorder with depression, schizophrenia and personality disorder. This may suggest that the altered 5HT metabolism may be primarily associated with suicidal behaviour, rather than depression per

7.3.2 Post-mortem studies

(a) Levels of 5HT and 5HIAA

Studies show contradictory results, but most studies favour low concentrations of 5HIAA in the cerebrospinal fluid, the cortex and the brainstem, especially the raphé nucleus of suicide victims. This finding is even more pronounced in patients who commit suicide by violent means (Mann *et al.* 1989, Brown *et al.* 1982).

Ante mortem and post mortem studies, measuring 5HIAA and HVA in the cerebrospinal fluid and the frontal cortex, show a positive correlation (Stanley and Stanley 1990).

Gottfries (1980) mentions that the changes in 5HT levels in suicide victims may be due to the variable length of time between death and autopsy. This is normally longer in suicide than in controls. Since 5HT may be more sensitive to this post mortem interval or delay, and be significantly metabolized postmortally, lower levels of 5HT may be shown without proving anything. This was confirmed by Stanley *et al.* (1986).

One of the other problems that can cloud the issue, is that overdoses and carbon monoxide poisoning as suicide methods, may alter the levels of 5HT or 5HIAA independent of the suicide itself.

(b) Imipramine binding site studies

This site is a pre-synaptic marker for the 5HT system and an index of the number and/or functional status of the 5HT nerve terminals. There is a significant reduction in number of these sites in the prefrontal cortex of suicide victims (Perry *et al.* 1983, Mann *et al.* 1989).

However, not all the studies confirm this and this could be due to the fact that impramine is a non-specific ligand and ante-mortem drugs can influence it. It may also be due to the asymmetry of imipramine binding. Stanley and Stanley (1990) mention studies where it was found that in controls the imipramine binding was higher in the right hemisphere, whereas in suicide victims it was higher in the left hemisphere.

(c) $5HT_2$ receptor binding studies

Some studies have shown an increased number of $5HT_2$ receptors in the prefrontal cortex of suicide victims, especially violent suicides (Mann *et al.* 1986, Arora and Meltzer 1989). There was, however, also an increase in $5HT_2$ binding in the prefrontal cortex of depressed patients dying from natural causes. This may suggest that part of the changes in the 5HT system may be due to the presence of major depression only (Mann *et al.* 1989).

These findings of increased $5HT_2$ receptor binding sites mean that there is a compensatory increase in the post synaptic binding secondary to a decrease in the pre-synaptic input.

7.3.3 Conclusion

In suicide victims one finds reduced 5HT and 5HIAA in the brain, reduced 5HIAA in the cerebrospinal fluid, reduced imipramine binding and increased $5HT_2$ receptor binding. These findings are all consistent with hypofunction of the 5HT system.

Antidepressants produce the opposite effect, making more 5HT available, and this may account for their antidepressant and anti-suicide action.

Because of these biochemical findings, it may be very important to do prospective studies, to try and predict suicidal behaviour in patients at risk.

7.4 5HT and Anxiety

In animal studies, the threat of punishment modifies behaviour, even before the shock is delivered. This threat of punishment is the animal behavioural model for anxiety and fear. According to Deakin (1990), the 5HT neurons mediate the effects of threat of punishment on animal behaviour.

Anxious people have the susceptibility to form conditioned fear responses which make them very sensitive to aversive stimuli. Anxiety and depression often occur together and there is a special association specifically between dysthymia and anxiety.

In anxiety one finds increased $5HT_2$ or $_3$ receptor transmission. $5HT_2$ receptor antagonists have some antipunishment activity (Colpaert *et al.* 1985) and Ritanserin, a $5HT_2$ antagonist, shows antiolytic activity (Ceulemans *et al.* 1985). $5HT_3$ antagonists may also be antiolytic - it was shown that Ondansetron was effective against anxiety in animals.

Benzodiazepines reduce meurotransmission and the $5HT_{1A}$ agonists and partial agonists (Buspirone) have antiolytic effects (Gonzales-Heydrich and Peroutka, 1990). Repeated administration of Buspirone causes $5HT_2$ receptor down regulation (Deakin 1990).

7.5 HT and Aggression

There is a clear association between 5HT levels and aggression. (Brown and Linnoila 1990). Presynaptic 5HT function is more likely related to the trait of aggressivity than to vulnerability to depression (Blier *et al.* 1987).

Very low cerebrospinal fluid 5HIAA levels were found in criminals with the 47 XYY syndrome who were institutionalized because of violence and aggression (Bioulac *et al.* 1980). Low levels are also associated with hot blooded murders, more so than with premeditated ones. It seems as if there is an association between low 5HIAA levels and impulsivity and lack of impulse control (Coccaro *et al.* 1989).

Suicide is seen as a form of self-directed aggression (Curzon 1988). Reduced 5HT levels correlate positively with the degree of violence in suicide attempts (Träskman *et al.* 1981). Receptor studies show that violent attempters have increased $5HT_2$ receptor binding (Stanley and Mann 1983, Mann and Stanley 1986). It is not clear whether this is only a marker for suicide, or whether it is a marker for low impulse control and aggression.

7.6 5HT and Food Intake

5HT regulates carbohydrate intake, and tryptophan enhances 5HT release. In animals 5HT drugs decrease carbohydrate consumption.

When one consumes food rich in carbohydrates, but low in protein, the plasma - tryptophan ratio increases and that stimulates brain tryptophan uptake with increased 5HT release.

5HT neurotransmission is increased by drugs like D-fenfluramine, which block the re-uptake of 5HT and increase the release of 5HT from the presynaptic terminals. When patients with carbohydrate craving are given D-fenfluramine, it reduces the intake of carbohydrate rich snack food by at least forty per cent (Wurtman, 1988).

Carbohydrate craving is especially noted in patients with low mood, premenstrual syndrome and in seasonal affective disorder (Wurtman 1988). In seasonal affective disorder, one finds that in mid-autumn, when the daylight hours get shorter, the patient's

calorie intake in sweet and starchy foods increases dramatically. There are also associated features of depression, fatigue, lethargy and hypersomnia. In Spring, there is an intake reduction of seven hundred to eight hundred calories per day as the daylight hours get longer (Rosenthal *et al.* 1984).

Patients with a low mood who crave carbohydrates, correctly anticipate that carbohydrate rich food will make them feel better. The increased 5HT release which follows the binge, has a similar effect to that of antidepressant drugs.

Some of the 5HT re-uptake inhibitors, like fluoxetine, cause weight reduction in depressed and non-depressed obese patients (Cooper 1988, Montgomery *et al.* 1988).

Halm *et al.* (1986) treated patients with anorexia nervosa with 5HT antagonists (cyproheptadine) and found that they induced appetite and resulted in a slight decrease in the time it took to regain normal weight.

7.7 5HT and Alcoholism

5HT activation reduces alcohol consumption and the short term memory defects associated with alcohol abuse. Gonzales-Heydrich and Peroutka (1990) describe alcoholics who were treated with buspirone, a $5HT_{1A}$ partial agonist. These patients were more compliant on medication, they had less alcohol craving and less psychopathology.

7.8 5HT and Schizophrenia

$5HT_3$ antagonists have an inhibiting effect on dopamine function and may improve psychosis (Gonzales-Heydrich and Peroutka 1990).

$5HT_2$ antagonists seem to be effective in the treatment of the negative symptoms of schizophrenia, while at the same time improving extrapyramidal side-effects of neuroleptics (Gelders *et al.* 1985, Janssen 1988, Gelders 1989).

7.9 5HT and Obsessive Compulsive Disorder

Obsessive compulsive disorder seems to be a "5HT-disorder". Placebo controlled studies have consistently shown the significant advantage of clomipramine and fluvoxamine in this disorder. The effect appears to be directly anti-obsessional, rather than depending on an antidepressant effect. The anti-obsessional effect is mediated by its 5HT uptake inhibiting activity (Perse *et al.* 1987, Goodman *et al.* 1989).

7.10 5HT and Sleep

5HT seems to play a part in sleep, since the $5HT_2$ antagonist, Ritanserin, dramatically increases slow wave sleep (Idzikowski *et al.* 1987).

7.11 5HT and Migraine

The $5HT_{1D}$ receptor, which is situated on or near cerebral blood vessels, seems to play a role in migraine.

A potent and selective $5HT_{1D}$ agonist, Sumatriptan, causes vasoconstriction of the cerebral arteries and is effective in the acute treatment of migraine with minimal side-effects. (Doenicke *et al.* 1988).

In the prophylaxis of migraine, $5HT_2$ receptor antagonists like methysergide, pizotifen, cyproheptadine and lisuride are effective. They are effective because due to the $5HT_2$ antagonism, the metabolism of phosphatidylinositol and arachidonic acid is inhibited, and this causes a sterile inflammatory reaction in the brain vasculature and prevents migraine (Ceulemans *et al.* 1985). They are, however, not effective in the acute episode when the inflammatory reaction has already started.

7.12 5HT and Pain

5HT seems to be involved in pain, because when 5HT is applied to a blister, it causes pain. $5HT_3$ antagonists inhibit the pain and the inflammatory flare response. (Gonzales-Heydrich and Peroutka 1990).

They might, because of this effect, also be useful in migraine.

7.13 5HT and Nausea

$5HT_3$ antagonists are new potent anti-emetics, especially in cytotoxic and radiation induced emesis. This effect is mediated via the $5HT_3$ receptors on the vagal afferent neurones or in the area postrema (Gonzales-Heydrich and Peroutka 1990).

7.14 5HT and Gastro Intestinal Motility Disturbances

In the carcinoid syndrome the gastro intestinal disturbance is caused by overproduction of 5HT. $5HT_3$ antagonists relieve the diarrhoea, but not the flushing (Anderson *et al.* 1987).

7.15 5HT and Cardiovascular Disease

The treatment of hypertension may be mediated via the $5HT_{1A}$ receptor.

The $5HT_2$ antagonist, Ketanserin, has been studied in peripheral vascular disease, thrombosis, emboli and cardiopulmonary emergencies. (Gonzales-Heydrich and Peroutka 1990).

CHAPTER EIGHT

8. ANTIDEPRESSANT TREATMENT USING 5HT MANIPULATION

8.1 Introduction

Depression involves an imbalance between reduced function in the pre-synaptic $5HT_1$ receptor systems and enhanced function in the post-synaptic $5HT_2$ receptor systems (Deakin 1990).

Many antidepressants reverse this imbalance by either being $5HT_2$ receptor antagonists or by inducing $5HT_2$ receptor down regulation. Virtually all effective antidepressants enhance neurotransmission across 5HT synapses after long term, but not short term administration (Delgado *et al.* 1990). The 5HT system may represent a final common pathway underlying the therapeutic effects. The specific means by which the functional enhancement is accomplished, vary according to drug class.

When looking at antidepressant treatment, one must consider three areas:

(a) The firing rates of the 5HT neurons

(b) The efficacy of synaptic transmission

(c) The sensitivity of the postsynaptic receptors

8.2 Tricyclic Antidepressants

Tricyclic drugs are the most commonly used agents in the treatment of depression. It is well known that they have a delayed therapeutic onset of action.

During the first fourteen days of treatment, there is no modification in the firing activity of the 5HT neurons or the terminal 5HT auto receptors.

After fourteen days postsynaptic sensitization to 5HT occurs in the hippocampus, the dorsal and ventral lateral geniculate nuclei, the facial motor nucleus, the suprachiasmatic nucleus and the somatosensory cortex (Blier *et al.* 1990). This may be mediated by the $5HT_{1A}$ receptor. The clinical relevance of this, is that the postsynaptic sensitization occurs in the areas of the brain concerned with behavioural functions in depression. The time course for the sensitization to develop, is consistent with the delayed onset of the therapeutic action in humans (Price *et al.* 1990).

Longterm tricyclic antidepressant treatment increases the prolactin response to L tryptophan (Charney *et al.* 1984), but this response does not differentiate between antidepressant responders and non-responders (Price *et al.* 1989). There is also no relationship between the magnitude of the prolactin response and the clinical ratings of the antidepressant effect.

8.3 Electro Convulsive Therapy (ECT)

The effects of ECT are very similar to those of the tricyclic antidepressants.

After one ECT or repeated subconvulsive shocks, there is no change in the 5HT pathway or receptors and no clinical response.

But after seven ECT's the ascending 5HT pathway is enhanced and there is sensitization of the postsynaptic $5HT_{1A}$ receptors in rats (Blier *et al.* 1990) as well as an increased number of $5HT_2$ receptors (Plaznik *et al.* 1989).

8.4 Sleep Deprivation

Sleep deprivation has the same biochemical effects as tricyclic antidepressants and ECT.

8.5 Mono Amine Oxidase Inhibitors

In the human brain mono amine oxidase (MAO) exists in two forms: A and B. MAO-A catabolizes 5HT and noradrenaline. The selective MOA-A inhibitors are effective antidepressants, because they enhance the availability of 5HT and noradrenaline. After two days of treatment, the firing rate of the 5HT neurons in the dorsal raphé is markedly reduced, but then it gradually recovers to normal after twenty one days of treatment. This is consistent with the delayed therapeutic effect.

Because the MAO inhibitors influence both the 5HT and the noradrenaline systems, it is important to note that Plaznik *et al.* (1989) claims that the 5HT neurons may be involved in beta-adrenoceptor downregulation. Noradrenaline may also be modulating 5HT transmission. These interactions may be essential for the antidepressant and antisuicidal effects of these drugs.

MAO inhibitors cause an increased prolactin response to L tryptophan at high levels.

8.6 Lithium

Lithium enhances the releasable pool of 5HT. There are conflicting results with regard to the effect of Lithium on the prolactin response to L tryptophan. This may be due to the fact that Lithium may have different effects on 5HT function in mood disordered patients and healthy subjects (Price *et al.* 1989, Glue *et al.* 1986, Price *et al.* 1990).

This enhancement effect of Lithium is often used in refractory depression (Price *et al.* 1989)

8.7 5HT re-uptake Blockers

These drugs are effective as antidepressants because they increase the synaptic availability of 5HT and they enhance 5HT transmission (Åsberg *et al.* 1985) secondary to desensitizing the 5HT auto receptor located on the 5HT nerve terminals.

The sustained increased availability of 5HT could result in postsynaptic desensitization. This does not however happen, because the firing rates of the 5HT neurons adapt (Blier *et al.* 1984, De Montigny 1981). The firing rates decrease after two days, after seven days they are partially recovered and by fourteen days they are back to normal. This progressive adaptation of the 5HT neurons with decreased responsiveness, is due to reduced density of the $5HT_{1A}$ binding sites. The enhanced synaptic transmissfon is probably due to presynaptic modification, but the 5HT re-uptake blockade will not result in increased 5HT transmission until the 5HT neurons have resumed their normal firing activity. Then the 5HT transmission is enhanced due to the reduced capacity of the terminal 5HT auto receptors to inhibit the release of 5HT. The delayed therapeutic effect is the result of the progressive recovery of firing activity and the desensitization of the terminal 5HT auto receptor.

The short term and long term administration of fluvoxamine, a selective 5HT re-uptake blocker causes an increased prolactin response to L-tryptophan (Price *et al.* 1989).

8.8 5HT Receptor Agonists

The $5HT_{1A}$ receptor agonists were originally developed as anxiolytic agents, but they also have antidepressant potential (Goldberg *et al.* 1979).

As with the other antidepressants, there is a progressive adaptation in the firing rate of the neurons up to day fourteen. This is due to somatodendritic 5HT auto receptor desensitization and reduced numbers of $5HT_{1A}$ binding sites in the dorsal raphé nuclei (Blier *et al.*, 1990).

These drugs are full agonists on presynaptic receptors, but partial agonists on post synaptic neurons (Blier *et al.*, 1990)

The antidepressant [illegible] done, is a strong 5HT re-uptake blocker, but its major [illegible]chlorophenyl-piperazine, is a potent postsynaptic 5H[illegible]ist.

8.9 5HT Receptor Antagonists

The 5HT an[illegible]ist properties of antidepressants such as amitriptyline and mianserin, are well known.

Another $5HT_2$ receptor antagonist, Ritanserin, seems to be effective in anxiety disorders and dysthymia (Ceulemans *et al.* 1985, Jarone *et al.* 1986).

Leander (1986) worked with a 5HT receptor antagonist, BW 501, which works peripherally and does not cross the blood-brain-barrier. He postulates that the peripheral action of the drug induces behavioural supression in rats (a model for depression) outside the blood-blain-barrier.

8.10 Other Antidepressants

L Tryptophan and 5-hydroxytryptophan, the precursors of 5HT, are effective antidepressents (Møller *et al.*, 1980). L tryptophan also potentiates the effects of the MAO inhibitors and clomipramine in major depression (Shopsin *et al.* 1976, Walinder *et al.* 1976).

The antidepressant properties of carbamazepine (Post *et al.* 1986), as well as salbutamol and clenbuterol, two beta$_2$-adrenergic agonists (Lecrubier *et al.* 1980) are probably due to their capacity to increase the levels of free plasma L tryptophan (Blier *et al.* 1987).

8.11 Conclusion

It is still unclear how some antidepressants exert their effects, and much more research will have to be done in this field. The diversity of the 5HT receptors will hopefully lead to the development of more selective and effective psychotherapeutic drugs.

PART III : RITANSERIN

CHAPTER NINE

9. RITANSERIN

9.1 Introduction

Serotonin (5HT) has been considered an important neurotransmitter in depression for many years.

Previous studies of the effects of 5HT antagonists on 5HT turnover, were complicated by the fact that the drugs lacked specificity. They either had mixed agonist-antagonist properties, like quipazine, methysergide or metergoline, or the antagonism of the 5HT receptor site was not the primary effect of the drugs, as in methiotepin, cyproheptadine and pizotifen.

When Ketanserin was discovered, it opened new perspectives, because it bound primarily and with high affinity to the $5HT_2$ sites. Ketanserin is under investigation as an antihypertensive agent. The action of Ketanserin is mainly peripheral, namely vasoconstriction, bronchoconstriction and platelet aggregation (Barone *et al.* 1986). However, some patients treated for hypertension with Ketanserin, occasionally reported an increased feeling of psychological well-being. This was a stimulus to explore the thymosthenic effects of Ritanserin, which acts centrally (Reyntjens *et al.* 1986).

Chemical formula :

6-[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidinin-5-one

Empirical formula :

$C_{27}H_{25}F_2N_3OS$

Structural formula :

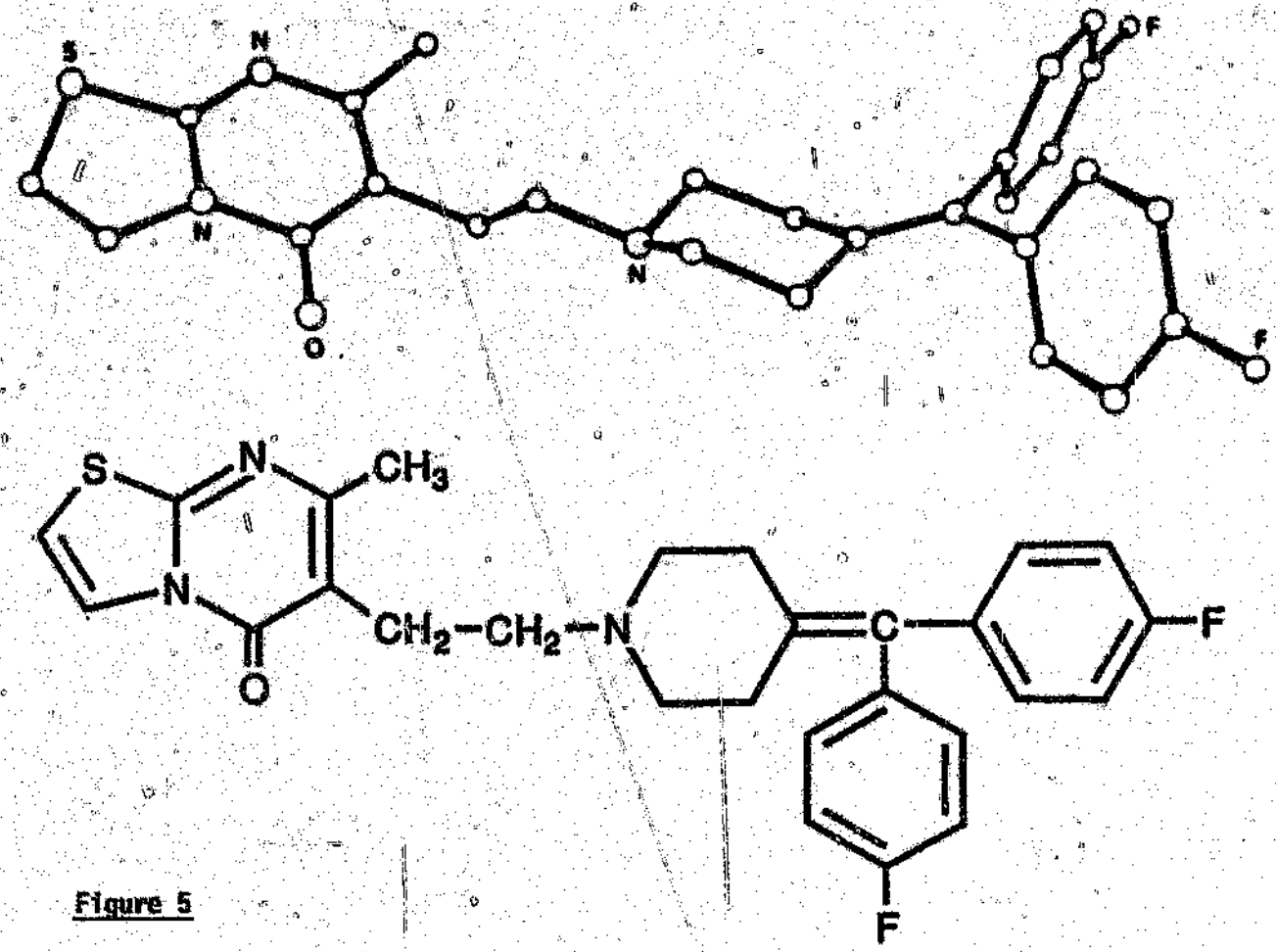


Figure 5

9.2 Pharmacology

Ritanserin is a centrally acting, relatively selective, extremely potent and long acting $5HT_2$ receptor antagonist, which easily passes the blood brain barrier (Janssen 1988). It is also a potent and pure antagonist of lysergic acid diethylamide (LSD) and other centrally acting serotonomimetic drugs. It is a new benzhydrilene piperidine derivative with the molecular structure as shown in Figure 5.

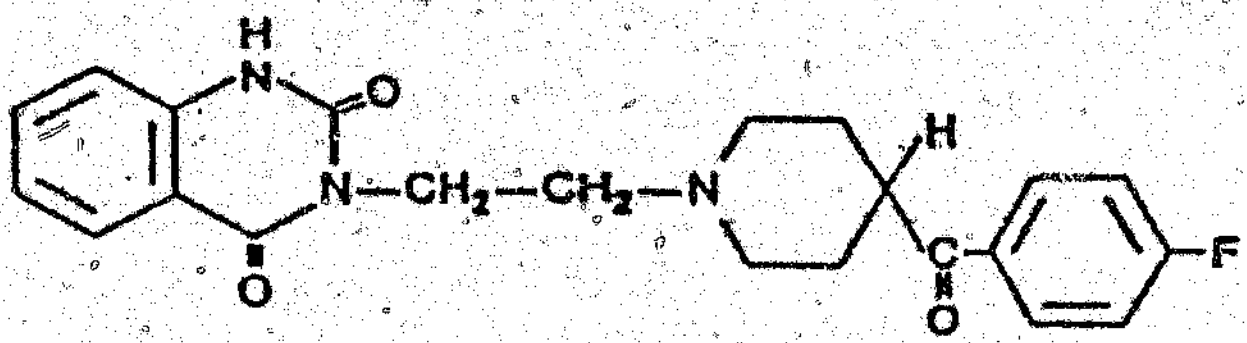


Figure 6 : Graphic formula of ketanserin

In *in vitro* binding studies, Ritanserin binds primarily and with high affinity (subnanomolar concentrations) to $5HT_2$ receptor sites. It does not interact with $5HT_1$ receptor sites even in micromolar concentrations.

Leysen *et al.* (1085) measured the dissociation time of the unlabelled drug from receptor sites, and found that Ritanserin dissociated very slowly from the $5HT_2$ and histamine - H_2 receptor sites. It dissociated rapidly from dopamine D_2 sites and with medium velocity from adrenergic alpha one and alpha two sites.

The slow dissociation time from $5HT_2$ sites is probably due to Ritanserin's ability to form an energetically stable complex with these sites and not with the others.

At a pH of 7,5, Ritanserin is 2,6 times more lipophilic than Ketanserin and its dipole moment is lower than that of Ketanserin

The plasma levels peak at 1,7 ± 0,06 hours and the half life ($T_{\frac{1}{2}}$) is 54 ± 11 hours after a twenty five milligram dose of Ritanserin. However, the plasma levels do not run parallel to the occupation of the 5HT[illegible] sites. Leysen *et al.* (1985) mention a study where rats were given Ritanserin orally or subcutaneously, and while the $5HT_2$ receptor sites remained eighty per cent occupied for more than twenty four hours, the plasma levels were undetectable after twenty four hours.

9.3 Safety Evaluations

Studies done by Barone *et al.* (1986) found that patients tolerated Ritanserin very well. The most common adverse experiences were somnolence and fatigue. These might have been drug related, but there was no general correlation between the intensity of adverse experiences and plasma levels.

Van Rooy *et al.* (1987) looked specifically at the cardiotoxic effects of Ritanserin. Healthy volunteers were given either placebo, or Ritanserin five milligrams, ten milligrams or twenty milligrams. In all the groups, the heart rate, the blood pressure, the PQ interval, the QRS interval and the systolic time interval were unchanged. However, the QT_c and QT_m intervals changed in a dose-dependent way:

(a) On five milligrams Ritanserin, the intervals were unchanged.

(b) On ten milligrams Ritanserin, the intervals were significantly prolonged, compared to baseline, but not significantly different from the changes in the placebo group.

(c) On twenty milligrams Ritanserin, the prolongation was statistically significant. Seven days after discontinuation of Ritanserin, all the values returned to normal.

9.4 Psychotherapeutic Indications

9.4.1 Dysthymia

Ceulemans *et al.* (1985) studied one hundred and twenty eight patients with dysthymia, and found that forty seven per cent of the patients on twenty milligrams Ritanserin did well or very well. In the placebo group thirty four per cent did well or very well.

Another study by Reyntjens *et al.* (1986) found similar results. They also compared depressive symptomatology in responders and non-responders. On the Hamilton Depression Rating Scale, the non-responders scored higher at the start of the study for hopelessness, early awakening, guilt feelings, suicide and diurnal variation. They concluded that the best results with Ritanserin were obtained in patients with dysthymic disorder without endogenous features.

In a study done by Janssen (1988) patients already showed a marked improvement on the Clinical Global Impression Scale, even after only ten days on Ritanserin, ten milligrams twice a day. After forty days, sixty three per cent showed a good or excellent therapeutic effect. The Hamilton Depression Rating Scale scores dropped by forty six per cent, specifically on the items depressed mood, early insomnia, agitation, psychic anxiety and retardation. Forty two per cent of the patients on Ritanserin had a better therapeutic effect on Ritanserin than with any other previously tried treatments for dysthymia.

Reyntjens *et al.* (1986) reported that the first observed effect of Ritanserin was improvement of fatigue and lack of drive: patients felt less tired and more energetic and more motivated. Overall, the patients felt less tense, less irritable, less anxious and less depressed and they were able to cope better with daily life and responsibilities.

9.4.2 Anxiety disorders

Benzodiazepines have been used in the treatment of anxiety disorders for many years. They enhance the inhibitory effect of gamma-aminobutyric acid (GABA) neurons and this inhibitory effect reduces the serotonergic activity indirectly.

Different classes of antidepressants all cause down-regulation of $5HT_2$ receptors and they also help in the treatment of anxiety disorders.

Methergoline, the $5HT_2$ antagonist, shows anti-punishment activity in pigeons, bit it causes anxiety in humans. The reason for this, is that Methergoline also has partial and mixed lysergic acid diethylamide (LSD) antagonist and agonist activity. It may thus cause partial LAD-like subjective effects in humans for instance anxiety, tension and depressed mood (Ceulemans *et al.* 1985).

Ritanserin is a better drug to study in anxiety, because it is a pure LSD antagonist with no LSD like agonist activity.

Janssen (1988) showed that there was a good to excellent response in seventy three per cent of patients with generalized anxiety disorder, after being on Ritanserin for four weeks. Even after one week, there was an improvement in insomnia. The patients felt calmer, more energetic, less anxious and depressed, more satisfied and tranquil, and more sociable. Seventy three per cent of the patients felt that the therapeutic effect of Ritanserin was better than that of any previous treatment they had had.

Ceulemans *et al.* (1985) compared the efficacy of Ritanserin and Lorazepam (four milligrams) in patients with generalized anxiety disorders. After two weeks, the patients showed marked improvement on both ten milligrams Ritanserin and four milligrams Lorazepam. Five milligrams Ritanserin was not superior to placebo. The patients on Lorazepam had more side-effects, especially sedation and dizzyness, than those on Ritanserin.

In another study Ceulemans *et al.* (1985), compared the efficacy of different dosages of Ritanserin to four milligrams Diazepam, in patients with generalized anxiety disorder. They found that there was a marked reduction of the Hamilton Anxiety Scale score on ten milligrams Ritanserin, and specifically the somatic symptoms improved markedly.

9.4.3 Chronic schizophrenia

Studies using setoperone, a potent 5HT and moderate dopamine antagonist, showed new possibilities for treating the negative symptoms of chronic schizophrenia (Ceulemans *et al.* 1985). Unfortunately, setoperone has a poor bio-availability, and more studies were done using the more bio-available $5HT_2$ antagonist, Ritanserin.

Ritanserin causes a reduction of the negative and affective symptoms of schizophrenia, such as anergia, anxiety and depression, possibly because it improves the slow wave sleep, which is often impaired in schizophrenic patients.

Another very interesting fact, is that the extrapyramidal side-effects of neuroleptics, improve significantly in patients on Ritanserin. The reduction of tremor was very striking and this effect was later confirmed when patients with Parkinson's disease were treated with Ritanserin (Gelders *et al.* 1985, Janssen 1988, Gelders, 1989).

9.4.4 Sleep

Sleep is restorative and of great importance in most psychiatric disorders. Sleep-wakefulness is the main human circadian rhythm.

Adam and Oswald (1983) did studies during sleep and found that cells divided more during sleep and that it took them less than half the time to divide. The human brain uses one-fifth of the resting body's blood supply. That means that sleep is very important to the body, to renew the brain's functional capabilities. The glucose utilization is reduced by thirty per cent during sleep, which means that there is a lower rate of cellular work, which leads to a higher energy charge and stimulation of protein synthesis. The generalized muscle tone falls to its lowest levels during sleep especially during rapid eye movement (REM) sleep. During slow wave sleep, the main secretions of growth hormone and prolactin occur. Secretions of luteinizing hormone and testosterone are also linked to sleep.

The 5HT system has long been considered important in the organization of sleep. In animals, 5HT levels correlate positively with the occurrence of slow wave sleep. When the brain 5HT levels are increased, by injecting 5HT, L tryptophan or 5-hydroxytryptophan, or by stimulating the raphé nuclei, or by administering MAO inhibitors, slow wave sleep increases. On the other hand, when the 5HT levels are reduced by electrolytic lesions or by the administration of parachlorophenylalanine, slow wave sleep is reduced, and it may even cause total insomnia. This effect could however be reversed by administration of 5-hydroxytryptophan (Idzikowski *et al.* 1987, Janssen 1988).

The concentration of 5HT in the brain and the cerebrospinal fluid has a circadian rhythm which peaks during the night, similar to that of growth hormone and prolactin. Human platelets also show a circadian rhythm of 5HT transport (Modai *et al.* 1986), and they have specific binding sites for lysergic acid diethylamide (LSD). These represent functionally active $5HT_2$ receptors, which resemble the $5HT_2$ receptors in the human brain.

Idzikowski *et al.* (1986) looked at the effect of various 5HT antagonists on sleep:

(a) Methysergide causes a large decrease in REM sleep and no overall change in slow wave sleep, although stage three increases and stage four decreases.

(b) Mianserin causes a decrease in REM sleep time, and in high doses, it increases slow wave sleep.

(c) FU 29-245, a mixed 5HT and dopamine antagonist, causes a fifty seven minute increase in slow wave sleep, but tolerance develops within one week.

(d) Trazodone causes an eleven minute increase in slow wave sleep initially, and a thirty seven minute increase three weeks later (Idzikowski *et al.* 1987).

(e) Ritanserin changes the sleep architecture without producing insomnia. On the polysomnograph, it decreases stages one and two, and increases stages three and four (slow wave sleep). Patients report improvement in the quality and the depth of their sleep.

Studies done to compare the efficacy of Ritanserin, Nitrazepam and placebo, showed that Nitrazepam reduced the REM sleep as well as the slow wave sleep. Ritanserin increased slow wave sleep (plus ninety seven per cent), but it had no effect on wakefulness or sleep onset latency. The REM sleep was unchanged, the duration of light sleep was shortened from one hundred and eighty minutes to one hundred and twenty minutes. The deep sleep was doubled, from ninety minutes to one hundred and eighty two minutes (Janssen 1988).

These effects are not only found after one single dose of Ritanserin, the effects are persistently sustained. Idzikowski (1987) showed that the slow wave sleep was persistently increased; the prolactin and growth hormone responses to L tryptophan were unchanged; and the platelet 5HT receptor binding was undetectable at the end of the treatment, but it recovered two weeks after withdrawal. This is because Ritanserin binds to the $5HT_2$ receptors with high affinity. Because of its very slow dissociation time, it behaves like a virtually irreversible ligand. After withdrawal of Ritanserin, the platelet binding recovers, because of the disappearance of Ritanserin from the plasma, or the renewal of the platelet population, or both.

Increasing doses of Ritanserin increase the duration of slow wave sleep significantly (Idzikowski and Mills 1987) See Figure 7.

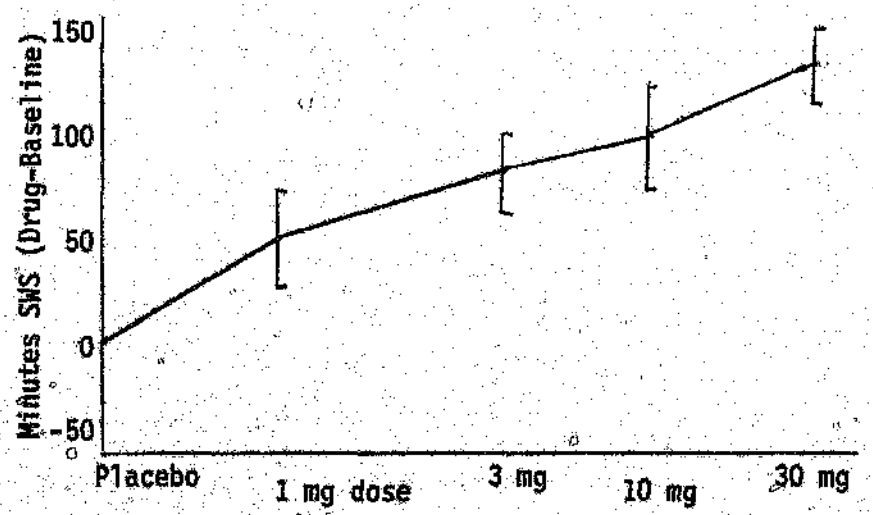


Figure 7: Means and standard errors of SWS duration

It seems paradoxical that 5HT antagonism increases slow wave sleep, but slow wave sleep is under the control of the inhibitory $5HT_2$ and facilitatory $5HT_1$ systems. That is why mixed 5HT antagonists have varying effects on the slow wave sleep and why $5HT_{1B}$ blockers, like propanol, cause insomnia. Ritanserin, which is a $5HT_2$ selective antagonist, causes increases in slow wave sleep. Idzikowski *et al.* (1986) postualted that there might be a link between the $5HT_2$ initiated behaviour and the behaviour itself, or that the $5HT_2$ sites modulate the $5HT_1$ responses.

The beneficial effects of Ritanserin on slow wave sleep (the restorative sleep) will specifically be very important to treat symptoms such as:

(a) sleep disturbances
(b) chronic fatigue and decreased activity
(c) feelings of inadequcy and pessimism
(d) decreased effectiveness
(e) decreased attention
(f) social withdrawl
(g) loss of interest
(h) irritability
(i) inability to respond to praise or reward

These symptoms are mostly found in disorders like dysthymia, generalized anxiety disorder and the negative features of schizophrenia (Janssen, 1988).

PART IV : RITANSERIN DRUG TRIAL

CHAPTER TEN

10. METHODOLOGY

10.1 Introduction

Ritanserin is a centrally acting, relatively selective, extremely potent and long acting $5HT_2$ receptor antagonist. It has been shown to be efficacious in dysthymia, anxiety and the negative features of schizophrenia. It also has a significant effect on the sleep architecture, producing an increase in slow wave sleep, the deep restorative state of sleep (Chapter 9).

The aim of this study was to compare the clinical efficacy of 2,5 mg, 5 mg and 10 mg Ritanserin daily in a placebo controlled way, in patients with dysthymia and the closely related adjustment disorder with depressed mood. It was important to obtain information about the minimum effective dose of Ritanserin in these disorders.

10.2 Patient Selection

10.2.1 Diagnosis

All potential patients were seen at a newly formed dysthymia clinic at Tara, the H Moross Centre. They were selected if they expressed feelings of chronic depression with a feeling of intolerance to these symptoms, according to:

Table 9 Diagnostic Criteria for Adjustment Disorder

A. A reaction to an identifiable psychosocial stressor (or multiple stressors) that occurs within three months of onset of the stressor(s).
B. The maladaptive nature of the reaction is indicated by either of the following: (1) impairment in occupational (including school) functioning or in usual social activities or relationships with others (2) symptoms that are in excess of a normal and expectable reaction to the stressor(s)
C. The disturbance is not merely one instance of a pattern of overreaction to stress or an exacerbation of one of the mental disorders previously described.
D. The maladaptive reaction has persisted for no longer than six months.
E. The disturbance does not meet the criteria for any specific mental disorder and does not represent Uncomplicated Bereavement.

Types of Adjustment Disorder. Code the type according to the predominant symptoms. Specify the stressor(s) and its (their) severity on Axis IV.

309.24 Adjustment Disorder with Anxious Mood
This category should be used when the predominant manifestation is symptoms such as nervousness, worry, and jitteriness.

309.00 Adjustment Disorder with Depressed Mood
This category should be used when the predominant manifestation is symptoms such as depressed mood, tearfulness, and feelings of hopelessness.

309.30 Adjustment Disorder with Disturbance of Conduct
This category should be used when the Predominant manifestation is conduct in which there is violation of the rights of others or of major age-appropriate societal norms and rules. *Examples:* truancy, vandalism, reckless driving, fighting, defaulting on legal responsibilities.

309.40 Adjustment Disorder with Mixed Disturbance of Emotions and Conduct
This category should be used when the predominant manifestations are both emotional symptoms (e.g., depression, anxiety) and a disturbance of conduct (see above).

309.28 Adjustment Disorder with Mixed Emotional Features
This category should be used when the predominant manifestation is a combination of depression and anxiety or other emotions. The major differential is with Depressive and Anxiety Disorders. *Example:* an adolescent who, after moving away from home and parental supervision, reacts with ambivalence, depression, anger, and signs of increased dependence.

309.82 Adjustment Disorder with Physical Complaints
This category should be used when the predominant manifestation is physical symptoms, e.g. fatigue, headache, backache, or other aches and pains, that are not diagnosable as a specific Axis III physical disorder or condition.

309.83 Adjustment Disorder with Withdrawal
This category should be used when the predominant manifestation is social withdrawal without significantly depressed or anxious mood.

309.23 Adjustment Disorder with Work (or Academic) Inhibition
This category should be used when the predominant manifestation is an inhibition in work or academic functioning occurring in a person whose previous work or academic performance has been adequate. Frequently there is also a mixture of anxiety and depression. *Example:* inability to study or write papers or reports.

309.90 Adjustment Disorder not Otherwise Specified
Disorders involving maladaptive reactions to psychosocial stressors that are not classifiable as specific types of Adjustment Disorder. *Example:* an immediate reaction to a diagnosis of physical illness, e.g., massive denial and noncompliance, that is too maladaptive to be categorized as the V code V15.81, Noncompliance with Medical Treatment (p. 380).

Table 10(a)

SCORE

HAMILTON DEPRESSION RATING SCALE (see annex for detailed explanation and scoring)	VISIT
Date	../../..
1. Depressive mood ..... (0-4)	
2. Feelings of guilt ..... (0-4)	
3. Suicide ..... (0-4)	
4. Insomnia (early) ..... (0-2)	
5. Insomnia (middle) ..... (0-2)	
6. Insomnia (late) ..... (0-2)	
7. Work and activities..... (0-4)	
8. Retardation ..... (0-4)	
9. Agitation ..... (0-2)	
10. Anxiety psychic ..... (0-4)	
11. Anxiety somatic ..... (0-4)	
12. Somatic sympt. - gastro-intest. (0-2)	
13. Somatic symptoms - general .... (0-2)	
14. Genital symptoms ..... (0-2 or 9)	
15. Hypochondriasis ..... (0-4)	
16. Loss of weight ..... (0-2)	
17. Insight ..... (0-2)	
Total score	
Body Weight (Kg)	

Table 10(b) Hamilton Depression Rating Scale*

1. **DEPRESSIVE MOOD: (sadness, hopeless, helpless, worthless).**
   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 = patient reports 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 at suicide (any serious attempt rates 4).

4. **INSOMNIA: EARLY:**
   0 = no difficulty falling asleep; 1 = complains of occasional difficulty falling asleep (more than ½ 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 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; 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: (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)**
   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 = "playing with hands", hair etc...; 2 = 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 apparent in face or speech; 4 = fears expressed without questioning.

11. **ANXIETY SOMATIC: Physiological concomitants of anxiety, such as: gastro-intestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching; cardiovascular - palpitations, headaches; respiratory - hyperventilation, sighing; urinary frequency; sweating.**
    0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = incapacitating.

12. **SOMATIC SYMPTOMS GASTRO-INTESTINAL**
    0 = none; 1 = loss of appetite but eating without staff encouragement. Heavy feelings 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, headache, muscle ache. Loss of energy and fatiguability; 2 = any clear-cut symptom rates 2.

14. **GENITAL SYMPTOMS: Symptoms such as loss of libido, menstrual disturbances.**
    0 = absent; 1 = mild; 2 = severe; 9 = not ascertained.

15. **HYPOCHONDRIASIS:**
    0 = not present; 1 = self-absorption (bodily); 2 = preoccupation with health; 3 = frequent complaints, requests for help, etc.; 4 = hypochondrical delusions.

16. **LOSS OF WEIGHT**
    0 = less than 1 lb (0.5 kg) weight loss in week; 1 = greater than 1 lb (0.5 kg) weight loss in week; 2 = greater than 2 lb (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.

* M Hamilton: "Development of a Rating Scale for Primary Depressive Illness". Brit. J. soc. clin. Psychol 6: 278-296 (1967).

Table 11a and b

VISIT

LEEDS DEPRESSION RATING SCALE

(Score: a = 3; b = 2; c = 1; d = 0 · EXCEPT for No.s 7, 11, 13 where the score should be reversed)

Patient's Initials: ..... ***Sex:*** ..... ***Qualifications:*** .....

Birth date: ...../...../..... ***Age:*** ..... ***Date:*** ...../...../.....

Please underline one of the options of each of the following 13 items according to how you are feeling now or have been feeling for the past two days:

Score

1. *I wake up very early and, if I go back to sleep, I sleep very badly.*
   a) always b) sometimes c) rarely d) never ☐

2. *I feel scared or frightened for no apparent reason.*
   a) always b) sometimes c) rarely d) never ☐

3. *I feel very down and sad.*
   a) always b) sometimes c) rarely d) never ☐

4. *I feel distressed when I go out alone.*
   a) always b) sometimes c) rarely d) never ☐

5. *I have lost all interest in everything.*
   a) always b) sometimes c) rarely d) never ☐

6. *I frequently experience palpitations and/or abdominal and chest discomfort.*
   a) always b) sometimes c) rarely d) never ☐

7. *I still like to do the things I used to do.*
   a) always b) sometimes c) rarely d) never ☐

continued/...

8. I feel scared or terrified.

a) always b) sometimes c) rarely d) never

9. I feel that there is no point in life.

a) always b) sometimes c) rarely d) never

10. I feel tense or anxious.

a) always b) sometimes c) rarely d) never

11. I think it is easy to do the things I used to do.

a) always b) sometimes c) rarely d) never

12. I feel dizzy or loosing my balance.

a) always b) sometimes c) rarely d) never

13. I have a good appetite.

a) always b) sometimes c) rarely d) never

14. I feel restless and cannot stand still for a moment.

a) always b) sometimes c) rarely d) never

15. I feel more irritable than usual.

a) always b) sometimes c) rarely d) never

TOTAL

Please make a m( ) on the line to show how anxious and tense you are feeli g at this moment:

For example, someone feeling just a little anxious would make a mark like this:

Very calm and relaxed _____|_____ Very anxious and tense

According to how you are feeling now, make a mark on this line:

Very calm and relaxed _____ Very anxious and tense

(a) DSM III R criteria for dysthymic disorder (Table 1)

(b) DSM III R criteria for adjustment disorder with depressed mood (Table 9)

10.2.2 Rating scales

Patients were scored on the Hamilton Depression Rating Scale (Table 10a and b). For the item "middle insomnia" an initial score of at least one was required, for the item "work and activities" the score at selection had to be at least two, and for the item "suicide" the initial score was not allowed to exceed one.

As a corellative exercise the Leeds Self Evaluation Scale was scored concomitantly (Table 11a and b).

10.2.3 Age

The patients had to be older than eighteen years.

10.2.4 Sex

Male and female patients were included. However, only those female patients who were using adequate contraception, those who had been sterilized, or postmenopausal women were included.

Table 12

INFORMED CONSENT

PATIENT DECLARATION

Ritanserin is a new Anxiety decreasing and Mood elevating agent which has been developed and extensively researched by Janssen Pharmaceutica.

In order to remove all causes of bias in the study it is necessary that the medication will be compared against an inactive tablet called a placebo tablet. Neither the patient or the doctor will know exactly which tablet is being taken until the study is finished.

If at any time you are unhappy with any aspect of this trial you will be free to leave it.

I _____ hereby certify that I have read the above statement and consent to take part in the trial.

SIGNED _____ this _____ day of _____ 199_

_____

_____

DOCTORS DECLARATION

I _____ hereby certify that I have explained the above trial and attendant risks to the above patient.

SIGNED _____

10.2.5 Informed consent

All patients were asked to give informed consent. A full explanation was given to patients about the disorder and the tri[illegible], and a lot of time was spent answering their questions or queries. This increased the compliance (Table 12).

10.3 Exclusion Criteria

10.3.1 Patients suffering from concomitant mental illness other than the target indication

10.3.2 Patients with serious physical illness affecting the liver, kidneys or thyroid.

10.3.3 Patients with significant cardiac conditions.

(a) Sinus bradycardia (less than fifty beats per minute).

(b) All heart blocks.

(c) Angina secondary to arteriosclerotic disease.

(d) Congestive heart or left ventrivular failure.

(e) Right ventricular failure secondary to pulmonary hypertension.

(f) Wolf Parkinson White Syndrome.

(g) Prolongation of QT_c interval greater than four hundred and fifty milliseconds.

10.3.4 History of abuse of alcohol and other psycho active drugs

10.3.5 Women who were breast feeding, pregnant or likely to become pregnant. Pre-menopausal women had to be using oral contraceptives or an intra-uterine device.

10.3.6 Patients with an initial score below eight on the Hamilton Depression Rating Scale; with initial score below one for "middle insomnia"; below two for "work and activities" and above one for "suicide".

10.3.7 Patients younger than eighteen years.

10.4 Concomitant Medication

Patients were allowed to continue using medication taken for chronic organic disorders, except for beta-blockers, which had to be discontinued. No psychotropic drugs were allowed, except benzodiazepines, and only if the patients were already on controlled benzodiazepine therapy, and the dosage had to stay the same.

10.5 Study Design

10.5.1 Medication

The patients were supplied with active tablets or placebo all identical in appearance from Janssen Pharmaceutica, Beerse, Belgium. The first seven days the patients received a single blind packet of placebo tablets as a run in period. After that ( ) tablets were dispensed in a double blind way. The daily dose was one tablet in the morning after breakfast with fifteen patients receiving Ritanserin two point five milligrams, fifteen receiving five milligrams, fifteen receiving ten milligrams and fifteen receiving matching placebo tablets.

10.5.2 Evaluations

The patients were always evaluated by the same clinician. They were seen on the day of selection (day -7), after the one week placebo run-in period (day 0) then at two weekly intervals: day 14, day 28 and day 42.

The following examinations were done:

(a) Behaviour examination

During every visit scores were done on the Hamilton Depression Rating Scale, the Leeds Self Evaluation Scale, and the Average Clinical Global Impression Scale (Table 13). Side-effects were also listed on Table 14.

Table 13

Clinical Global Impression CGI Part 1		Score	Visit 1 D-7	Visit 2 D0	Visit 3 D14	Visit 4 D28	Visit 5 D 42
Severity of Disease	Impossible to evaluate	9					
	Not ill	0					
	Barely ill	1					
	Slightly ill	2					
	Moderately ill	3					
	Obviously ill	4					
	Severely ill,	5					
	Extremely ill	6					
Global Development. Note change as compared to onset of study)	Impossible to Evaluate	9					
	Striking Improvement	0					
	Apparent Improvement	1					
	Slight Improvement	2					
	No change	3					
	Slight Deterioration	4					
	Obvious Deterioration	5					
	Striking Deterioration	6					

Clinical Global Impression CGI Part 2		Score	Visit 1 D-7	Visit 2 D 0	Visit 3 D 14	Visit 4 D 28	Visit 5 D42
Therapeutic Effect	Impossible to Evaluate	9					
	Excellent: (almost) total disappearance of all symptoms	0					
	Adequate: apparent improvement – incomplete disappearance of symptoms	1					
	Weak: insufficient improvement – treatment is continued	2					
	THERAPEUTIC EFFECT NIL OR DETERIORATION	3					
Side-Effects	Impossible to evaluate	9					
	Nil	0					
	Slight	1					
	Severe	2					
	Therapeutic Effect is abolished	3					

Table 14

Side Effect Checklist	Visit 1 (Recruitment) Day-7		Visit 2 Day 0		Visit 3 Day 14		Visit 4 Day 28		Visit 5 Day 42	
	*	**	*	**	*	**	*	**	*	**
1. Fatigue										
2. Drowsiness										
3. Aggressiveness										
4. Muscle Rigidity										
5. Muscle Weakness										
6. Sleep Disturbances										
7. Tremor										
8. Dizziness										
9. Blurred Vision										
10. Heavy Headed										
11. Light Headed										
12. Headache										
13. Concentration										
14. Speech Difficulty										
15. Dry Mouth										
16. Constipation										
17. Nausea										
18. Other										

* Degree: 0 = Absent, 1 = Slight (Not uncomfortable), 2 = Moderate (uncomfortable), 3 = severe (Interruption of Medication necessary)

**Frequency: A = at onset of therapy, b = after each dose, c = continuously.

Table 15

Investigator:	Med No.:	Pat. Init.: .....

Parameters		Units	Normal values	Day 0 (- end run-in period)	Day 42 (- week 6 of DB-medicat.)
			Date	../../..	../../..
HEMATOLOGY					
RBC		(x 10^{12}/ℓ)			
Hematocrit		(g%)			
Hemoglobin		(mmol/ℓ)			
WBC		(x 10^{9}/ℓ)			
Differ.	Total neutrophils	(%)			
	Lymphocytes	(%)			
	Monocytes	(%)			
	Eosinophils	(%)			
	Basophils	(%)			
Segmented polys		(%)			
Platelet count		(x 10^{8}/1)			
Sedimentation rate (1 h)		(mm)			
BLOOD CHEMISTRY					
Sodium		(meq/ℓ)			
Potassium		(meq/ℓ)			
Chloride		(meq/ℓ)			
Calcium		(meq/ℓ)			
Glucose (fasted)		(mg/100 mℓ)			
Bilirubin (total)		(mg/100 mℓ)			
Creatinin		(mg/100 mℓ)			
Protein (total)		(g/100 mℓ)			
- Albumin		(g/100/mℓ)			
- Globulin		(g/100 mℓ)			
Cholesterol		(mg %)			
Alkaline phosphatase		(U/ℓ)			
AST (GOT)		(U/ℓ)			
ALT (GPT)		(U/ℓ)			
URINALYSIS					
Specific gravity		--			
pH		--			
Albumin		(g/ℓ)			
Glucose		--			
Acetone		--			
Microscopic examination (if abnormal specify):					

(b) Physical examination

Upon selection, the patients had to have a full physical examination and thereafter body weight, blood pressure and pulse rates were done at every visit.

(c) Special investigations

A battery of investigations was done after the one week placebo run in period and again at the end of the study. That included an electrocardiogram and the investigations as listed in Table 15

(d) Global evaluation of treatment

At the end of the study the overall therapeutic result was compared with that of previously administered psychotropic medications.

10.5.3 Interruption or Premature Discontinuation

The duration of each interruption and/or the date of premature discontinuation, plus the reason for it was recorded clearly.

CHAPTER ELEVEN

11. RESULTS

11.1 Recruitment

The recruitment of patients for the study was very slow. It took two years to find sixty suitable patients, despite the fact that all the psychiatrists in the area, were aware of the project.

There must be many dysthymic patients who never came to the attention of the dysthymia clinic. Most of these patients are probably seen by general practitioners with somatic complaints and anxiety. They are also seen by clinical psychologists or church counsellors because of complications of their dysthymia, namely marital problems, relationship problems or suicide attempts.

Some patients who had benefited from the clinic, were referring relatives or friends to the clinic.

11.2 Compliance

Overall, the compliance was very good. Unfortunately though, seven patients did not quite finish the study, but enough data could be obtained from them, to be able to use them in the study.

11.3 Sociodemographic Data

Although it was a small sample, some interesting data could be obtained.

11.3.1 Patient age

The age of the patients was between twenty years and above sixty years. The biggest percentage was between thirty years and fifty years (see figure 8). Some of the patients older than sixty years had been depressed for more than forty years of their lives.

11.3.2 Patient sex

From the onset a predominance of female patients was expected, but in the end the ratio males to females was forty three per cent to fifty seven per secent (Figure 9).

11.3.3 Marital status

Dysthymic patients are apparently not good marriage material. Even though the biggest proportion was married, they were mostly unhappily married, or in stagnant marriages where they could not decide whether to continue in an unhappy marriage or to get divorced. Twenty seven per cent of the sample had never been married before, and if one takes into account that the main age group was between thirty years and fifty years, it probably shows that many dysthymics remain single into middle age (Figure 10).

PATIENT AGE

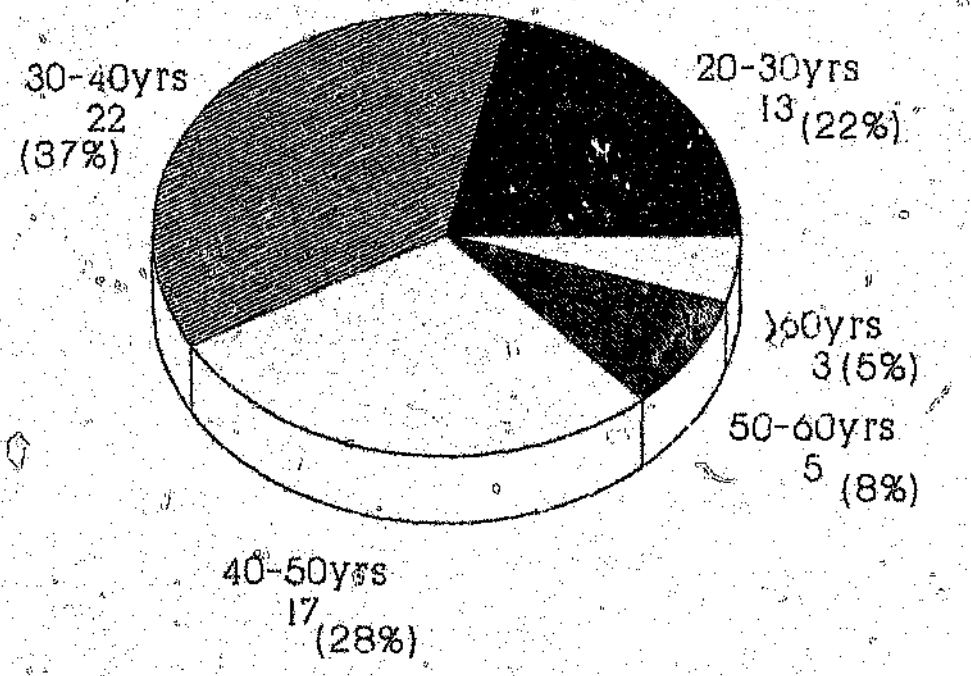


Figure 8

PATIENT SEX

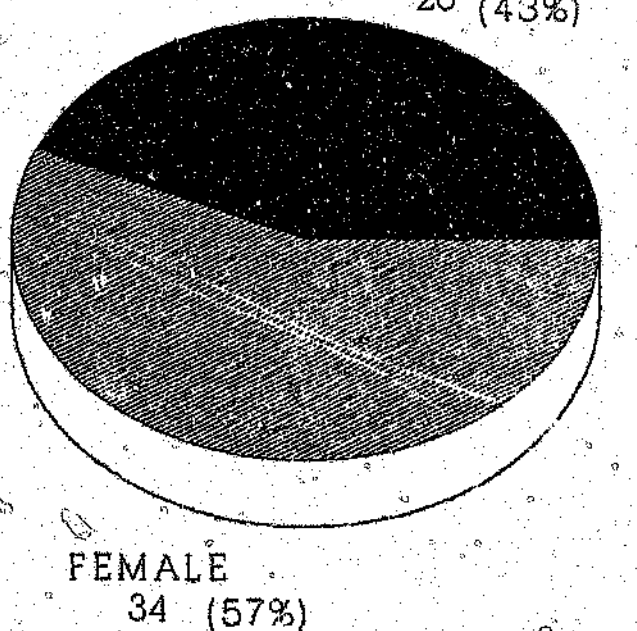


Figure 9

MARITAL STATUS

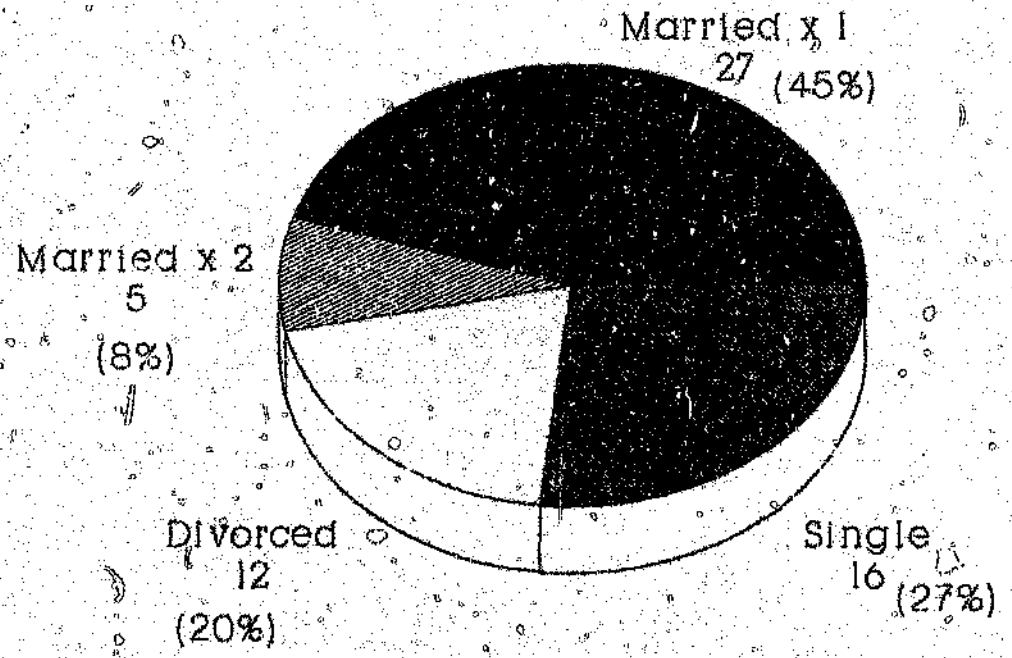


Figure 10

11.3.4 Culture

Figure 11 has to be interpreted with caution, since it was very dependent on referral sources. There was a big input from Afrikaans church counsellors, whereas the Jewish population was probably under-represented. Under "other" - there was one German patient, one Black patient, one Indian patient, one Lebanese patient and one French patient.

11.3.5 Academic qualifications

The general subjective feeling was, that the patients who attended the dysthymia clinic had higher qualifications and relatively better functioning than the usual Tara Hospital out patients.

The data in Figure 12, did indeed show that the largest percentage of patients had at least passed matric and thirty five per cent had a university degree. It was also interesting that twenty two per cent of the patients were professional people. Twenty eight per cent of the patients did creative activities (Figure 13) such as being painters, musicians, poets and writers. They were often very philosophical people who struggled with existential issues.

CULTURE

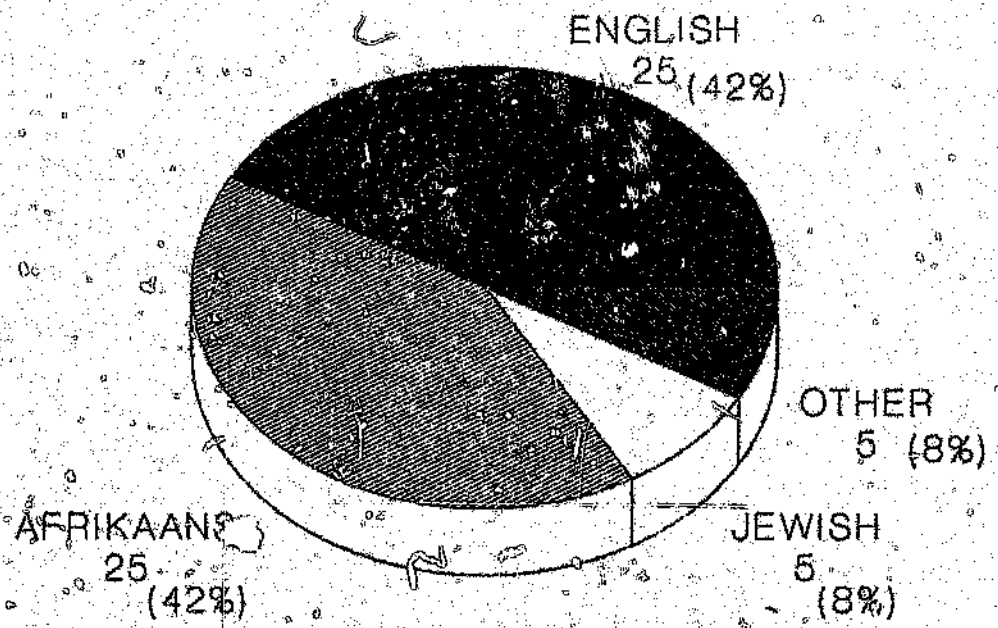


Figure 11

ACADEMIC QUALIFICATIONS

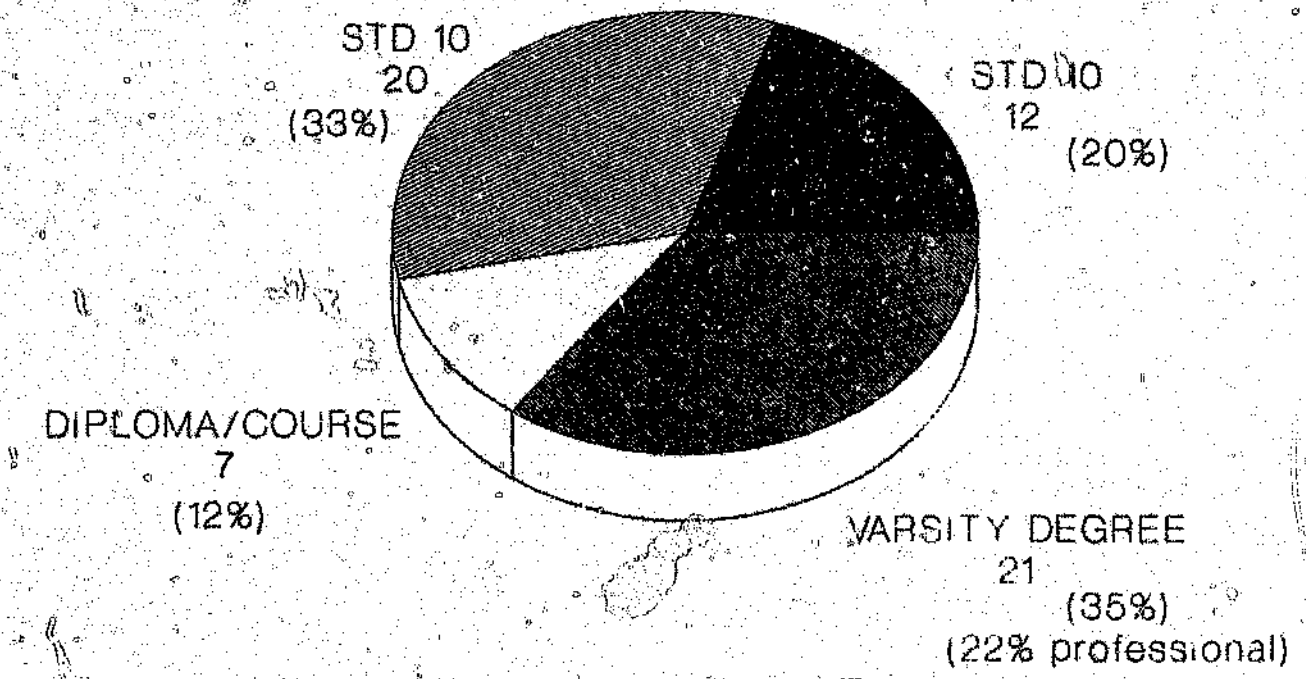


Figure 12

CREATIVITY

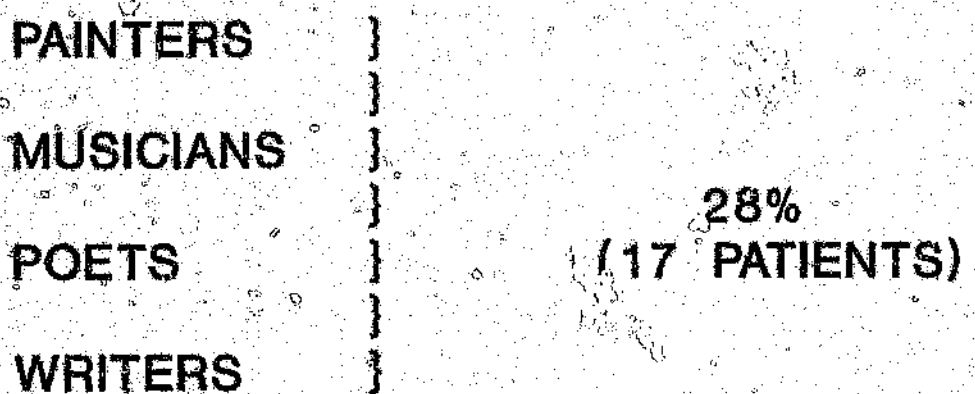


Figure 13

11.4 Other Factors

11.4.1 Family history of psychiatric disorders

A positive family psychiatric history was amazingly high in this group of patients. Many patients had more than one affected family member with different diagnoses, for instance, a paternal uncle who suffered from major depression and a father who was an alcoholic.

Figure 14 shows that the largest percentage of dysthymic patients had a positive family history of mood spectrum disorders (dysthymia, unipolar depression, bipolar mood disorder). Suicide and alcohol related problems were also quite frequently encountered in the family history.

11.4.2 Duration of symptoms

In most cases the patients had been depressed for much longer than the specified two years as required by the DSM III R cirteria for dysthymic disorder.

Many patients could recall being unhappy, serious and over-compliant children and adolescents. Many patients used the phrases "I have been depressed as long as I can remember" or "I was born depressed". This meant that they had been depressed and miserable for such a long time, that they had difficulty describing their "premorbid" personalities. It also made them very difficult and demanding patients and they were quite desperate to try any help that was offered.

FAMILY PSYCHIATRIC HISTORY

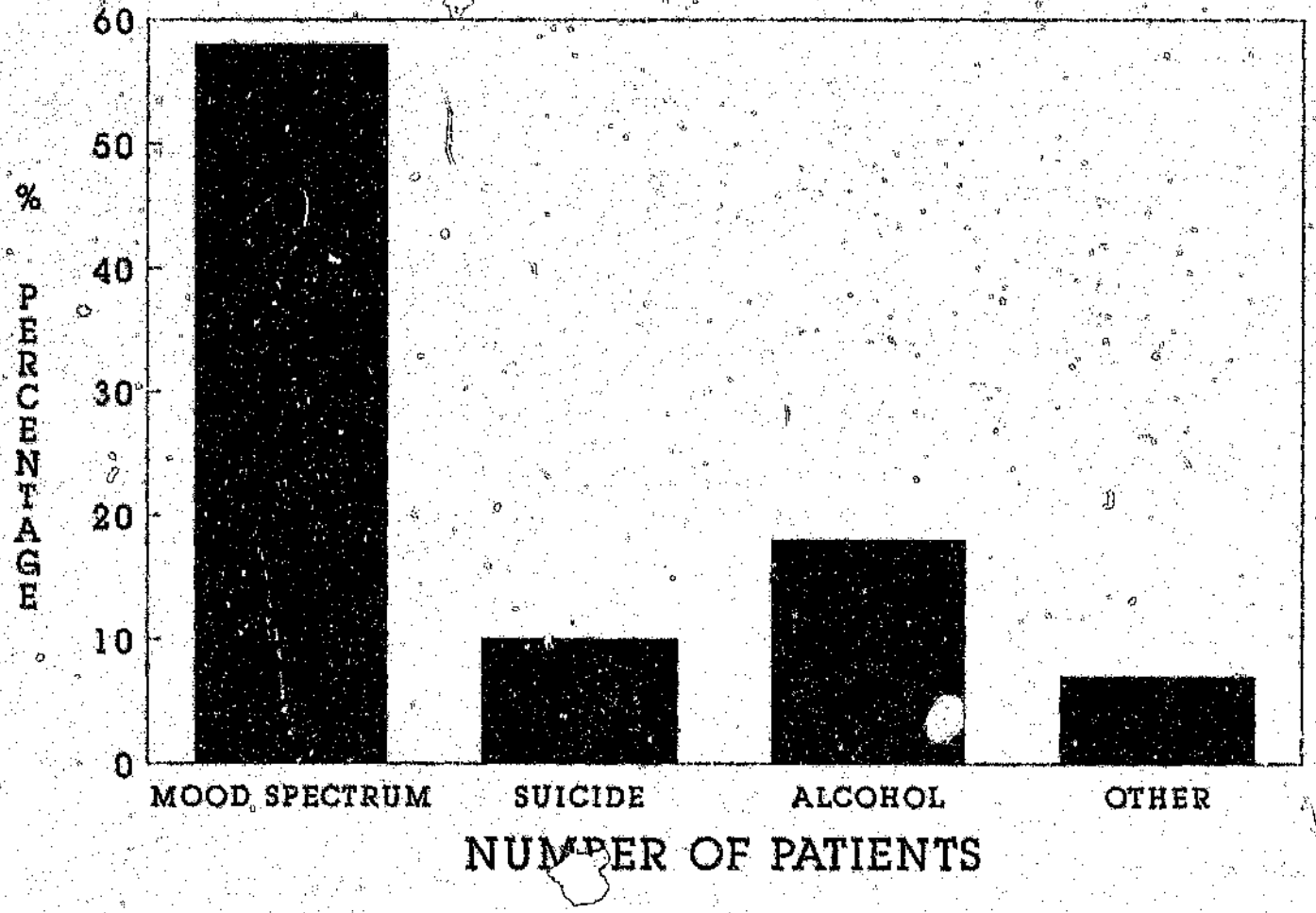


Figure 14

11.5 Side-Effects

The side effects were very mild and very few and occurred in all four groups (also the placebo group). Many of the "side-effects" were compatible with symptoms of anxiety and depression, which are symptoms of dysthymia. The side-effects were recorded at every visit and the patients usually only complained about them at one or two visits, with no complaints at other times. Those patients who did have side-effects though, still found them much less severe than the side effects they experienced on other antidepressants in low dosages.

The minor side-effects that were found, included nausea, headaches, dizzyness, dry mouth, blurred vision, fatigue, muscle weakness, nightmares and aggression.

The patients were weighed at every visit and there was specifically no weight increase while the patients were taking Ritanserin. Many other antidepressants cause weight gain which is often a reason for non-compliance.

The blood tests, uninalysis and electrocadiogram showed no changes before and after treatment.

11.6 Rating Scale Results

The Bonferroni multiple comparison procedure of one way analysis of variance was used to compare the changes in the Hamilton Depression Rating Scale and the Leeds Self Evaluation Scale from day 0 (start of double blind medication) to day 42 (the end of the study). For the Clinical Global Impression scale the Chi-squared text was used.

Figures 15, 16 and 17 show the mean values on the three rating scales for each group.

It is clear that all four groups showed significant improvement in all the scores, even the placebo group.

Table 16 shows clearly that there was no statistically significant difference between the groups on the Hamilton Depression Rating Scale scores.

11.7 Conclusion

Major problems arose in recruiting patients although there was an impression that there were many dysthymics in the community. The problem of the rarity of "pure dysthymics" as described by Akiskal (1981), Keller and Sessa (1990) and Keller and Lavori (1984) probably played a major role in this problem. One should also look critically at the criteria of DSM III R, which on the one hand exclude many patients, and on the other hand include many patients who probably are suffering more from anxiety or even personality disorders. The validity of dysthymia may be questionable.

The sociodemographic data were consistent with that of the literature, although the sample size was small.

The results showed that all four groups improved significantly on the Hamilton Depression Rating Scale score and the Leeds Self Evaluation Scale, but there was no significant difference between the groups. So, although the patients in all four groups improved objectively and subjectively (even in the placebo group) there was no difference between these patients on any dose of active medication and placebo.

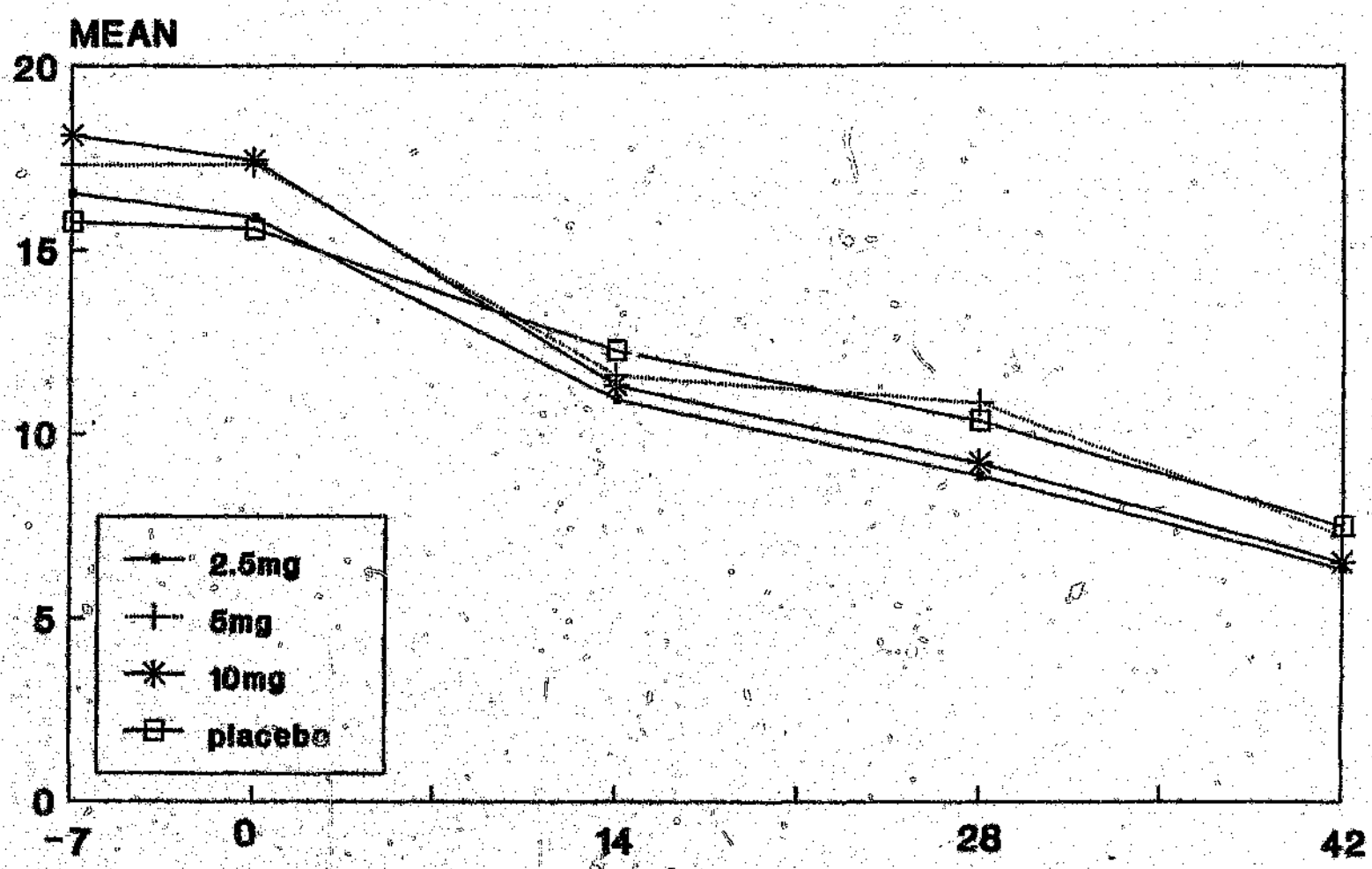
There are some possible explanations for these results:

1. The sample size was too small (only fifteen per group).
2. The study was too short. Six weeks of treatment after the one week placebo run in is very short when one is treating a disorder that has been there for more than two years, and often a whole lifetime. No consideration was given to the follow-up time after the trial, when many patients who originally seemed to be responding, relapsed and stopped the trial medication.
3. This group of patients is known to respond to placebo. They are so desperate, that they are willing to try anything, because they have all been told in the past to pull themselves together. They were not able to unload their burdens and to get regular focused attention by the same clinician and that must surely have influenced their response.

4. Because of the vagueness of the DSM III R criteria, one was probably not looking at a homogenous group of patients.
5. The results were based on the scores on the rating scales and that was very dependent on what kind of a day the patient was having at the time. It might also not have been measuring real improvement.

In future one might have to do studies with larger sample sizes, for longer periods of time, and maybe using different criteria and rating scales. Unfortunately the dose of Ritanserin could not be increased safely, because of its cardiotoxicity in larger doses (Van Rooy *et al.* 1987).

It might be appropriate to do more studies on sleep disorders, since Ritanserin seems to have such a clear beneficial effect on especially slow wave sleep.



Average Hamilton Depression score

Figure 15

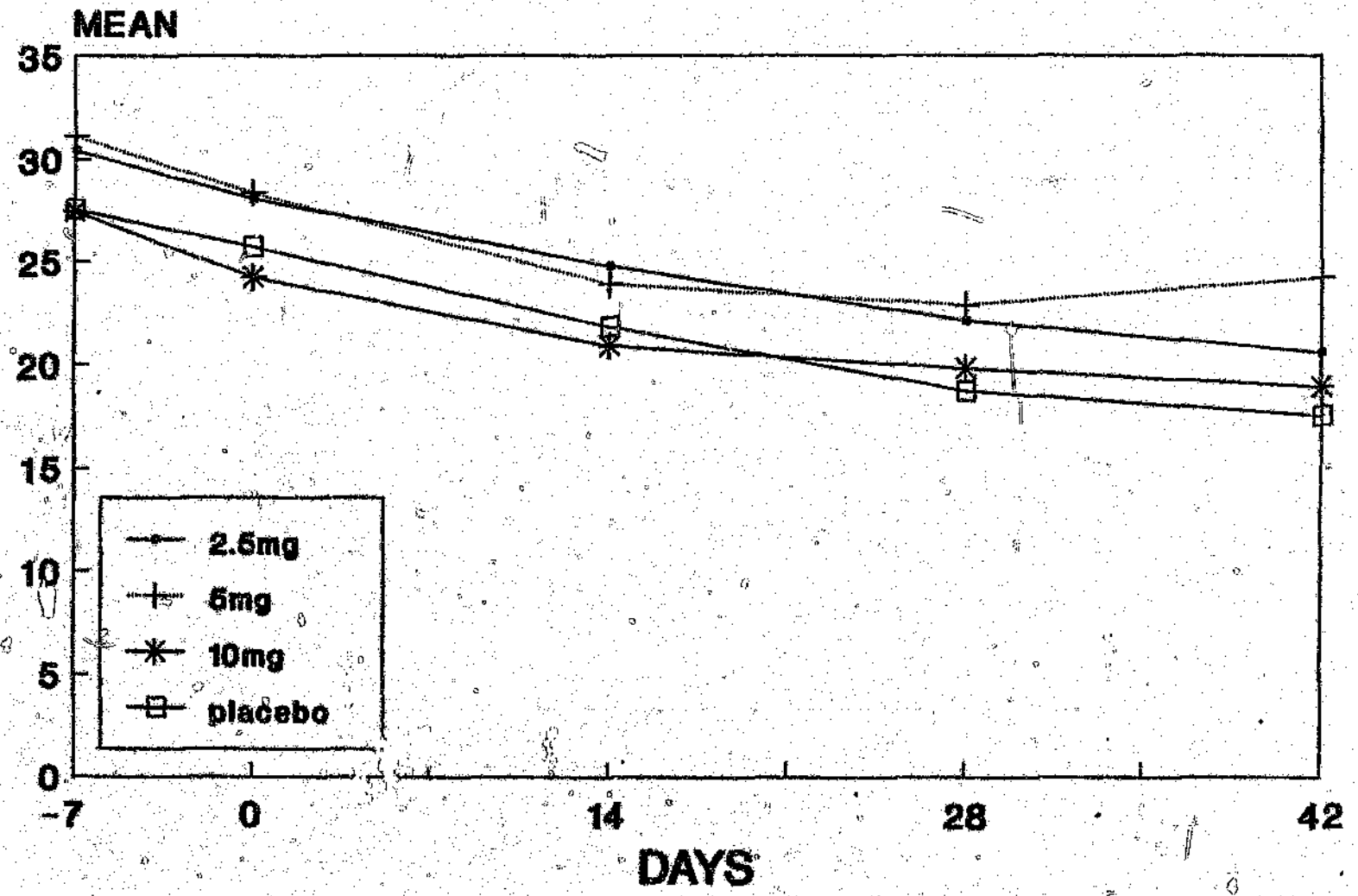


Figure 16

Average Leeds Depression score

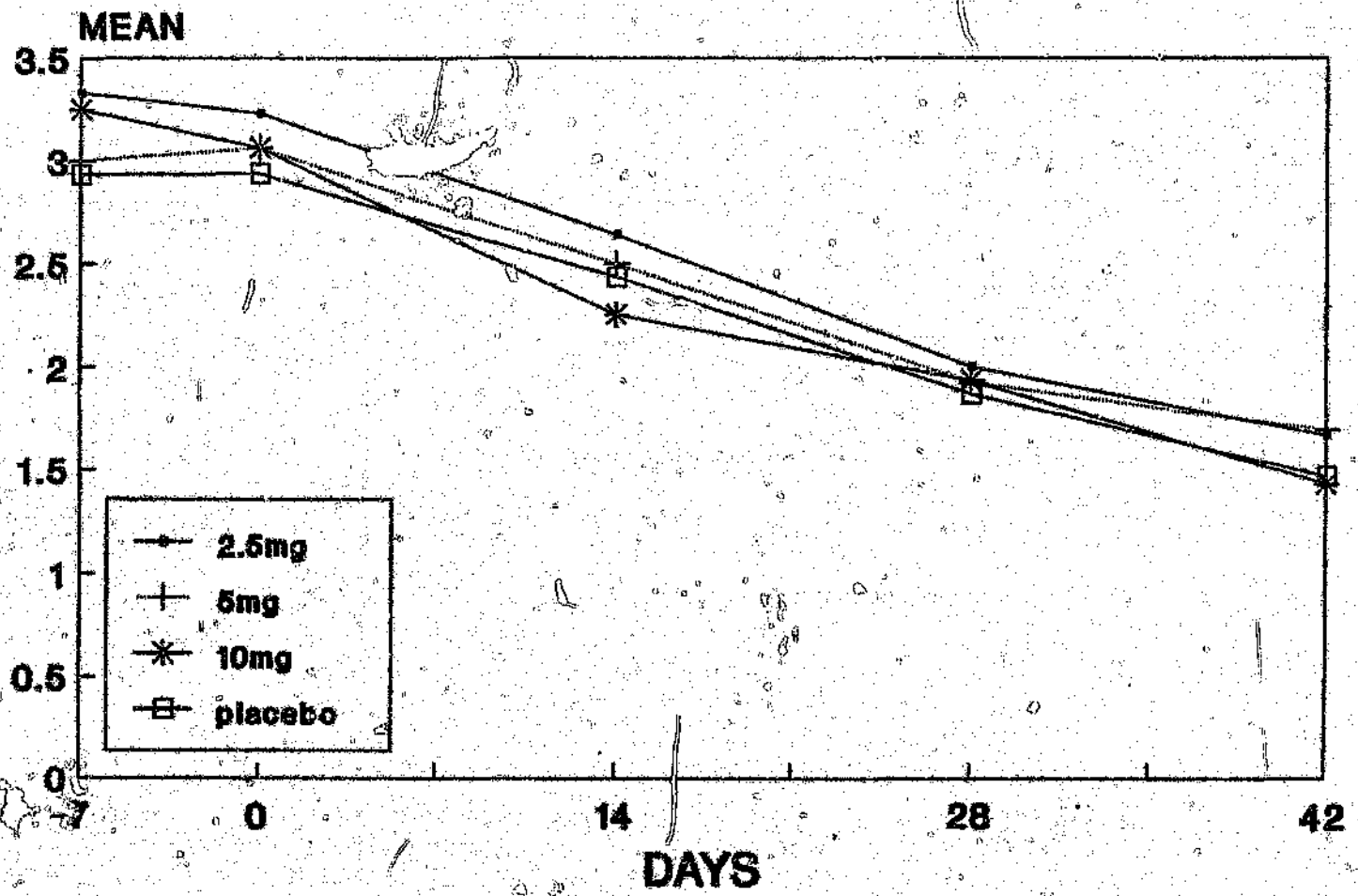


Figure 17 Average Clinical Global Impression

Table 16

COMPARATIVE CHANGES DAY 0 TO DAY 42

(HAMILTON DEPRESSION RATING SCALE)

		2.5 mg	5 mg	10 mg	Placebo	P value
Day 0	Mean	15,867	17,333	17,437	15,562	
	S.D.	4,486	7,575	5,853	3,741	0,7011
	number	15	15	16	16	
Day 42	Mean	6,333	7,231	6,500	7,467	
	S.D.	5,105	5,134	5,488	7,140	0,9477
	number	12	13	14	15	
Change from Day 0 to Day 42	Mean	-9,750	-10,833	-11,000	-8,000	
	S.D.	3,911	7,4813	4,0950	5,2508	0,4192
	number	12	12	14	15	
	p-value	<0.0001	0,0004	0,0000	0,0000	

(Bonferroni multiple comparison procedure used)

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