# LITHIUM THERAPY AND THE EFFECTS OF ITS DISCONTINUATION IN AFFECTIVE DISORDERS

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# DEDICATION

This thesis is dedicated to

My wife and sons

My parents and family

and to all researchers who live and work in developing countries

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Needless to say, the individuals mentioned here are responsible only for the virtues and none of the vices of what follows.

# DECLARATION

This thesis was composed and the work done by myself apart from the contributions which have been acknowledge above.

Fabio Gomes de Matos e Souza

# PAPERS

SOUZA FGM, MANDER AJ, GOODWIN GM (1990) The efficacy of lithium in prophylaxis of unipolar depression. Evidence from its discontinuation. *British Journal of Psychiatry* **157**, 718-722.

SOUZA FGM, GOODWIN GM (1991) Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. *British Journal of Psychiatry* **158**, 666-675.

SOUZA FGM, MANDER AJ, FOGGO M, DICK H, SHEARING CH, GOODWIN GM (1991) The effects of lithium discontinuation and the non-effect of oral inositol upon thyroid hormones and cortisol in patients with bipolar affective disorder. *Journal of Affective Disorders*, **22**, 165-170.

AUSTIN M-P V, SOUZA FGM, GOODWIN GM (1991) Lithium augmentation in antidepressant resistant patients: a quantitative analysis. *British Journal of Psychiatry* **159**, 510-514.

## ABSTRACT

The study assessed the evidence for the efficacy of lithium in the acute treatment and prophylaxis of unipolar depression and as an augmentation drug in treatment resistant depression. It examined the relationship between hormonal changes, lithium discontinuation and relapse in bipolar illness. Finally, it investigated the addition of inositol in the diet of bipolar patients as an alternative treatment for lithium side effects.

The specific aims were:

1) to assess the efficacy of lithium in unipolar depression by comparing readmission rates in patients after lithium discontinuation and in patients who continued to take lithium as a prophylactic agent, and evidence for a lithium withdrawal syndrome in unipolar patients during the first three months of discontinuation.
2) to analyze quantitatively the results of lithium trials in the acute treatment and prophylaxis of unipolar depression in order to estimate the therapeutic value of lithium by measuring an overall effect size.
3) to investigate the neuroendocrine changes involving thyroxine (T4), thyroid stimulating hormone (TSH) and cortisol before and after lithium discontinuation in bipolar patients and to test whether they are related to the withdrawal syndrome observed in these patients.
4) to evaluate the effects of adding inositol to the diet of clinically stable bipolar patients on prophylactic lithium upon thyroxine (T4) and thyroid stimulating hormone (TSH) concentrations and on other peripheral side-effects of lithium, comparing the results to those found in a group of normal controls not taking lithium.
5) to assess the efficacy of lithium augmentation in treatment resistant depression by reviewing, using quantitative techniques, the controlled trials on the topic.

RESULTS

1) forty patients who discontinued lithium therapy were compared with 105 patients who continued the drug and served as a control group. The time to readmission from starting on lithium was compared in a phase while both groups were still on lithium and in a second phase after discontinuation in one group and further continuation in the control group. The progressive increase in the probability of recurrence over a two year follow-up interval was greatest after discontinuation of lithium. For the patients who eventually discontinued lithium, the cumulative probability of recurrence in two years was 0.08 on lithium and 0.58 after stopping it. The probability of recurrence was unchanged over the duration of the study for patients who continued to take lithium. There was no evidence of a lithium withdrawal syndrome within three months of stopping the drug. No evidence of a seasonal pattern in readmissions of the patients who discontinued lithium was found. The results provide evidence for a major benefit from lithium prophylaxis of unipolar depression under ordinary clinical conditions and no evidence of a withdrawal syndrome.

2) meta-analysis was used to establish the efficacy of lithium in acute treatment and prophylaxis of depressive illness from existing published trials. Effects sizes were measured by the odds ratio and Pearson correlation coefficient. Some benefit from lithium, compared with other treatments, emerged from trials of acute treatment. Lithium was superior to placebo in the acute treatment of bipolar depression. In the controlled studies of lithium prophylaxis, a substantial effect was revealed when lithium was compared with placebo. For uncontrolled trials a similar effect size was found, which corresponded to an improvement in the rate of favourable outcome from 35% for placebo to 70% with lithium treatment. The comparison of lithium with other antidepressants in prophylaxis showed no clear advantage for lithium in unipolar illness.

3) thyroid and adrenal functions were assessed in euthymic bipolar patients stable on prophylactic lithium for at least one year before and after lithium discontinuation in a randomised double-blind placebo-controlled trial. All hormonal measurements were within the normal range, but a significant increase ($p<0.001$) in serum T4 levels and decrease ($p<0.01$) in TSH levels were observed after one month of lithium withdrawal while cortisol

concentrations showed a non-significant decrease in the same period. This result suggests that long-term lithium did not induce evident hypothyroidism but it has lowered thyroid function (T4) to the bottom segment of the normal range while elevating TSH to the top region of the normal values. Both alterations were reversible after lithium discontinuation.

4) a pilot trial was designed to add inositol to the diet of bipolar patients being treated with prophylactic lithium and to that of normal controls for eleven days. No modification was shown in thyroid (T4) and pituitary (TSH) function in either group before or after inositol administration. Inositol did not alleviate other side-effects such as tremor and thirst in the patient group. This result suggests that short-term dietary inositol is of little use in reducing thyroid and other adverse effects of lithium prophylaxis.

5) a quantitative analysis was used to examine the efficacy of lithium augmentation in the acute treatment of depressed patients resistant to a standard trial of an antidepressant. Effect sizes were measured by the odds ratio using the Mantel-Haenszel method. Only controlled trials were included in order to minimise methodological bias. A highly statistically significant effect for lithium augmentation was found, measured by the pooled odds ratio (0.14) and its 95% confidence interval (0.05 to 0.44). In other words the odds of remaining ill are reduced by between 56% and 95% with the use of lithium treatment. While these results support the case for lithium augmentation in treatment-resistant depression, there remains considerable uncertainty over the duration of treatment necessary to see and sustain a response to lithium augmentation.

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# CHAPTER 1

# INTRODUCTION

Psychopharmacology is certainly one of the most important instruments in modern psychiatric practice. The prescription of drugs for treatment and prophylaxis of mental disorders has changed the management of the mentally ill dramatically in the last 40 years. The introduction of effective drugs in the treatment of severe mental illness has allowed patients to live in their communities instead of being isolated in mental institutions. A wide range of pharmacological products are now available (antidepressants, anticonvulsants, neuroleptics, tranquillisers, etc) for the different psychiatric syndromes. In the therapy of affective disorders, lithium was one of the first psychotherapeutic drugs to be introduced.

The importance of lithium therapy has changed considerably since 1960. In that year, the textbook *The Pharmacological Basis of Therapy* by Goodman and Gilman stated that the lithium ion has "no therapeutic applications". At the moment, lithium is probably the most widely investigated psychoactive drug (Prien and Potter, 1990). By the mid-1970's there were approximately 3000 medically-related articles on lithium. This number increased by an average of 1000 a year so that the medical literature related to lithium totaled well over 19000 articles by 1990 and continues to expand rapidly (Jefferson, 1990). In clinical practice, the importance of lithium can be measured by its widespread use. In the United Kingdom, approximately one person per 2000 of the population is taking lithium (Johnson, 1984).

Important advances have been made in understanding how lithium acts and its biochemical, therapeutical and psychological effects. Despite 40 years of lithium research, however, significant gaps still exist in our knowledge of the

use of lithium in affective disorders and especially in depressive illness. These gaps defined the aims of the present investigations.

*AIMS*

The main objectives of this study were to examine the usefulness of lithium in unipolar depression; to assess the consequences of lithium discontinuation; to investigate the addition of inositol as an alternative treatment to lithium's thyroidal side effects; and to evaluate the augmenting action of lithium in treatment resistant depression. The specific aims of the study were:

1) to assess the efficacy of lithium in unipolar depression by comparing readmission rates in patients after lithium discontinuation and in patients who continued to take lithium as a prophylactic agent.

2) to consider whether a lithium withdrawal syndrome occurs in unipolar patients during the first three months of discontinuation as has been found in bipolar patients (Mander, 1986-b).

3) to examine whether there is an increase in the number of hospital readmissions in autumn-winter versus spring-summer and spring-autumn versus summer-winter in recurrent unipolar patients after lithium withdrawal, and to determine whether the seasonal pattern in these patients is different from that observed in patients on prophylactic lithium.

4) to analyze quantitatively the results of lithium trials in the acute treatment and prophylaxis of unipolar depression in order to estimate the therapeutic value of lithium by measuring an overall effect size.

5) to investigate the neuroendocrine changes involving thyroxine (T4), thyroid stimulating hormone (TSH) and cortisol before and after lithium discontinuation in bipolar patients and to test whether they are related to the withdrawal syndrome observed in these patients.

6) to evaluate the effects of adding inositol to the diet of clinically stable bipolar patients on prophylactic lithium, thyroxine (T4) and thyroid stimulating hormone (TSH) concentrations and on other peripheral side-effects of lithium, comparing the results to those found in a group of normal controls not taking lithium.

7) to assess the efficacy of lithium augmentation in treatment resistant depression by reviewing, using quantitative techniques, the controlled trials on the topic.

*STRUCTURE OF THE THESIS*

The structure of the thesis is briefly described below. Chapter 2 gives a brief description of the historical, epidemiological, aetiological, classificatory, and clinical aspects of affective disorders. Treatment and prophylaxis of affective disorders including the role of lithium are briefly reviewed.

Chapter 3 briefly reviews the pharmacology of lithium. The history, chemistry, metabolism, doses, levels, side effects, toxicity and contraindications of lithium are described.

Chapter 4 presents the findings of the retrospective study comparing readmission rates in unipolar depressed patients after lithium withdrawal and in patients who continued to take lithium, using case notes from the Royal Edinburgh Hospital. The possibility of a withdrawal syndrome in patients with unipolar depression is discussed. The seasonal pattern of patients who had their lithium discontinued is considered.

Chapter 5 shows the results of a meta-analysis of all studies on the use of lithium in the treatment and prophylaxis of unipolar depression. The relative advantages of lithium versus placebo, antidepressants, and lithium plus imipramine in the treatment and prophylaxis of unipolar depression are discussed in the light of the effect sizes found.

Chapter 6 reviews the studies undertaken in affective disorder patients in which thyroid and adrenal function are reported to be altered. Studies reporting hormonal alterations induced by lithium in affective disorder patients are also reviewed. The TSH, T4 and cortisol concentrations in bipolar patients before and after lithium discontinuation are presented. The relationship between hormonal status, lithium discontinuation and relapse is discussed.

Chapter 7 describes the rationale for the addition of inositol to the diet of in affective disorder patients on prophylactic lithium. The results of a pilot study on the dietary supplementation of inositol in bipolar patients is shown. The

relationship between side effects of lithium, inositol and affective disorders is analyzed.

Chapter 8 describes the results of a meta-analysis of controlled trials on lithium augmentation in refractory depression. The concept of treatment resistant depression and the mechanism by which lithium exerts its potentiating action are discussed.

Chapter 9 draws the general conclusions from the studies and discusses the implications for future research in the field.

# CHAPTER 2

# AFFECTIVE DISORDERS

## *2.1. HISTORICAL ASPECTS*

Mania and melancholia were described in the first treatise on psychiatric nosology - *Corpus Hippocraticum.* Hippocrates distinguished various forms of mania,melancholia and swings of mood. In the first century AD, the Cappadodian physician, Arateus, described both conditions in detail and pointed out a connection between the two conditions. He acknowledged the intermittent character of the illness (Arieti, 1974). In the last century, Falret and Baillanger, in Paris, described a circular form of insanity (*folie circulaire*) in which patients suffered from episodes of mania and depression alternatively with intervening normal periods (Jampala, 1988). The modern concept of affective illness, however, was proposed by Kraeplin (1921) who described bipolar and unipolar mood swings as manic depressive illness. He concluded that mania and depression were part of the same illness, differing from dementia praecox, by virtue of their episodic nature and preservation of intellectual function despite chronicity. The term affective disorders was introduced by Manfred Bleuler in the 1930's (Kaplan and Sadock, 1989).

## *2.2. PREVALENCE AND INCIDENCE OF AFFECTIVE DISORDERS*

The use of different diagnostic criteria makes the estimation of prevalence and incidence of affective disorders difficult. Only recently with the use of standardized diagnostic schedules has it become possible to gather reliable data in this area. Major depressive disorders are among the most prevalent psychiatric disorders (Robins *et al*, 1984). Between 5-26% of women and 2-12% of men will suffer from at least one episode of major depression at

some time during their lives (Boyd and Weissman, 1981; Clayton, 1983). In industrialized countries, the point prevalence is between 1.8 and 3.2 per 100 for men and 2.0 and 9.3 per 100 for women (Boyd and Weissman, 1982). Depression is certainly more common among women, but reports that depression is found more frequently in the lower socioeconomic groups (Kaplan and Sadock, 1989) has been disputed by Robins *et al* (1984).

Bipolar affective disorder is the least common of the principal psychotic conditions. It has been estimated to occur less than half as often as schizophrenia (Tsuang and Lyons, 1988). Boyd and Weissman (1982) reported that the lifetime risk for bipolar disorder is just less than one percent, and the incidence varies between 9-15 per 100 000 a year for men and between 3-30 per 100 000 a year for women. Estimates of the male:female ratio range from 1.3:1 and 2:1 (Krauthammer and Klerman, 1978).

### *2.3. AETIOLOGY*

As with most psychiatric illnesses, the cause of mood disorders is unknown. At present, all that can be said is that a number of aetiological factors, which may be potentially linked, have been identified, such as heredity, biochemical aspects and personality.

In order for a genetic aetiology of affective disorder to be proven, several factors should be evident. Firstly, illness should cluster within families. Secondly, studies of twins should show that the disorder is more prevalent among monozygotic than dizygotic twins. Thirdly, adoption studies should reveal that subjects with a biological parent with the illness would develop the

illness even if raised in a foster home. The prevalence of affective illness in relatives of affective disorder patients is higher than in controls (Goldin and Gershon, 1988). A higher concordance rate for bipolar illness in monozygotic (approximately 50%) compared to dizygotic (approximately 25%) twins were reported by Berthelsen *et al* (1977) and Torgensen (1986). Adoption studies have also suggested a genetic influence in affective disorders (Mendlewicz and Rainer, 1977). Although methodological issues have been raised in relation to the design of these studies, the available evidence is suggestive of a genetic component in affective disorder.

Since the introduction of the first therapeutic drugs for depression in 1950's, the biochemistry of affective disorders has been an active area of research. In order to explain the aetiology of affective disorders, several biochemical hypotheses have been put forward: the catecholamine hypothesis, the serotonergic hypothesis, the acetylcholine hypothesis (Schildkraut, 1965; Meltzer, 1987; Kaplan and Sadock, 1989). Recently, it has been speculated that second messengers, such as adenyl cyclase and phosphatidylinositol, are involved in mood disorders (Wachtel, 1989).

Finally, a constellation of personality characteristics (cyclothymic, hyperthymic, irritable temperament, subaffective dysthymic temperament) can be implicated as predisposing factors for depressive illness (Akiskal *et al*, 1983-b). These factors might be associated with each other, so that biochemical function may be a reflection of genetics and personality may be a reflection of biochemistry.

## *2.4. CLASSIFICATION OF AFFECTIVE ILLNESS*

The classification of affective disorders is undoubtedly controversial. The debate whether depression, for example, is a single disease that varies form mild to severe along a continuum or whether it represents subtypes that differ in phenomenology, pathophysiology and aetiology has been long-standing among clinicians and researchers (Kendell, 1976). Three broad approaches to classification of depressive disorders have been tried, based on aetiology, symptoms, and course of the disorder, respectively.

A classification based on aetiology discriminates two groups: endogenous and reactive or exogenous. Endogenous depression is defined as an episode of depression which is precipitated by biological factors independent of outside factors, and is unresponsive to the environment but responsive to somatotherapy (Kendell, 1976). In reactive disorders, symptoms are a response to external stress. Robins and Guze (1972) also proposed a classification based on aetiology. They introduced the concept of primary/secondary depression. A primary depression is defined as one that has not been preceded by and is not associated with any other non affective psychiatric disorder.

Based on symptoms, neurotic and psychotic depression have been identified (Gelder *et al*, 1989). Neurotic depression is defined by the absence of psychotic symptoms (delusions, hallucinations, thought disorder or grossly inappropriate behaviour) which are the main features of psychotic depression. Note the overlap with reactive/endogenous depression.

Differentiation by course results in the classification of unipolar and bipolar depression (Leonhard, 1957; Leonhard *et al*, 1962; Perris, 1966; Winokur, 1973). This was slow to receive wide acceptance causing inconsistencies in some of the earlier trials which may have used mixed groups of patients. This distinction has been supported by several findings, reporting familial and genetic factors (Leonhard *et al*, 1962; Winokur, 1979), epidemiological factors (Weissman *et al*, 1984), biochemical and physiological factors (Joyce *et al*, 1988), and verbal memory and fluency (Wolfe *et al*, 1987). In unipolar probands, a bipolar heredity was estimated to occur in 0.5% and a unipolar heredity in 10.6% of cases while in bipolar probands bipolar and unipolar heredities were respectively 16% and 0.8% of cases (Perris, 1966). Twin studies have revealed a greater concordance between bipolar monozygotic pairs than between unipolar monozygotic pairs (Allen, 1976; Berthelsen *et al*, 1977).

For research purposes, the Diagnostic and Statistical Manual (DSM-III-R) and Research Criteria (RDC) classifications have been widely accepted. A detailed comparison between DSM-III-R and RDC is found in Spitzer *et al* (1985). The major affective disorders are referred to as mood disorders in DSM-III-R, and are further classified as depressive (major depression) or bipolar. The minimal criteria for major depression require the presence of five symptoms lasting for a duration of two weeks. Bipolar illness is characterized by a presence of one or more episodes of mania (bipolar I) or hypomania (bipolar II) which are usually accompanied by a history of major depressive episodes. RDC divides affective disorders into primary and secondary types. Primary affective disorder consists of depression and mania of an endogenous nature. A diagnosis of depression based on RDC, requires a psychiatric illness

lasting at least one month and a diagnosis of mania requires a psychiatric illness lasting at least two weeks. Operational criteria for these subtypes have been an important step for ensuring greater reliability (Duggan *et al*, 1991).

The uniform acceptance of operationalized diagnoses is now to be reflected in the International Code of Diseases (ICD). Its tenth revision is under way (ICD 10) and in classifying affective disorders, ICD 10 will parallel DSM IV in most aspects.

### *2.5. COURSE OF THE ILLNESS*

Psychiatric theory held the view that affective disorders are characterized by an episodic course, with periods of recovery likely but often followed by relapse and recurrence while schizophrenia is considered to have a more chronic course. These patterns of outcome have differentiated affective disorders from schizophrenia (Kraeplin, 1921). Other researchers, however, are opposed to this view of a clear distinction between these two entities, and have proposed a continuum in which at some point they would merge into one another (Kendell, 1970). Thus, longitudinal follow-up studies are important in describing and differentiating the natural history of these disorders. For psychiatric research, course and outcome are recognized as important external validators of nosological classes (Robins and Guze, 1972). Accurate predictors of course and outcome are also essential for clinicians responsible for patients' care and for public health planning. Studying the course of affective disorders, however, raises numerous methodological problems; for example, most of the studies are based on hospitalized patients and hence they are biased toward

the more severe illnesses; and no prospective population surveys including the course of untreated patients have been carried out, due to ethical reasons.

### *2.5.1. Unipolar Affective Disorder*

The onset of unipolar depression is highly variable. Most typically it emerges gradually over a few months: occasionally it develops over days or weeks. Between 10 to 20% of patients previously diagnosed as unipolar will subsequently suffer from a manic or hypomanic episode (Runck,1985). This risk, however, decreases with longer illness duration (Winokur and Wesner, 1987). Akiskal *et al* (1983-a) have reported that a number of associated features are present in these patients who switch from unipolar to bipolar affective disorder, such as onset before age of 25, acute onset, and psychotic depression.

### *2.5.2. Bipolar Affective Disorder*

The first episode may be either manic or depressive, and about 10% of patients may have only manic episodes. Unipolar manics are not different from bipolar manics in terms of demographic and clinical characteristics. A majority of patients can lead relatively normal lives between episodes, but some patients may exhibit significant reductions in social functioning (e.g. inability to hold a job) despite the absence of the manic syndrome. Mania may occur suddenly or may be preceded by a prolonged hypomanic episode or a depressive state. Some patients may have only hypomanic episodes (bipolar II). The somatic treatment of depression may result in an abrupt switch of mood. Attacks of

depression are much more common than those of mania. About 7% of bipolar patients will be rediagnosed as schizoaffective (Kaplan and Sadock, 1989).

### *2.5.3. Age of Onset*

The median age of the onset of unipolar disorder is late 40's for both men and women. A prominent peak is observed at ages 50 to 60 and another peak at 20 to 30 years (Kaplan and Sadock, 1989).

The average age of onset of bipolar illness is in the early 30's. Two peaks have been identified, one before age 30 and another during the mid to late 40's (Kaplan and Sadock, 1989). The peaks are not absolute as the range of onset is broad in unipolar and bipolar disorders varying from childhood to elderly population

### *2.5.4. Duration of Episodes*

An untreated episode of mania or depression has an average duration of 6 months to a year before remitting spontaneously, but some episodes may last for longer periods. More than two thirds of the episodes will last for less than 6 months. Eighty percent of patients with an episode of major depression recover within two years (Keller *et al*, 1982).

### *2.5.5. Number of Episodes*

The number of episodes experienced in manic-depressive illness is variable. Bipolar disorder is associated with a greater number of episodes than

unipolar disorder. Estimations of the proportion of patients who experience a single episode of depressive illness with no recurrence vary greatly. Angst *et al* (1973), in a 12 year follow-up, found only 5% of unipolar patients and 0.5% bipolar patients had had a single episode, but Lundquist (1945), in a 10 to 13 year follow up, found that 61% of unipolar patients and 55% of bipolar patients had had only a single episode. It has been reported that bipolar illness show more hospital readmissions than unipolar patients (Perris, 1968). The course of unipolar depression is more variable and less well established than bipolar illness, but between 50 and 85% of patients with one depressive episode will have at least one subsequent episode in their lives (Keller, 1985).

It has been reported that between 10 and 20% of all patients diagnosed as having major depression will manifest a chronic course (Robins and Guze, 1972). In a proportion of patients, a major depressive episode is superimposed on dysthymic disorder that preceded the onset of the major depression by at least two years (Keller and Shapiro, 1982). Further discussion on recovery and recurrence of depression is found in Chapter 4.

### *2.5.6. Cycle or Period Length*

Cycle length refers to the length of time between the onset of one episode and the onset of the next. There is a trend for the first several cycles to become successively shorter. A shorter cycle has been associated with later age of onset (Tsuang and Lyons, 1988).

### *2.5.7. Morbidity*

There is a high rate of comorbidity of depression and alcoholism and eating disorders (Keller *et al*, 1986-a). Around 15% of a cohort of patients with unipolar depression will be dead after 10 years (Guze and Robins, 1970). Suicides and accidents account for almost all the excess mortality.

## *2.7. OUTCOME*

Between the extremes of full recovery and chronicity , depression shows a wide variation of outcome. Often the boundaries between depressive and manic phases and the intervening periods are blurred. Earlier studies have found that affective disorders have a more favourable outcome than schizophrenia (Kaplan and Sadock, 1989). More recent studies, however, have shown that affective disorder patients may have a poorer outcome than previously reported (Lee and Murray, 1988; Kiloh *et al*, 1988).

## *2.8. THERAPY OF AFFECTIVE DISORDERS*

### *2.8.1. ACUTE EPISODE*

For the treatment of affective disorder patients a variety of therapies have been used: psychotherapies, sleep deprivation, electroconvulsive therapy, light treatment, psychosurgery and psychopharmacology (Joyce and Paykel, 1989). Three main classes of drugs have been used in the therapy of acute depression: tricyclics, monoamine oxidase inhibitors (MAOI) and lithium. The first two classes of drugs, however, are not reviewed here (comprehensive

reviews are available in Meltzer, 1987; Kaplan and Sadock, 1989). This review will focus on the use of lithium only.

*2.8.1.1. Lithium*

Lithium was first used in psychiatry by Lange in 1887 and has been called the first psychotropic drug in western medicine (Johnson, 1984). Lithium is the oldest psychotropic drug still in use, preceding chlorpromazine by three years (Plenge and Mellerup, 1988). The modern use of lithium started in 1949, when it was introduced by Cade in Australia for the treatment of manic patients (Cade, 1949). Lithium, however, was rarely used in psychiatric practice before 1969. Several reasons appear to be responsible for this. Firstly, its discovery in Australia and Cade's multiplicity of other interests did not promote its acceptance. Secondly, there is a narrow range between therapeutic and toxic dose. Thirdly, psychiatrists 40 years ago were not oriented to pharmacological intervention. Fourthly, phenothiazines with their broader therapeutic application were almost simultaneously introduced. Finally, ready availability rendered it commercially nonprofitable.

*2.8.1.1.1. Lithium in Acute Mania*

Since its introduction into modern psychopharmacology by Cade (1949), several studies and reviews have evaluated the usefulness of lithium in the treatment of a manic episode. The findings of the initial studies were disputed because of the uncontrolled design that had been used, but the benefit of lithium in acute mania has also been consistently found in controlled trials which are more methodologically sound. The full list of these studies is

available elsewhere (see reviews by Schou, 1959; Noyes, 1969; Davis and Fann, 1971; Goodwin and Ebert, 1973; Georgotas and Gershon, 1979; Gershon and Goodnick, 1981; Lewis and Winokur, 1982). Regarding the symptoms specific to mania, most showed the results with lithium were superior to those obtained with conventional neuroleptics, such as chlorpromazine (Gershon and Goodnick, 1981; Rosenthal and Goodwin, 1982; Prien and Potter, 1990). Chlorpromazine is probably better than lithium in terms of having a faster action and in controlling agitated patients more rapidly (Rosenthal and Goodwin,1982; Prien and Potter, 1990). At the moment, however, lithium is considered to be one of the best treatments for acute episodes of mania.

*2.8.1.1.2. Lithium in Acute Depression*

The indications for lithium in acute depression are less clear. Three designs have been used to study the role of lithium in unipolar depression: totally uncontrolled studies (e.g. case reports, single blind studies), cross-over (a period on lithium followed by other treatment or vice-versa) and controlled studies (double-blind randomized trial). Each of these will be discussed separately. The methodology of the first two designs are flawed in several ways, consequently subjected to bias. Firstly, the practice of separating unipolar from bipolar depression only became widespread in late 1970's, so the majority of the studies used heterogeneous populations comprising a mixture of bipolar and unipolar depressed patients. This meant that no firm conclusion could be drawn as to which group of patients found lithium more effective. All the studies of this topic which satisfy the minimum methodological standards will be discussed in detail in Chapter 5. The findings of other studies which do not meet these criteria will be discussed here.

## TABLE 2.1

Uncontrolled studies of lithium in acute depression.

| STUDY | DIAGNOSIS | N | PATIENTS IMPROVING | COMMENT |
|---|---|---|---|---|
| LITHIUM INEFFECTIVE | | | | |
| Cade (1949) | manic depression | ? | ? | no effect in depression |
| Noack and Trautner (1951) | manic depression | ? | ? | some patients seem to become worse |
| Zall *et al* (1968) | depressed or mixed phase of manic depression | 14 | 7 | 5 improved markedly, 2 moderately but lithium considered ineffective as antidepressant |
| Van der Velde (1970) | manic depression | 75 | ? | in 8 patients lithium appeared to precipitate depression |
| LITHIUM EFFECTIVE | | | | |
| Vojtechovsky (1957) | manic depression | 14 | 8 | - |
| Andreani *et al* (1958) | manic depression | 24 | 10 | - |
| Dyson and Mendels (1968) | depression | 31 | 19 | 7 depressed phase (bipolar),2 recurrent depression, 10 cyclothymic |
| Dyson and Mendelson (1968) | recurrent depression | 5 | 5 | 3 bipolar<br>2 unipolar |
| Nahunek *et al* (1970) | endogenous depression | 98 | 53 | effective in 54% of the sample (endogenous/involutional depression) |
| Johnson (1974) | bipolar (2), unipolar (6), neurosis (4) | 12 (2 dropout) | 5 | 5 (1 bi, 4 uni) marked improvement<br>5 minimal or no improvement |
| Bennie (1975) | depression | 14 | 14 | all patients improved |
| Neubauer and Bermingham (1976) | Unipolar (12), bipolar (8), all with obsessions | 20 | 20 | remission of symptoms within 3-7 days of treatment |

*2.8.1.1.2.1. Uncontrolled studies*

From 1949 to 1976, twelve uncontrolled studies of lithium in acute depression were conducted (see Table 2.1). Four studies found lithium to be ineffective in depression while eight studies have reported mild to moderate improvement with lithium. A meta-analysis of these uncontrolled studies is not possible due to a lack of comparison groups, but the numbers of patients improving with lithium gives an idea of the effectiveness of lithium.

*2.8.1.1.2.2. Cross-over trials*

Eight cross-over trials have compared lithium with placebo in acutely depressed patients (Hansen *et al*, 1958; Goodwin *et al*, 1969, 1972; Noyes *et al*, 1971; Stokes *et al*,1971; Noyes *et al*, 1974; Baron *et al*, 1975; Mendels, 1976). None of these studies reported an antidepressant effect of lithium in acute unipolar depression.

Three studies were not included in the meta-analysis of Chapter 5 (Hansen *et al*, 1958, Noyes *et al*, 1971, Stokes *et al*, 1971). Hansen *et al* (1958) studied 12 severely endogenous depressed patients who were given lithium for two weeks and then switched to placebo. Only one patient suffered a relapse synchronously with placebo substitution, after having improved on lithium. No mention was made about the criteria to diagnose severe endogenous depression nor to measure improvement. Furthermore, this study was reported only in summary form and therefore can not be properly evaluated (Schou, 1968). Noyes *et al* (1971) found that four of the five depressed patients (2 unipolar, 3 bipolar) became symptom free with lithium but two

relapsed with placebo substitution. Stokes *et al* (1971) also found no significant difference for 18 patients who were treated with lithium or placebo for 26 depressive episodes. The drawbacks of this trial were that the treatment period (7 to 10 days) may have been too short to allow lithium to have any effect; the distinction between unipolar and bipolar patients was not made, no mention of lithium doses and plasma concentrations was made and no details of the rating scale used to classify the improvement of patients were given.

*2.8.1.1.2.3. Controlled trials*

Three trials were excluded from the analysis to be described in Chapter 5 (Fieve *et al*, 1968; Arieli and Lepkifker, 1981; and Bennie *et al*, 1983). Fieve *et al* (1968) compared 17 depressed patients who received lithium with 12 patients who were treated with imipramine. Imipramine appeared to exert a strong to moderate effect whereas lithium showed only mild antidepressant effect after seven weeks of treatment. A number of short-comings were evident in this study; for example, no information was given about the exact number of unipolar and bipolar patients in the sample, nor were doses and plasma concentration of lithium or imipramine given. Arieli and Lepkifker (1981) in a double-blind study compared 12 patients on lithium, 10 on clomipramine and 10 on placebo. Lithium and clomipramine were found to be superior to placebo, but no significant difference between them was detected. The studied sample consisted of a mixture of unipolar, bipolar and involutional depressed subjects. Some weakness were observed; such as there was no mention of the method used to assign patients to each group and the number of patients in these groups was very small making any inference meaningless. Bennie *et al* (1983) compared lithium versus amitriptyline in a three week period in 60

patients with different diagnoses; unipolar, bipolar and schizoaffective depression. The numbers in each sub-group, however, were too small to establish whether any particular type of disorder responded to either lithium or amitriptyline. Overall, the results of these trials tend to support a moderate effect of lithium in acute depression.

### *2.8.2. PROPHYLAXIS*

The majority of patients who have had an episode of major depression are likely to suffer a recurrence (Greenhouse *et al*, 1991). A variety of approaches have been used to treat recurrent depression: psychotherapies, sleep deprivation, electroconvulsive therapy, light treatment, psychosurgery and psychopharmacology (Joyce and Paykel, 1989). The first modern prophylactic treatment of depression was ECT. In 1943, a pilot study indicated that prophylactic electro-shock might be effective in recurrent affective disorders (Moore, 1943). This form of prophylaxis did not receive widespread acceptance, however, due to the refusal of patients (Quitkin *et al*, 1976). Probably the most used prophylactic approach is psychopharmacology. Drugs which effectively prevent new episodes are a desirable tool in modern psychiatry. During the 1960's, the possibility of an effective prophylactic treatment for affective disorders arose with the advent of two classes of drugs; antidepressants for unipolar depression and lithium for bipolar and unipolar affective disorder.

*2.8.2.1. Antidepressants*

Antidepressant drugs are one of the main options for treating moderate and severe recurrent depression. Several trials have shown good results with the use of antidepressants in depression. Hordern *et al* (1964) found that patients on amitriptyline or imipramine for six months had a lower relapse frequency than patients in a control group. The control group, however, consisted of patients with more severe illness who were given ECT because they did not respond to amitriptyline or imipramine. Seager and Bird (1962) gave ECT followed by imipramine or placebo for six months. Eleven of 16 placebo patients relapsed while only 2 of the 12 imipramine patients relapsed. The advantages of treating recurrent depression with antidepressants or lithium will be discused in Chapter 5.

*2.8.2.2. Lithium*

Lithium has been used in a variety of other psychiatric illnesses such as schizophrenia, paranoid reactions, catatonia, confusional states, epilepsy, oligophrenia and delirious reaction (for a detailed review see Schou, 1979-b). The efficacy of lithium in the prophylaxis of mood swings in affective illness, however, has ensured that it is one of, if not the most important, drug in the therapy of affective illness.

The prophylactic action of lithium in manic depression was first noted by Noack and Trautner (1951) and Schou (1954) who observed that the continuation of lithium treatment following remission of mania may prevent recurrence. Hartigan (1963) and Baastrup (1964) were the first to report a

similar finding concerning the prevention of recurrence in depression. Lithium was the first drug to show a clear-cut prophylactic effect (Baastrup and Schou, 1967). The design of these first studies were far from ideal; trials were neither controlled (random assignment to lithium and control groups) nor they were evaluated blindly. The predominance of uncontrolled studies until the early 70's made clear interpretation of the data difficult. Another issue which also made these studies difficult to interpret was the distinction between unipolar and bipolar illness. The first studies did not separate unipolar and bipolar illness and the term, manic depressive disorder, included patients who had experienced both mania and depression and those with a history of depression only (Schou, 1968). The first extensive study of lithium separating bipolar and unipolar patients was by Baastrup and Schou (1967). In that study, a time factor seemed to be involved. In one third of the cases, relapses occurred in the first six months of treatment only. It was proposed that it might be months before full stability could be obtained. The design of the study was open and consequently a psychological effect could not be ruled out.

*2.8.2.2.1. Lithium in Bipolar Illness*

Numerous uncontrolled and controlled studies have provided strong support for the prophylactic effect of lithium in bipolar illness (for a description of these studies see the reviews by Gershon and Goodnick 1981; Murray 1984; Prien 1988). It is so widely accepted that lithium is the treatment of choice in the prophylaxis of bipolar affective illness (Baastrup *et al*, 1970; Zis and Goodwin, 1979; Prien *et al*, 1973, 1984) that there has been no placebo controlled study of maintenance lithium therapy in bipolar disorder since the early 1970's (Prien and Potter, 1990).

*2.8.2.2.2. Lithium in Unipolar Depression*

The prophylactic efficacy of lithium in unipolar depression, however, has been the subject of considerable debate. The earliest report of lithium prophylaxis in unipolar depression was in England. Hartigan (1963) reported success in six of eight unipolar patients with long-term lithium treatment.

*2.8.2.2.2.1. Uncontrolled studies*

This initial report was followed by a number of uncontrolled studies which also discerned a positive effect of lithium in reducing the frequency of relapse (Baastrup and Schou, 1967; Melia, 1967; Fieve *et al*, 1968; Gottfries, 1968; Zall *et al*, 1968; Laurrell and Ottosson, 1968; Angst *et al*, 1970; Persson, 1972; Bennie, 1975; Lepkipker *et al*, 1985; Page *et al*, 1987; Souza *et al*, 1990). Some studies were excluded from the analysis, as described in Chapter 5, due to the absence of a comparison group (Gottfries, 1968; Zall *et al*, 1968; Bennie 1975; Page *et al*, 1987), lack of clarity as to how the comparison was made (Fieve *et al*, 1968) or small sample size (Melia, 1967). Melia (1967) observed that 2 out of 4 patients with recurrent depression who had been taking lithium on a long-term basis had new episodes. Fieve *et al* (1968) found no difference in five patients who were on both placebo and lithium and imipramine was more effective in six patients who were on lithium and imipramine. Gottfries (1968) described the effect of lithium in 4 patients as ++, in 4 other patients as + and in seven as zero. Zall *et al* (1968) found that out of 12 subjects, eight were poor responders, 3 showed moderate improvement and 1 was completely recovered. Bennie (1975) followed 14 patients for six months and found that none had

and found that none had recurrences. Page *et al* (1987), in a group of 59 patients followed for 12 years, reported that 49% showed complete recovery, 41% partial recovery and 10% an insignificant response.

Four uncontrolled studies have failed to find such an effect (Stancer *et al*, 1970; Freyhan *et al*, 1970; Smigan, 1985; Bouman *et al*, 1986). Two trials were excluded from the analysis in Chapter 5 (Stancer *et al*, 1970; Freyhan *et al*, 1970). Stancer *et al* (1970) did not use a comparison group and only used a small number of unipolar patients (2) in the sample. Freyhan *et al* (1970) found that the rate of readmission in 7 unipolar patients while on lithium was greater than during the pre lithium period, but the periods of observation were not equal. Information was sought to clarify these points (see Chapter 5).

*2.8.2.2.2.1. Controlled studies*

Two trials were excluded from the meta-analysis reported in Chapter 5 due to the small numbers of unipolar patients in the samples (Laurell and Ottosson, 1968; Cundall *et al*, 1972). Laurell and Ottosson (1968), in an eleven months double-blind randomized trial, observed the following rates of recurrence: lithium (2/4), amitriptyline (4/6) and placebo (5/6). Cundall *et al* (1972) reported, in a cross over design of lithium and placebo (six months on each drug), that of the five unipolar patients, two withdrew from the trial, one preferred placebo and the other two showed no clear preference.

One controlled trial lithium versus antidepressant was excluded from the analysis in Chapter 5. Platman (1970) compared 49 patients on lithium versus 21 on imipramine, but the number of unipolar patients could not be estimated

since the entry criteria required patients to have two previous episodes of mania and/or depression, so no meaningful interpretation of this study can be made.

In summary, several problems prevented a consensus on the role of lithium in the treatment and prophylaxis of unipolar depression. Firstly, the poor design used in many trials. Secondly, the inclusion of patients with different diagnoses. Finally, different drugs were compared with lithium. Based on different criteria of study inclusion, or even analysing the same sample of studies, traditional reviewers reached opposite conclusions as demonstrated in Chapter 5. A meta-analysis of these studies was, therefore, relevant in order to overcome these obstacles.

# CHAPTER 3

# LITHIUM

*3.1. HISTORY*

In the beginning of the 18th century, the Father of the Brazilian Independence, Jose' Bonifa'cio de Andrada e Silva, discovered the mineral petalite (Johnson, 1984). In 1817, a Swedish researcher, Johann August Arfvedson, isolated lithium from petalite. The name lithion was proposed by Berzelius since it was found in a rock. In 1843, Ure presented a successful reduction of a urinary calculus (which contained uric acid) by immersion of the stone in lithium carbonate solution. In 1859, influenced by the experiments of Ure, Sir Alfred Baring Garrod introduced lithium in medicine by recommending lithium bromide for gout, rheumatism and allied disorders (Johnson and Amdisen, 1983). He also proposed the use of lithium carbonate in combination with uric acid to dissolve urate deposits in the cartilage, but the salt proved to be of no therapeutic value in these disorders (Schou, 1968). Garrod also suggested the use of prophylactic lithium to prevent the symptoms of uric acid diathesis, including the mood disturbances, which was thought to be related to the excretion of uric acid. But, it was Carl Lange, in 1886, who gave the first unequivocal account of lithium prophylaxis for a psychiatric condition when he observed that, in conditions involving both gout and depression, the use of lithium improved depression. It is interesting to note that Lange's ideas, despite being accepted at the time, were subsequently forgotten for more than 60 years (Johnson, 1984).

### *3.2. CHEMICAL CHARACTERISTICS*

Lithium is a monovalent cation and it is the smallest of the alkali metals. It has the highest electrical field density and it is the hardest of this group. It is the lightest of the solid elements. Lithium is extremely reactive and it never occurs freely in nature, usually it is found as salt. It accounts for 0.006% of the earth's crust (Lazarus,1986). It is found in various minerals, plants and animals in small quantities. There are two stables isotopes: $^{6}Li$ and $^{7}Li$ and three radioactive ones: $^{5}Li$, $^{8}Li$ and $^{9}Li$ (Schou, 1968). Since it is the lithium ion that is the active agent, any soluble salt might, in principle, be used for treatment (Schou, 1968).

### *3.3. ABSORPTION*

Lithium is not metabolized; its pharmacokinetics are determined only by absorption, distribution and excretion (Schou, 1976-b). It is absorbed mainly from the intestine but also from subcutaneous, intramuscular and intraperitoneal depots. Peak levels occur about 2 to 3 hours after an oral dose and absorption is complete in 8 hours.

### *3.4. DISTRIBUTION*

Lithium is distributed in many tissues in the body but it has a different pattern from those exhibited by sodium and potassium. Lithium is not bound to proteins and it has been reported to be actively transported across cell membranes (Lazarus, 1986). In most tissues, the tissue/serum ratios are less than one. Values greater than one, indicating lithium accumulation, are found

in bone, thyroid and salivary glands (Lazarus, 1986). The equilibrium is rapid in some tissues (e.g. liver, kidney, and skin) and slower in others such as bone, muscle and brain. Lithium concentration in the brain is the same as that in the blood serum whereas the concentration in the spinal fluid is about one fourth of that (Schou, 1976-b). The lithium concentration in cerebro-spinal fluid is about half of that in the blood stream (Schou, 1968).

### *3.5. EXCRETION*

Excretion occurs almost exclusively by the kidneys. Lithium excretion is dependent on glomerular filtration rate and proximal reabsorption. Like sodium, it is freely filtered at the glomerulus and 75% is reabsorbed in the proximal tubules and loop of Henle. Less than one percent is excreted in faeces. The amount of lithium loss in the sweat is negligible. In normal adults, the renal lithium clearance rate is 15-30 ml/min. Lithium clearances decreases with age and clearances of 10-15 ml/min are not unusual in older persons. In the average adult the half life for lithium is around 24 hours, but in older people, it may be as much as 30-36 hours. 45 to 75% of a given dose is excreted in 24 hours. Little is retained after five days (Schou, 1968). An important implication for the renal handling of the lithium ion is that it is not possible to increase its rate of removal by the administration of most saluretic drugs (Baldessarini and Lipinski, 1975).

### *3.6. FORMULATIONS*

Given in equal dosage, lithium carbonate, lithium citrate and lithium acetate are of equal therapeutic value but the carbonate has one practical

advantage: its anion weights half as much. This means that relatively large amounts of lithium can be contained in one lithium carbonate tablet making lithium carbonate the most used form of lithium. Lithium chloride is an extremely hygroscopic substance and therefore unsuitable for incorporation into tablets (Schou, 1968). There are several formulations of lithium carbonate on the market, e.g. Priadel, Camcolit, and Phasal (Shelley and Silverstone, 1988). Because differences in pharmacokinetic profile among the different formulations are found, care should be taken in choosing which formulation should be prescribed for any individual patient (Shelley and Silverstone, 1988).

### *3.7. DOSAGE*

In adults with normal kidney function maintenance dosage may vary from 25 to 50 meq per day, corresponding to 900 and 1800 mg of lithium carbonate, respectively (Schou, 1968). There are also slow release forms of lithium. The major disadvantages of conventional lithium carbonate are the frequency of dosage that is required (2 or 3 times a day) and the resulting erratic peak levels of lithium (up to 2 fold variations). The slow absorption lithium formulations were developed to decrease the adverse effects associated with peak and rapidly rising serum concentrations as well to increase compliance (Lazarus, 1986). The delayed release formulations have also been associated with less renal damage (Perry and Alexander, 1988).

### *3.8. LITHIUM LEVELS*

Plasma lithium should be measured 12 hours after administration of the drug. The recommended lithium levels for acute treatment is 0.8 to 1.2 meq/l.

Lower serum levels between 0.4 and 1.0 mEq/l is sufficient for prophylaxis (Lazarus, 1986).

Atomic absorption spectrometry (AAS) and flame emission spectrometry (FES) are the two most widely used analytical chemistry instruments for the determination of metals. Recent developments in the atomisation source has improved the sensitivity of the AAS and FES measurements. Other methods are also available to measure lithium levels: spetrophotometry, molecular fluorescence and lithium ion-selective electrode method (Xie and Christian, 1988).

### *3.9. MECHANISMS OF ACTION*

The mechanism of action of lithium is unknown. Several tentative hypotheses have been put forward (Wood and Goodwin, 1987). For a detailed discussion see Chapters 7 and 8.

### *3.10. SIDE EFFECTS*

Adverse effects of lithium are common in the first 2 or 3 weeks of treatment. These signs are usually transient , but in some patients they may be more persistent and this is the main reason for discontinuing lithium therapy (additional discussion on the topic is found in Chapter 4 ). T-wave flattening or inversion of electrocardiogram (ECG) recordings are the most common cardiac alterations. Approximately 20% of patients show some alterations in the ECG (Lydiard and Gelenberg, 1982). A fine tremor in the hands is the most common neurological sign, and it can be alleviated by dose reduction or administering a

low dose of propanolol. Some patients may complain of memory loss and reduced performance in some learning tasks (Vestergaard *et al*, 1988). Nausea, vomiting, and diarrhoea are commonly reported (Vestergaard *et al*, 1980, 1988; see also Chapter 8). The most frequent haematological change is a benign leukocytosis (Lydiard and Gelenberg, 1982). This leukocytosis may persist or decrease over time and it is reversible. The renal effects of lithium have prompted more than 2400 reports in the literature (Jefferson, 1990). Polyuria and polidpsia are the most common side effects. Lithium blocks the effect of the antidiuretic hormone on adenylate cyclase, which in turn reduces water reabsorption. The risk of developing chronic renal damage with therapeutic doses of lithium, however, is small (Jefferson, 1990). Lithium concentration in the thyroid is 2 to 5 times the concentration in serum and causes a decrease in the secretion of thyroid hormones which may lead to hypothyroidism (Schou, 1976-b). The effects on the thyroid will be discussed in detail in Chapter 6. About 15 to 20% of patients on prophylactic lithium gain weight (Teixeira and Karniol, 1985). This is quoted as one of the most troublesome effects in young women (Vestergaard *et al*, 1980, 1988). Lithium may cause muscular weakness and fatigue and exacerbate a variety of skin conditions (Vestergaard *et al*, 1980, 1988). Lithium passes freely through the placental membrane and is excreted in low concentration in the milk (Schou, 1976-b). Teratogenic effects of lithium have been demonstrated in mice and rats.

### *3.11. TOXICITY*

If lithium concentrations are high (that is, above 1.5 meq/l, lithium poisoning may occur (Schou, 1968). There are some practical steps that

should be taken to to avoid lithium intoxication, such as: a) frequent monitoring of lithium levels; b) educating patients and their families about the early signs of lithium intoxication; and c) special care of possible patients who are more susceptible to this condition due to old age, kidney disease or the use of diuretics.

### *3.12. CONTRAINDICATIONS*

The strongest contraindications of lithium are: a) severe renal disease; b) acute myocardial infarction; c) myasthenia gravis; d) first trimester of pregnancy; and e) breast feeding mothers. Other situations where lithium intake requires special attention are: cardiac conduction defects, Parkinson disease, second and third trimester of pregnancy, and concomitant intake of thiazide diuretics.

In prescribing lithium for depression, its effectiveness has to be counterbalanced by its possible adverse effects. Firstly, side effects are frequent and distressing. Young women may feel discouraged to continue therapy because of the weight gain. Other patients due to the severity of some side effects need to stop the treatment. Secondly, there is the danger of teratogenesis. Discontinuation of the therapy is recommended during pregnancy, especially during the first three months. The possibility of pregnancy should always be investigated by direct questionning and laboratory testing. Thirdly, the risk of toxic levels is always present due to its low therapeutic window, therefore determinations of lithium levels should be performed frequently. Finally, its use in patients with renal and cardiac syndromes should be carefully monitored.

# CHAPTER 4

# LITHIUM PROPHYLAXIS AND DISCONTINUATION IN UNIPOLAR DEPRESSION: EFFICACY, WITHDRAWAL SYNDROME AND SEASONAL PATTERN OF READMISSION

# 4.1. INTRODUCTION

## *4.1.1. LITHIUM PROPHYLAXIS IN UNIPOLAR DEPRESSION*

The prophylactic efficacy of lithium in unipolar depression has been the subject of considerable debate. The conflicting findings are reviewed in Chapters 2 and 5. The findings from lithium withdrawal are reviewed here.

## *4.1.2. DISCONTINUATION AND WITHDRAWAL SYNDROME*

A withdrawal syndrome, characterized by an increase in the symptomatology and readmission rates, has been described after the discontinuation of antidepressants in major depression (Dilsaver and Greden, 1984; Dilsaver, 1989). Kramer *et al* (1961) estimated in their retrospective studies that 55% of patients experience withdrawal symptoms after discontinuation of imipramine. The evidence of a similar a similar syndrome after lithium withdrawal has been the subject of intense debate.

The first lithium discontinuation studies in affective disorders, using mainly bipolar patients, focused on the efficacy of lithium as a prophylactic agent rather than the possibility of relapse being caused by its withdrawal. Little attention was paid to the possible causal relationship between discontinuation and relapse. The natural course of illness was assumed to be the cause of these relapses rather than a drug-related state. Later studies have tried to answer this question of a possible withdrawal syndrome after lithium discontinuation.

In bipolar illness, an apparent withdrawal syndrome has been reported in some uncontrolled studies (Lapierre *et al*, 1980; Mander, 1986-b). Lapierre *et al* (1980) reported an open study in which lithium was withdrawn for five days; of the 20 cases, four patients relapsed within this time. Mander (1986-b) studied 29 patients who had their lithium discontinued and 50 patients who continued to take the drug. He found a significant difference in the relapse rate in the first three months (8 patients in the discontinuation group and 4 in the control group). Three uncontrolled studies, however, have failed to replicate these findings. No withdrawal syndrome was found by Sashidharan and McGuire (1983) who studied 20 bipolar and two unipolar patients nor by Goodnick (1985) who studied a small group of 12 bipolar patients. Molnar *et al* (1988) also failed to find evidence of a lithium withdrawal syndrome (Table 4.1). Failure to replicate the findings could be explained in the later study by the high motivation of patients to stay off the drug with a possible failure to report minor affective episodes to General Practioners.

Controlled studies have also reported a lithium withdrawal syndrome in bipolar patients (Baastrup *et al*, 1970; Melia, 1970; Cundall *et al*, 1972; Fyro and Peterson, 1977; Margo and McMahon, 1982; Mander and Loudon, 1988). Baastrup *et al* (1970) showed that 12 out of 22 patients relapsed within 5 months after lithium discontinuation. Melia (1970) reported four relapsed out of eight patients within two months off lithium. Cundall *et al* (1972) found that 10 patients out of 12 had relapsed after six month of placebo substitution. Fyro and Peterson (1977) divided 18 patients into pairs (one on lithium the other on placebo). They reported that all nine patients on placebo were first to relapse (seven within three months). Margo and McMahon (1982) showed that all 4 patients relapsed within 11 days after substitution of lithium for placebo but none of the 11 patients who continued to be treated with lithium. Mander and Loudon (1988) studied 14

bipolar patients randomly assigned to 4 weeks each of placebo or continued lithium treatment under double blind conditions. They found that seven patients relapsed within the first two weeks of placebo substitution.

Some controlled trials failed to find evidence of a lithium withdrawal syndrome, for example Christodolou and Lykouras (1982) reported that only three out 17 patients relapsed. These conflicting results may also be attributed to heterogeneity of patient population, especially the proportion of bipolar I and bipolar II in the sample (Mander, 1986-b).

Other withdrawal studies, although reporting withdrawal syndrome in affective disorder, are unreliable due to their methodological deficiencies. Klein *et al* (1981) reported a discontinuation syndrome in 21 patients, but the use of unspecified diagnostic criteria of affective illness and the loose definition of the nature of relapse were serious methodological shortcomings. King and Hullin (1983) reported the finding of a withdrawal syndrome in a survey of patients who had discontinued their lithium, but their findings are marred by various methodological pitfalls, including a biased, very low response rate and a dependence on the subjective recall of elderly subjects of their withdrawal symptoms with a mean of 4.45 years of lithium discontinuation. Other publications are flawed by small samples (five patients or less) and case reports, mostly involving bipolar patients (Small *et al*, 1971; Wilkinson, 1979; Cordess, 1982; Margo and Mahon, 1982), and also by poorly defined patient population such as 'unstable character disorder' (Rifkin *et al*, 1975).

In unipolar depression, the literature regarding the existence of a withdrawal syndrome in patients with recurrent illness discontinuing lithium is sparse. Earlier

relapses were noted but not in sufficient numbers to warrant further investigations (Baastrup *et al*, 1970; Melia, 1970). In a double blind discontinuation trial involving 17 unipolar patients on lithium and 17 on placebo, Baastrup *et al* (1970) observed earlier relapses but there was no indication of a rebound or abstinence effect. Melia (1970) studied in a double blind trial nine (7 bipolar, 2 unipolar) patients on lithium and nine (8 bipolar, 1 unipolar) on placebo. He reported that one recurrent depressed patient relapsed after 24 days of stopping lithium (see Table 4.1). The only study with reasonable numbers (seventeen recurrent depressed patients) provided no evidence of a lithium rebound or withdrawal phenomenon (Baastrup *et al*, 1970).

Overall, there appears to be some reliable evidence to suggest that a lithium withdrawal syndrome does occur in some bipolar patients, but the proportion of patients presenting the syndrome and the time that it occurs is a matter of dispute (Table 4.1). In unipolar depression, there was no reliable evidence for a lithium discontinuation syndrome and this justified further investigation.

**TABLE 4.1**

CHARACTERISTICS OF DISCONTINUATION LITHIUM STUDIES IN AFFECTIVE DISORDERS WITH LITHIUM.

| STUDY | DESIGN | TRIAL DURATION | DISORDER (No. DISCONTINUING LITHIUM) | No. OF PATIENTS RELAPSING AFTER LI DISCONTINUATION (%) | TIME TO RELAPSE (MONTHS) |
|---|---|---|---|---|---|
| CONTROLLED | | | | | |
| Baastrup *et al* (1970) | double-blind randomized | 5 | Bipolar (22)<br>Unipolar (17) | 12 (55)<br>9 (52) | 5 |
| Melia (1970) | double-blind randomized | 24 | Bipolar (8)<br>Unipolar (1) | 4 (50)<br>1 (100) | 2 |
| Small *et al* (1971) | single-blind cross over | 2.5 | Bipolar (4) | 4 (100) | 2.5 |
| Cundall *et al* (1972) | double-blind cross over | 12 | Bipolar (12) | 10 (83) | 6 |
| Fyro and Peterson (1977) | double-blind randomized | 7.8 | Bipolar (9) | 7 (77) | 3 |
| Christodoulou and Lykouras (1982) | double-blind cross over | 0.5 | Bipolar (17) | 3 (18) | 0.5 |
| Margo and McMahon (1982) | double-blind randomized | 12 | Bipolar (4) | 4 (100) | 0.4 |
| Mander and Loudon (1988) | double-blind cross over | 1 | Bipolar (14) | 7 (50) | 1 |
| OPEN | | | | | |
| Lapierre *et al* (1980) | cross over | 1 | Bipolar (4) | 4 (100) | 0.75 |
| Sashidharan and McGuire (1983) | cross over | 67 | Bipolar (20) | 15 (75) | 12 |
| Goodnick (1985) | cross over | 0.75 | Bipolar (12) | 0 | 0.75 |
| Mander (1986) | retrospective | 24 | Bipolar (29) | 8 (28) | 3 |
| Molnar (1988) | cross over | 16 | Bipolar (6) | 0 | 6 |

### *4.1.3. SEASONALITY AND AFFECTIVE DISORDERS*

The observation that affective disorder is sensitive to seasonal influences has been made since ancient times (Hippocrates, transl. 1979). At present, the issue of seasonality in affective illness has been highlighted by the inclusion in the revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1987) of the term "seasonal pattern" as a description of recurrent major depression and bipolar disorder. In considering the possible relevance of biological rhythms in depression it is important to remember that, because of its inherent cyclicity, depression itself is a kind of abnormal biological rhythm spanning weeks,months or years (Wehr and Goodwin, 1983). Circadian rhythms are implicated in some of the symptoms of depression, such as early awakening and diurnal variation of mood. The role of seasonal patterns, however, has not yet been fully investigated.

A variety of events which are associated with depression have been shown to have a seasonal distribution, for example suicide rates, use of electroconvulsive therapy (ECT), consultations for depression, prescription of antidepressants and hospital admissions for depression (for a review see Wehr and Rosenthal, 1989). For these phenomena, most studies find two seasonal peaks, one in spring and one in autumn. Suicide has been observed to have a maximum incidence in the spring and in the autumn in countries of the northern hemisphere, such as Scotland (McKinlay, 1948) and Canada (Eastwood and Peacocke, 1976). Electroconvulsive therapy is given most often in May and from November to January (Eastwood and Peacocke, 1976). The number of consultations for depression in London was greatest in spring and autumn (Harris, 1984). The

prescribing of antidepressants by general practioners again shows peaks in spring and autumn (Harris, 1986).

Seasonal variations in the number of admissions to hospital for depression have long been observed (Slater,1938; Hare and Walter, 1978; Wehr and Rosenthal,1989). Peaks have been observed mainly in spring (Eastwood and Stiasny,1978; Frangos *et al*, 1980; Rihmer, 1980), in autumn (Eastwood and Stiasny,1978) and in winter (Parker and Walter, 1982). Absence of seasonal pattern has also been noted (Zung and Green, 1974). Unfortunately, the majority of these studies did not take into consideration the heterogeneity of depressive illness and bipolar patients were studied together with unipolar patients (Zung and Green, 1974; Hare and Walter, 1978). The failure to record whether patients were taking medication or not is another drawback in these studies (Eastwood and Stiasny,1978; Parker and Walter, 1982). Studies where these aspects have been taken into consideration, such as Rosenthal *et al* (1984), are mainly based on samples of bipolar patients.

Studies reporting seasonal influences in the rate of readmission of individuals with recurrent unipolar depression are rare. These patients are usually receiving some form of drug therapy which may modify the natural course of illness. Therefore, withdrawal from medication represents an interesting opportunity to observe the natural history of severe unipolar depression since one would expect factors such as seasonality to be more clearly expressed. Discontinuation of lithium prophylaxis for this purpose is particularly favourable for two reasons: first, no short term withdrawal syndrome of lithium discontinuation has been reliably found in unipolar patients, as already discussed and second, lithium prophylaxis is

commonly used in patients with regular recurrence of depressive illness (Consensus Development Panel, 1985).

It was hypothesized that unipolar patients on lithium would not show seasonal differences in readmission as the prophylactic effect of lithium would mask any seasonality effects. Such seasonality effect, if there are any, would, however, be evident in unipolar patients who had discontinued taking lithium.

### *4.1.4. AIMS OF THE PRESENT STUDY*

The present study aimed to examine retrospectively the outcomes of lithium discontinuation in a clinic population of unipolar depressed patients. These were all patients who had been previously admitted to the Royal Edinburgh Hospital, who had been taking lithium and who met the criteria for the study. Outcome was defined as the rate of recurrence of a depressive episode. A group of patients who discontinued lithium was compared with another group of patients who continued to take it . The specific aims of the study were: (i) to assess the efficacy of lithium by comparing outcome in these two groups; (ii) to consider whether a lithium withdrawal syndrome occurs in unipolar patients during the first three months of discontinuation as has been found in in bipolar patients (Mander, 1986-b); (iii) to examine whether there is an increase in the number of hospital readmissions in autumn-winter versus spring-summer and spring-autumn versus summer-winter in recurrent unipolar patients after lithium withdrawal, and to determine whether the seasonal pattern in these patients is different from that observed in patients on prophylactic lithium.

## 4.2. - METHODS

### *4.2.1. COLLECTION OF DATA*

Any retrospective study is dependent on the accuracy of records. In this respect, the Royal Edinburgh Hospital is an excellent centre for retrospective studies, because all clinical notes are typewritten and comprehensively assembled. In addition, demographic details are recorded in a computerized data base by the Lothian Psychiatric Case Register (LPCR). The lithium office separately records biochemical data for all patients taking lithium, noting the serum levels and reminding doctors of the need for further checks. These data bases enabled identification of all patients with a diagnosis of manic depressive illness - depressed type (World Health Organisation, ICD-9, 296.1), who were discharged on lithium between 1st January, 1970 and 31st December, 1986. These records formed the source from which information for the present study was obtained.

### *4.2.2. SUBJECTS*

Patients were included in the study if, at the index admission (admission when lithium was introduced), they:

(i) satisfied DSM-III criteria for major depression (American Psychiatric Association, 1980).

(ii) Had remained symptom free for at least three months following discharge.

(iii) Had no diagnosis other than unipolar depression prior to starting lithium.

(iv) Were established at this index admission on lithium alone for prophylaxis of their recurrent unipolar illness for at least three months.

The number of lithium treated patients was 158 out of a total of 2301 patients identified over the study interval with a diagnosis of unipolar depression. They were further divided into those who eventually discontinued lithium (53) and those who continued to take it (105). Both groups had to be on lithium only. Patients who discontinued lithium had also to fulfil an additional criterion: a) they had not used any psychiatric medication after lithium withdrawal. Thirteen patients from this group failed to meet the above criteria and were excluded because:

(i) Other psychotropic medication was being taken at the time of subsequent discontinuation of lithium.

(ii) It was not clear from their case notes or contact with the patient's general practitioner when lithium treatment was discontinued.

(iii) They were clearly unwell at the time of lithium discontinuation.

The remaining group consisted of 40 patients.

### *4.2.3. OUTCOME AND DISCONTINUATION CRITERIA*

Outcome was determined by time to readmission (again with unipolar depression). Since the patients remained resident in Edinburgh, they were unlikely to be admitted to any other centre. Although this could not be determined with certainty, no particular bias should have been introduced if any admissions were lost in this way. Since multiple readmissions in a single individual are not independent events, only the first readmission of each patient in each interval analysed was counted. In other words, only the first readmission in the period between admission to the study and time zero (as used in survival analysis described in the statistical analyses section) and only the first readmission in the

second interval (after time zero) were used. Only the first discontinuation was taken into account when patients stopped lithium on more than one occasion.

After discharge, three months without readmission was required to exclude the possibility of early relapse. After this period, any readmission was considered to be a recurrence.

### *4.2.4. LITHIUM LEVELS*

Lithium levels were available from routine monitoring and provided a check on compliance. Most levels will have been determined 12-14h following the last lithium dose. The normal range of these measurements was considered to be 0.4 - 1.2 mmol/l.

### *4.2.5. SEASONS*

Seasons were defined by equinoxes and solstices, i.e. spring (23rd March - 22nd June), summer (23rd June - 22nd September), autumn (23rd September - 22nd December) and winter (23rd December - 22nd March).

### *4.2.6. STATISTICAL ANALYSES*

Survival analysis is a method to examine data where the outcome of interest is length of time until an event occurs, in this case readmission to a hospital. The survival function or survival curve represents the cumulative proportion of patients who have not responded, i.e. were not readmitted to a hospital, by a fixed point of time, say t, for T>0. For time =0, the survival function take the value of 1, because

by definition the proportion of patients who have not responded at T=0 is 100%. Over time, as subjects are readmitted, the survival curve decreases. If all subjects eventually respond, the survival curve will decrease to zero. For patients who discontinued lithium (Group A), the first phase was defined as the time from admission to the study (three months after index admission) to the time of lithium discontinuation. For patients who did not discontinue lithium (Group B), the first phase was defined as three months after the index admission, exactly as for patients who discontinued to duration of lithium treatment in A plus/minus 2 years for a matched patient from group A. This allowed an arbitrary time (time zero) in the follow-up of the patients in group (B) to be defined equal to the time of discontinuation of cases in group A. Their outcome could then be determined in two intervals of time equivalent exactly to those for group A but not including lithium discontinuation.

Calculation of the life table was performed as recommended by Fliess *et al* (1976). The estimation of the 95% confidence intervals for the cumulative probability of remaining continuously well in each interval is described in Appendix 4.1. Cumulative probabilities from life table analysis have been compared as a summary chi square and individual probabilities from a critical ratio derived from their standard errors, and this is also demonstrated in appendix 1 (Mantel, 1966; Fliess *et al*, 1976). The variance estimate of the survival curves was measured by Greenwood's (1926) formula.

Clinical data have been compared for the group taking lithium and the lithium discontinuation group using Student's t-test and Mann Whitney test for parametric and non-parametric data, respectively. Both tests were two-tailed. Categorical data was analysed by chi-square. Cox regression model (1972) was

applied to the life table in search of predictors of outcome and discontinuation. One-way analysis of variance and the chi-square with Yates correction were used to compare the various demographic, historical and clinical parameters of the readmitted, remained well and dropout groups. The Scheffe's multiple comparison test was used to determine significant differences on the ANOVA between the groups (dropout vs readmitted plus remained well, readmitted vs remained well). The SPSS-X statistical software program was used for most of the data analysis (Nie *et al*, 1975).

## 4.3. - RESULTS

### *4.3.1. CLINICAL CHARACTERISTICS OF PATIENTS BEFORE STARTING LITHIUM*

The patients in this study were middle aged, predominantly female, and had, on average, at least three admissions to hospital with unipolar depression before starting lithium (Table 4.2). The group who subsequently discontinued lithium were entirely comparable with those who did not. There were no statistically significant differences in sex ratio, the duration since the first illness episode, the annual admission rate, the time spent hospitalised, the number of admissions that had occurred prior to lithium introduction or their lithium levels after its introduction. The only factor on which the groups differed was age at first episode; those who subsequently discontinued lithium were slightly younger (51.8 (14.9) vs 44.8 (15.3), p=0.03) (Table 4.2). The mean duration of treatment with lithium of all patients was 29 months (range 4 months - 11.5 years).

## TABLE 6.4

Demographic and clinical characteristics of patients discontinuing lithium. Values are mean ± standard deviation.

| | |
|---|---|
| Age at trial (years) | 52.7 (16.4) |
| Sex (M,F) | 5, 9 |
| Illness duration (years) | 9.8 (4.7) |
| Episode frequency (per year) | 0.2 (0.2) |
| Duration of lithium therapy (years) | 9.7 (4.9) |
| Last lithium level before discontinuation (nmol/l) | 0.72 (0.1) |

### *4.3.2. PHASE I: BOTH GROUPS TAKING LITHIUM*

Life tables of discontinued and continued groups during phase one are displayed in Tables 4.3 and 4.4. The analysis of these life tables revealed that patients who subsequently discontinued their lithium had been significantly more likely to stay well in the two years after starting it than those who continued it . Because of this, the probability of being well after two years of lithium prophylaxis, as shown in figure 4.1, was significantly higher in the group who then discontinued (0.92 vs. 0.57, $z = 5.20$, $p < 0.01$). The annual rate of readmission of this group during this phase was significantly lower (0.22 (0.69) vs 0.54 (0.88), $p=0.023$). In other words, discontinuation was strongly associated with successful treatment.

### *4.3.3. PHASE II: GROUP A DISCONTINUES, GROUP B CONTINUES*

Tables 4.5 and 4.6 display the life tables of discontinued and continued groups during phase II. The cumulative probability of remaining well for the group who discontinued lithium after two years shows a poor outcome (Figure 4.2). This is true when comparing their probability (0.42 after 2 years) with that of Group A at the end of phase I (0.92) and with the probability of Group B in phase I (0.57) and phase II (0.65) after two years of follow-up.

The risk of recurrence over the first three months following withdrawal (the period when lithium withdrawal admissions occur in bipolar patients) is not significantly increased (Figure 4.2). After three months of discontinuation, the probability of remaining well was 0.83 versus 0.82 of the continued group in phase two.

## TABLE 4.3

Life table of the discontinued group before time zero.

| INTERVAL (MONTHS) | (A) N0. OF PATIENTS STARTING THE INTERVAL WELL | (B) NO. OF PATIENTS DROPPING OUT IN THE INTERVAL | (C) ADJUSTED NO. OF PATIENTS IN THE INTERVAL | (D) NO. OF PATIENTS FAILING IN THE INTERVAL | (E) INTERVAL SPECIFIC PROBABILITY OF REMAINING WELL | (F) CUMULATIVE PROBABILITY OF REMAINING WELL | (G) 95% CONFIDENCE INTERVAL OF THE CUMULATIVE PROBABILITY |
|---|---|---|---|---|---|---|---|
| O-3 | 40 | 1 | 39.5 | 0 | 1 | 1 | 1 |
| 4-6 | 39 | 4 | 37 | 1 | 0.98 | 0.98 | 1.0-0.94 |
| 7-9 | 34 | 8 | 30 | 2 | 0.94 | 0.92 | 1.0-0.82 |
| 10-12 | 24 | 2 | 23 | 0 | 1 | 0.92 | 1.0-0.82 |
| 13-15 | 22 | 5 | 19.5 | 0 | 1 | 0.92 | 1.0-0.82 |
| 16-18 | 17 | 3 | 15.5 | 0 | 1 | 0.92 | 1.0-0.82 |
| 19-21 | 14 | 1 | 13.5 | 0 | 1 | 0.92 | 1.0-0.82 |
| 22-24 | 13 | 1 | 12.5 | 0 | 1 | 0.92 | 1.0-0.82 |

**TABLE 4.4**

Life table of the continued group before time zero.

| INTERVAL (MONTHS) | (A) N0. OF PATIENTS STARTING THE INTERVAL WELL | (B) NO. OF PATIENTS DROPPING OUT IN THE INTERVAL | (C) ADJUSTED NO. OF PATIENTS IN THE INTERVAL | (D) NO. OF PATIENTS FAILING IN THE INTERVAL | (E) INTERVAL SPECIFIC PROBABILITY OF REMAINING WELL | (F) CUMULATIVE PROBABILITY OF REMAINING WELL | (G) 95% CONFIDENCE INTERVAL OF THE CUMULATIVE PROBABILITY |
|---|---|---|---|---|---|---|---|
| O-3 | 105 | 3 | 103.5 | 17 | 0.83 | 0.83 | 0.90-0.76 |
| 4-6 | 85 | 7 | 81.5 | 6 | 0.93 | 0.77 | 0.85-0.69 |
| 7-9 | 72 | 18 | 63 | 7 | 0.89 | 0.69 | 0.78-0.60 |
| 10-12 | 47 | 5 | 44.5 | 1 | 0.98 | 0.68 | 0.78-0.58 |
| 13-15 | 41 | 7 | 37.5 | 3 | 0.92 | 0.63 | 0.74-0.52 |
| 16-18 | 31 | 5 | 28.5 | 2 | 0.97 | 0.61 | 0.72-0.50 |
| 19-21 | 24 | 1 | 23.5 | 1 | 0.96 | 0.59 | 0.70-0.47 |
| 22-24 | 22 | 0 | 22 | 1 | 0.96 | 0.57 | 0.69-0.45 |

## TABLE 4.5

Life table of the discontinued group after time zero.

| INTERVAL (MONTHS) | (A) N0. OF PATIENTS STARTING THE INTERVAL WELL | (B) NO. OF PATIENTS DROPPING OUT IN THE INTERVAL | (C) ADJUSTED NO. OF PATIENTS IN THE INTERVAL | (D) NO. OF PATIENTS FAILING IN THE INTERVAL | (E) INTERVAL SPECIFIC PROBABILITY OF REMAINING WELL | (F) CUMULATIVE PROBABILITY OF REMAINING WELL | (G) 95% CONFIDENCE INTERVAL OF THE CUMULATIVE PROBABILITY |
|---|---|---|---|---|---|---|---|
| O-3 | 40 | 1 | 39.5 | 7 | 0.82 | 0.82 | 0.94-0.70 |
| 4-6 | 32 | 1 | 31.5 | 4 | 0.87 | 0.72 | 0.86-0.58 |
| 7-9 | 27 | 1 | 26.5 | 2 | 0.92 | 0.66 | 0.81-0.51 |
| 10-12 | 24 | 1 | 23.5 | 3 | 0.88 | 0.58 | 0.74-0.42 |
| 13-15 | 20 | 3 | 18.5 | 3 | 0.84 | 0.48 | 0.64-0.32 |
| 16-18 | 14 | 0 | 14 | 0 | 1 | 0.48 | 0.64-0.32 |
| 19-21 | 14 | 1 | 13 | 2 | 0.85 | 0.42 | 0.59-0.25 |
| 22-24 | 11 | 1 | 10 | 0 | 1 | 0.42 | 0.59-0.25 |

**TABLE 4.6**

Life table of the continued group after time zero.

| INTERVAL (MONTHS) | (A) N0. OF PATIENTS STARTING THE INTERVAL WELL | (B) NO. OF PATIENTS DROPPING OUT IN THE INTERVAL | (C) ADJUSTED NO. OF PATIENTS IN THE INTERVAL | (D) NO. OF PATIENTS FAILING IN THE INTERVAL | (E) INTERVAL SPECIFIC PROBABLITY OF REMAINING WELL | (F) CUMULATIVE PROBABILITY OF REMAINING WELL | (G) 95% CONFIDENCE INTERVAL OF THE CUMULATIVE PROBABILITY |
|---|---|---|---|---|---|---|---|
| 0-3 | 105 | 9 | 100.5 | 19 | 0.82 | 0.82 | 0.90-0.75 |
| 4-6 | 77 | 5 | 74.5 | 2 | 0.98 | 0.80 | 0.88-0.72 |
| 7-9 | 70 | 4 | 68 | 2 | 0.98 | 0.78 | 0.86-0.70 |
| 10-12 | 64 | 4 | 62 | 1 | 0.99 | 0.77 | 0.85-0.69 |
| 13-15 | 59 | 4 | 57 | 1 | 0.99 | 0.76 | 0.84-0.68 |
| 16-18 | 54 | 5 | 51.5 | 4 | 0.93 | 0.70 | 0.79-0.61 |
| 19-21 | 45 | 2 | 44 | 2 | 0.96 | 0.67 | 0.77-0.57 |
| 22-24 | 41 | 0 | 41 | 1 | 0.98 | 0.65 | 0.74-0.58 |

## FIGURE 4.1

Life table presentation of the cumulative probability of recurrence of Group A (above) is shown after starting lithium (filled symbols) and after its discontinuation (open symbols). The difference between the two profiles was unlikely to have arisen by chance (Chi-square = 11.85, $p < 0.001$).

## FIGURE 4.2

Group B is shown for two treatment phases in both of which the patients took lithium. Phase I (closed symbols) shows the probability of recurrence after starting lithium prophylaxis and is directly comparable with the phase of lithium treatment for Group A. Phase II (open symbols) shows the probability of recurrence in Group B for a second period of continuing lithium treatment. Its start was arbitrarily defined by matching to the times of lithium discontinuation of patients in Group A. The two phases of lithium prophylaxis are associated with a very similar probability of recurrence.

FIGURE 4.1

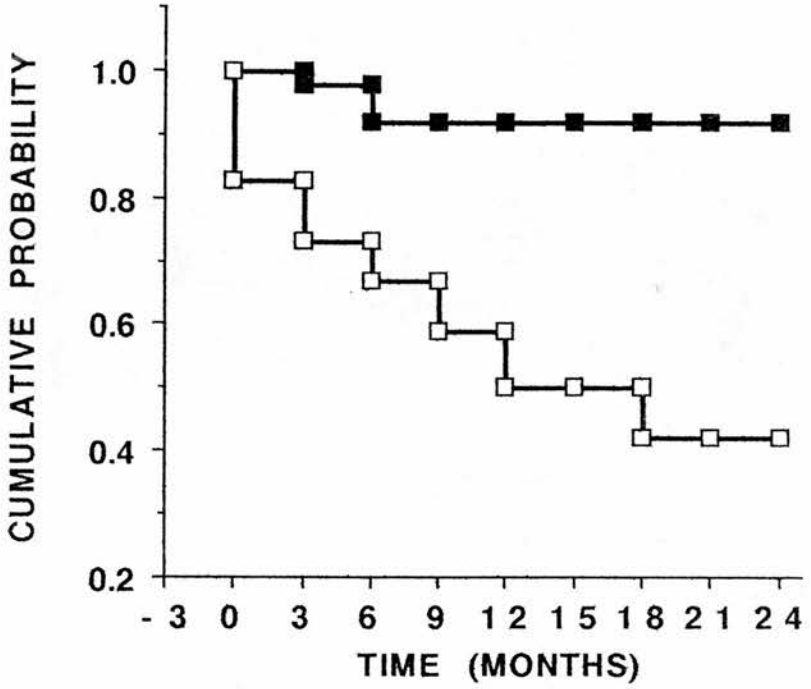
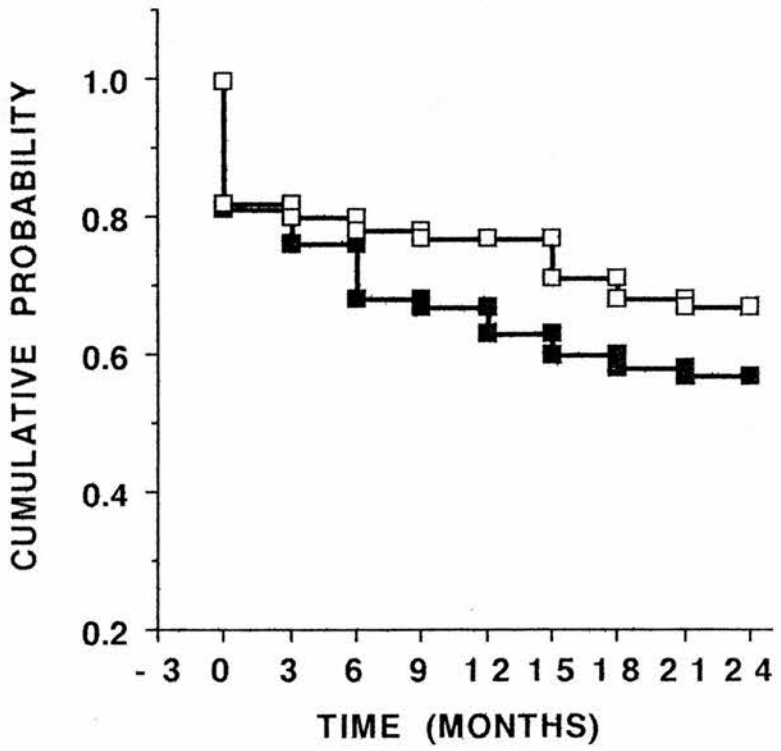



FIGURE 4.2



### *4.3.4. COMPARISON BETWEEN TWO SURVIVAL CURVES*

Table 4.7 displays the significance levels when comparing between the two groups in both phases (the tables are presented in Appendix 4.2). The summary chi-square for the discontinued group comparing before and after lithium withdrawal shows a significant difference ($x^2$= 11.85, p< 0.001) while the equivalent analysis for the continued group was not significant ($x^2$= 0.74, NS). The comparison between phase I of the discontinued group with phases I and II of the continued group were both significant ($x^2$ = 9.74, p<0.005 and $x^2$ = 5.71, p< 0.025, respectively). The comparison between both groups after lithium discontinuation was also significant ($x^2$ = 5.20, p<0.025). However, the probability of detecting a difference between the groups when no true difference exists (Type I error) increases with the number of comparisons conducted between groups. Bonferroni's technique is used to compensate this inflation in type I error (Lachin, 1982). Comparisons of four phases would required a p= 0.008 to achieve a true type I error of 0.05. Using this more rigourous criterion, only the comparison of phases I and II of the discontinued group is statistically significant.

**TABLE 4.7**

Summary chi-square comparison between two survival curves.

| GROUP | CONTINUATION GROUP | | DISCONTINUATION GROUP | |
|---|---|---|---|---|
| | BEFORE TIME 0 | AFTER TIME 0 | BEFORE TIME 0 | AFTER TIME 0 |
| CONTINUATION GROUP BEFORE TIME 0 | - | | | |
| CONTINUATION GROUP AFTER TIME 0 | 2.0 | - | | |
| DISCONTINUATION GROUP BEFORE TIME 0 | 8.5 ** | 5.7 * | - | |
| DISCONTINUATION GROUP AFTER TIME 0 | 0.9 | 5.5 * | 11.8 *** | - |

*=p<0.05, **= p<0.01, ***= p<0.001

### *4.3.5. CLINICAL CHARACTERISTICS AND OUTCOME*

The findings of the previous sections suggest that lithium withdrawal was the major factor associated with the probability of recurrence. However, the clinical features of patients who were readmitted were also of interest and are shown in Table 4.8. Fifty-three patients from both groups (21 discontinuing, 32 continuing lithium) who were readmitted in phase II were compared to the 50 in either group (10 discontinuing, 40 continuing lithium) who remained well and were followed up throughout the 24 month follow-up interval. As would be expected, there were more cases admitted in phase II from the group who discontinued lithium ($x^2 = 3.8$, df=1, $p < 0.05$). They did not differ on any of the other factors examined (Table 4.8) when the Scheffe's test was used.

### *4.3.6. DROPOUTS*

There were no statistical differences in the clinical and demographic characteristics of patients dropping out (patients that discontinued lithium for reasons not related to clinical outcome - moved away, death, etc.) during phase I were compared with patients who were readmitted or remained well for 24 months. The only significant ANOVA was the number of admissions before prophylaxis (F=3.8, df=2,133, p=0.05), where the group who were readmitted had a slight increase in the number of previous admissions (Table 4.8). However, when the readmitted and remained well group were combined, the comparison with the dropping out group was not significant. A similar pattern was observed with no significant differences emerging when the clinical features of patients dropping out during phase II when compared with either patients who were readmitted or remained well for 24 months (Table 4.9).

## TABLE 4.8

Clinical and demographic characteristics of patients who dropped-out, were readmitted and remained well before time zero. All values are mean ± standard deviation. In parentheses are number of patients in each group.

| VARIABLE | READMITTED | REMAINED WELL | DROPPED-OUT | F ratio | p |
|---|---|---|---|---|---|
| Sex (male:female) | 10:25 | 7:29 | 24:50 | | |
| Age at first episode | 50.2 ± 14.7 (33) | 49.2 ± 15.1 (33) | 45.9 ± 17.4 (70) | 1.0 | NS |
| Duration of illness before lithium prophylaxis (years) | 7.2 ± 8.4 (33) | 6.8 ± 6.6 (33) | 7.9 ± 9.7 (70) | 0.06 | NS |
| Number of admissions before lithium prophylaxis | 3.5 ± 3.0 (33) | 2.6 ± 2.0 (33) | 2.1 ± 2.0 (70) | 3.8 | 0.05 |
| Number of weeks in hospital before lithium therapy | 20.9 ± 24.3 (29) | 15.5 ± 16.9 (26) | 13.7 ± 15.6 (55) | 1.4 | NS |
| Mean lithium level before time zero (mmol/l) | 0.71 ± 0.11 (33) | 0.73 ± 0.10 (33) | 0.68 ± 0.15 (70) | 2.1 | NS |

**TABLE 4.9**

Clinical and demographic characteristics of patients who dropped-out, were readmitted and remained well after time zero. All values are mean ± standard deviation. In parentheses are number of patients in each group.

| VARIABLE | READMITTED | REMAINED WELL | DROP-OUTS | F ratio | p |
|---|---|---|---|---|---|
| Sex (male:female) | 15:38 | 11:39 | 16:26 | | |
| Age at first episode | 49.3 ± 16.5 (51) | 50.0 ± 14.6 (48) | 43.6 ± 17.5 (38) | 1.6 | NS |
| Duration of illness before lithium prophylaxis (years) | 6.9 ± 8.3 (51) | 7.0 ± 8.1 (48) | 8.4 ± 9.8 (38) | 0.2 | NS |
| Number of admissions before lithium prophylaxis | 3.0 ± 2.6 (51) | 2.4 ± 1.9 (48) | 2.2 ± 2.3 (38) | 1.4 | NS |
| Number of weeks in hospital before lithium therapy | 18.5 ± 20.6 (40) | 15.0 ± 19.2 (40) | 13.7 ± 15.0 (30) | 0.5 | NS |
| Mean lithium level before time zero (mmol/l) | 0.70 ± 0.14 (51) | 0.70 ± 0.13 (48) | 0.69 ± 0.13 (38) | 0.2 | NS |

### *4.3.7. PREDICTION OF OUTCOME AND DISCONTINUATION*

The readmitted - remained well groups and the discontinued - continued groups were very similar in almost all clinical and demographic variables (see Table 4.2 and Table 4.8). As would be expected, no clinical or demographic predictor of outcome and discontinuation of lithium using the Cox regression analysis could be found. The dependent variables included in the analysis were: age at first episode, sex, number of previous episodes, duration of illness, weeks in hospital before lithium therapy duration. Age at first episode, which was significantly different in the continuation and discontinuation group, is only of marginal importance in the discontinuation of lithium ($p<0.10$: risk of discontinuation decreases with age).

### *4.3.8. SEASONALITY*

Of 105 patients on prophylactic lithium 62 were readmitted during the follow-up period of 4.5 (3.4) years and of the 40 patients who discontinued lithium 28 were readmitted in a follow-up period of 3.7 (3.0) years. These follow-up periods were not significantly different ($t= -1.35$, $df= 78.2$, $p=0.18$). The clinical and demographic characteristics of the patients who were readmitted on lithium and those who were readmitted after its withdrawal were entirely comparable. There were no significant differences in sex ratio (19:43 vs. 7:21, $x^2= 0.08$, p=NS), time since the first illness episode (6.9 (8.5) vs. 6.8 (7.5) years, $U=772.0$, $p=0.62$), the time spent in hospital 17.9 (19.1) vs. 16.7 (17.5) weeks, $U=531.0$, $p= 0.73$), or number of admissions before the introduction of lithium (3.1 (2.6) vs. 2.5 (2.2), $U=734.0$, $p= 0.46$). The only factor on which the groups differed was age at first

episode: those who subsequently discontinued lithium were slightly younger (42.1 (15.7) vs. 51.6 (15.5) years, U= 610.0, p<0.02).

Table 4.10 summarizes the months of the first readmission after the introduction of lithium in both patients who continued to take lithium and those in whom lithium was discontinued. All readmissions in March, June, September and December occurred before the 22nd, therefore they were included in the winter, spring, summer and autumn, respectively.

In the continued group, the comparisons between the observed and expected number of readmissions in autumn-winter and spring-autumn were non significant ($x^2$ = 1.2, and $x^2$ = 0.37, respectively). The 95% confidence interval of these proportions (autumn-winter 44-69%, and spring-autumn 41-66%) again suggesting a non significant finding. In the discontinued group, no comparisons were significant ($x^2$ = 0) and their 95% confidence intervals ranged from 31 to 69%, indicating a non significant result. When the two groups were compared, no seasonal pattern was identified when the readmissions in the autumn-winter were compared with the readmissions occurring in the spring-summer ($x^2$ = 0.13, NS), nor did a seasonal pattern emerge from the comparison between spring-autumn and summer-winter ($x^2$ = 0.01, NS).

## TABLE 4.10

Months of first readmission in unipolar patients during lithium therapy and after its discontinuation.

| MONTHS OF READMISSION | PATIENTS ON LITHIUM | PATIENTS OFF LITHIUM |
|---|---|---|
| January | 6 | 2 |
| February | 6 | 1 |
| March | 5 | 4 |
| April | 6 | 0 |
| May | 1 | 5 |
| June | 6 | 2 |
| July | 4 | 2 |
| August | 6 | 2 |
| September | 2 | 3 |
| October | 5 | 2 |
| November | 7 | 4 |
| December | 8 | 1 |
| Total | 62 | 28 |

## 4.4. - DISCUSSION

### *4.4.1. WHY PATIENTS DISCONTINUE LITHIUM?*

There is no single concept or definition of adherence and compliance (for a review see Jamison and Akiskal, 1983). In this study, the term "nonadherence" describes the discontinuation of lithium prophylaxis while "non-compliance" implies the irregular intake of medication or the premature discontinuation of the treatment (Maarbjerg *et al*, 1988). The expression "drop-out" refers to patients being censored from the continued and discontinued groups.

Adherence and compliance to lithium therapy is dependent on several factors: 1) patient variables - patient's understanding of disease; the quality of the illness free interval, the patient general attitude to psychiatry,e.g. label of mentally ill; 2) illness variables - chronicity, severity and frequency of episodes; 3) drug variables - side effects, reminder of being ill; 4) delivery of care - availability of service, physician attitudes towards lithium; 5) cultural factors - anti-drugs campaigns, health system seen as repressive and punitive (Blackwell, 1976; Muller-Oerlinghausen, 1982; Jamison and Akiskal, 1983).

A major problem in patients continuing to take lithium on a long-term basis is their adherence to treatment. In practical terms, the effects of lithium non-adherence are equivalent to those of lithium non-responsiveness. The only difference is that lithium nonadherence is reversible and carries the possibility of change while lithium nonresponse does not (Jamison and Akiskal, 1983). Because of the vast clinical repercussions the study of lithium discontinuation is an interesting area of research in psychopharmacology.

The problem of lithium discontinuation is as old as the treatment of affective disorders with lithium, and in fact the first patient ever treated successfully with lithium discontinued the medication after six months (Cade, 1949). This phenomenon occurs in spite of many lithium clinics providing information about therapy with lithium (Frank *et al*, 1985; Schou, 1989-b; Walker, 1981). However, written information may only be effective in the short term but not in the longer term (Stitt and Trinca, 1979). Earlier estimates of non-adherence to lithium treatment ranged from 20-30% (Van Putten, 1975; Bech *et al*, 1976), and have been recently revised to 20-50% (Jamison *et al*, 1979; McCreadie *et al*, 1985; Frank *et al*,1985). Education of patients about their disease was reported to improve adherence (Seltzer *et al*, 1980).

An increased risk of recurrence is associated with non-adherence; 20-30% of bipolar patients stop prophylactic treatment against medical advice (Blackwell, 1976) and seventy-five percent of recurrences among lithium users were thought to be due to poor adherence (Baastrup, 1971). Later reports found similar results (Frank *et al*, 1985). The present study supports these findings which show a poorer outcome being associated with lithium discontinuation.

The main reasons for non-adherence to prophylactic lithium in unipolar depression are lithium's side-effects and the belief that they no longer need the treatment (Jamison and Akiskal, 1983; McCreadie *et al*, 1985; Aagaard *et al*, 1988; Schou, 1988). Due to the retrospective nature of this study, we were not able to measure with certainty the proportion of patients who discontinued lithium because of side-effects, and the existence of a state of well-being while on medication. In most cases, no clear reasons for discontinuation were given in the

hospital notes. However, the reduced rate of readmission in the discontinued group suggests that the main reason for lithium discontinuation was the feeling that the medication was no longer necessary. This finding is in agreement with other authors (Schou *et al*,1970; Maj *et al*, 1989-a) who found the conviction of being cured was the most frequently reported reason for interruption of prophylaxis in a group of bipolar and unipolar patients. In other long-term medical treatments, the absence of symptoms is again regarded as a very important factor in the nonadherence of patients (Becker and Mainman, 1980). A contributory factor in the process of refusing to take the medication is the denial of having a serious life-long illness reinforced by the absence of episodes (Jamison and Akiskal, 1983).

### *4.4.2. ARE UNIPOLAR PATIENTS COMPLIANT WITH LITHIUM?*

Different methods to measure compliance have been proposed: interrogation, tablet estimates, drug markers and drug detection (for further discussion see Blackwell, 1976; Jamison and Akiskal, 1983), but all methods have problems of reliability and validity. The non-compliance category is composed of two types of patients: the first group consists of patient who discontinue lithium prematurely (in this study, prematurely means less than three months of lithium therapy). It has been estimated that around 40% of patients discontinue lithium in the first month (Vestergaard, 1983). This group was excluded from this investigation because one of the criteria for inclusion is to have taken lithium for at least three months with the objective of separating true recurrences from relapse of the ongoing episode.

The second group is composed of patients who take lithium intermittently. Patients who continued to take lithium were regarded as compliant judged by the

periodicity of their lithium checks (usually every two-three months) and results of their lithium levels within the normal range (0.40 to 1.2 mmol/l). As these measurements were spaced, we were not able to measure compliance between laboratory measurements, but there was no reason to believe that the pattern of intake was modified in those periods.

### *4.4.3. IS DISCONTINUATION OF LITHIUM ASSOCIATED WITH ITS EFFICACY?*

The probability of remaining well for those that continued lithium was found to be similar to the previous results of Schou (1979-a) who reported a one year probability of 78%, but greater than that of Peselow *et al* (1982) whose two year probability was only 37%. These figures illustrate the quite poor prognosis of many patients with recurrent depressive illness.

Aagaard and Vestergaard (1990) reported that a mixed group of affective disorder patients (unipolar, bipolar and uncertain diagnosis) who later discontinue lithium had more admissions during the two year lithium prophylaxis. The findings of the present study point in the opposite direction, that is patients who stopped their lithium were those who were deriving the most benefit. Further, they may be more likely to do so when young. It is reasonable to assume that psychiatrists are also more likely to agree in these circumstances. Furthermore, patients who continued to take lithium did not derive as much benefit from lithium treatment as did the patients who chose to discontinue. While this appears paradoxical, it is a corollary of what was discussed above: those patients who are doing rather less well, and are slightly older, may be prevailed upon to continue the drug more

readily. Nevertheless, their prognosis on continuing lithium was significantly better than that for patients who stopped lithium.

It is unlikely that the discontinued group had less severe illnesses, since they had spent the same time in hospital as the continued group before the introduction of lithium. Even if their illnesses had been less severe, this would result in a bias in phase II against the demonstration of a deleterious effect of lithium withdrawal.

The possibility that a subtherapeutic level of lithium might explain the poorer outcome of the continued group in either phase compared with the discontinued group before time zero was excluded because no difference in the mean lithium levels could be found when these groups were compared (see Table 4.7). The lack of association between lithium level and outcome is is in agreement with other studies where the lithium levels of responders and non-responders are similar (Maj *et al*, 1985; Smigan, 1985).

The importance of controlling for duration of lithium therapy during phase I refers to the fact that the recurrence rate is dependent on the length of follow-up and a bias could be introduced if one group had a longer follow-up than the second. The definition of a time zero when both groups were matched for duration of lithium therapy avoided this bias.

There have been anecdotal reports that some patients have a poorer outcome in spite of an initial good response to lithium prophylaxis (Dotti and Bernini, 1979). Recurrences after four years of successful treatment with lithium were observed in 11 patients of the continued group; this outcome happened

despite an apparently good compliance to prophylaxis. Until more data are disclosed in relation to these matters, further speculation is of limited value.

### *4.4.4. IS THERE A LITHIUM WITHDRAWAL SYNDROME IN UNIPOLAR PATIENTS?*

The terms withdrawal symptoms and rebound phenomenon have been discussed (Lapierre *et al*, 1980; Christodolou and Lykouras, 1982). The first have been defined by a withdrawal state - hyperactive deep tendon reflexes, tremor of hands and fatigue (Christodolou and Lykouras, 1982) while the second would explain the relapse after lithium discontinuation. In this study, we are unable to measure the first category and consequently only the second is analysed.

The life table shows no excess of recurrences of illness in the first three months in phase II. Therefore, there is no evidence of admissions occurring purely as a result of lithium withdrawal as seen in bipolar patients. Bipolar patients showed an appreciably increased rate of readmission in the three months following lithium withdrawal in a retrospective study fully comparable with this one (Mander, 1986-b). Furthermore, the early appearance of manic symptoms following the withdrawal of lithium was confirmed in a prospective, double-blind, placebo controlled design (Mander and Loudon, 1988). We cannot conclude that depressive symptoms do not appear after lithium withdrawal in unipolar patients, only that the recurrence of symptoms is not severe enough to cause admission, but this is still an important finding. It may explain some of the controversy in the literature regarding the lithium withdrawal syndrome because in different studies, different proportions of bipolar and unipolar patients have been used (e.g. Sashadhiran and McGuire, 1983).

### *4.4.5. WHICH ARE THE PREDICTORS OF OUTCOME AND DISCONTINUATION?*

Demographic,clinical, neurochemical, neuroendocrine, physiological, and psychological predictors of response to lithium therapy have been investigated but with no consensus about their importance (for reviews see Abou-Saleh and Coppen, 1986, 1990; Joyce and Paykel, 1989). In studies of clinical prediction of outcome and lithium response in bipolar affective disorder, conflicting results are shown. Good outcome was not correlated with demographic and clinical variables (Kocsis and Stokes, 1979). Nonetheless, poor outcome has been associated with more frequent admissions before starting lithium (O'Connell *et al*, 1991). Illness duration was the only factor that predicted readmission in a multiple regression analysis where the introduction of lithium was one of the independent variables but it account for only 4% of the variance (Mander, 1986-a).

In this sample, the only difference in the clinical and demographic characteristics was in the number of previous admissions (see Table 4.7). Patients who were readmitted after time zero had been hospitalized more frequently, but no significant difference emerged when this group was compared with the remained well group using the Scheffe's test. As no demographic or clinical variables were found to be significantly different between the groups, the search for factors that would predict outcome in unipolar illness was fruitless. However, this is consistent with other studies which have addressed the question of who is at high risk of recurrence in lithium prophylaxis (Bouman *et al*, 1986).

Similarly, the findings of this study could not predict which patients would discontinue lithium. Of the clinical and demographic variables pre lithium

prophylaxis, only age of first episode was significantly different between the group who continue and the group who discontinue lithium. It should be mentioned that in the discontinued group, outcome was not related to duration of lithium therapy. Of 12 patients who discontinued lithium after being on the drug for over 24 months, five patients remained well for two years, six were readmitted and one dropped out.

In summary, after 40 years of lithium use, its clinical indications are still empirical. No predictive factor has yet been found that would lead any clinician to advise for or against lithium treatment and a clinical trial with the drug is the only way to determine who will respond (Carroll, 1979). Similarly, no predictive variable to identify who will discontinue lithium prophylaxis has been identified.

### *4.4.6. SHOULD LITHIUM EVER BE DISCONTINUED?*

Possible indications for the discontinuation of lithium include the judgement that the risk of relapse is low, the development of intolerable side-effects, the availability of more effective or safer drugs and the ineffectiveness of lithium (Jefferson *et al*, 1983). Different approaches are observed in relation to the possibility of lithium discontinuation. Lithium may be discontinued after some months of therapy if the current episode has been controlled and there is no history of previous episodes (Jefferson *et al*, 1983). Baastrup (1980) recommended that the therapy should be continued for 3 to 4 months following the first acute episode. Krauthammer and Klerman (1978) suggested that lithium could be discontinued in cases where the affective disorder is secondary and the primary cause is successfully treated. Another alternative proposed by Ayd (1981) is the partial discontinuation of lithium through the institution of lithium holidays (e.g., withholding lithium for a period of time).

### *4.4.7. IS THERE A SEASONAL PATTERN OF READMISSION?*

This study provides no evidence for an increased number of readmissions during the autumn-winter months or in the spring-autumn in unipolar depression, either on or off lithium. Winter and summer recurrences were equally likely in patients continuing on lithium. The concept of seasonal affective disorder (Rosenthal *et al*, 1984; Thompson, 1989-b) implies that depression should occur more frequently in the autumn and winter. Seasonal affective disorder has been reported to occur in 16 to 38% of patients with recurrent depression (Wehr and Rosenthal, 1989). Clearly, this does not appear to be true for patients with unipolar depressive disorder at high risk of recurrence on or off lithium. Seasonal peaks for hospital admission for depression in spring and autumn have also been proposed (Thompson, 1989-a; Wehr and Rosenthal, 1989). This study could not confirm the occurrence of this pattern in hospital readmission rates of recurrent depressed patients.

A possible reason for the absence of a seasonality effect found in this study relates to the characteristics of the sample - a homogeneous group of recurrent unipolar depressed patients. Depression is not a unitary condition, and unipolar patients might have a different seasonality of depressive episodes to bipolar patients (Thompson, 1989-a). Considering this hypothesis, two alternative explanations for this negative finding may be raised: first, unipolar patients do not show seasonality at all or alternatively, if a seasonal effect is present it may be restricted to the milder forms of the disease. In seasonal affective disorder, the relative proportions of patients who have a diagnosis of unipolar and bipolar depression have been the subject of controversy and it illustrates conflicting views

about which group more clearly shows a seasonal effect. Some studies have argued that the majority of the patients with seasonal affective disorder were bipolar (Rosenthal *et al*, 1984; Garvey *et al*, 1988), while other groups have found a greater proportion of unipolar patients in their samples (Wirz-Justice *et al*, 1986). At the present moment, it is not yet clear to what extent unipolar depression, or some subgroups of this disorder, show a seasonality effect.

The role of lithium itself in modifying seasonal patterns, e.g. circadian rhythms, has been investigated. Lithium slows or delays circadian rhythms in plants (Engelman, 1973), animals (McEachron *et al*, 1982), and humans (Kripke *et al*, 1979). In fact, the therapeutic effects of lithium in affective disorders have been suggested to arise from a slowing of their uncoupled accelerated circadian rhythms (Tupin, 1970). The influence of lithium in seasonal or annual rhythms is not yet fully understood but there is not enough evidence to permit us to endorse the view that these rhythms are altered by lithium in a significant way.

Some methodological considerations concerning this study of the seasonality of readmission in unipolar depression have to be discussed. First, numbers of patients in the discontinued group are small. Nevertheless, they are relatively homogeneous and representative of recurrent unipolar depression. To examine the natural course of unipolar depression for any length of time without the contamination of prophylactic medication poses serious difficulty for any study. In the present case, the use of lithium provides a more controlled example.

Secondly, there is a potential lag between onset of an episode and admission to hospital. It was observed that some depressive episodes began in the autumn but the hospital admission occurred only in the following spring

(Rosenthal *et al*, 1983). However, in the present patient group, the need for medical supervision of lithium treatment and its withdrawal meant such delays were unlikely to have occurred.

Thirdly, how many seasons are required to establish a seasonal pattern? The period of follow-up was only four years and consequently it may not have been long enough to establish a seasonal pattern.

Fourth, the year might be divided in other ways, but from the monthly distribution of readmission (see Table 4.10) it does not seem plausible that by defining seasons in a different way, a seasonality effect would appear.

### *4.4.8. IS THE SAMPLE HOMOGENEOUS?*

Between 10 to 15% of patients previously diagnosed as unipolar will subsequently suffer from a manic or hypomanic episode (Runck, 1985), but, this risk decreases with longer illness duration (Winokur and Wesner, 1987). As this sample had a mean of 2.5 (2.3) previous admissions, this risk is minimised but not completely ruled out.

### *4.4.9. WERE THE INCLUSION CRITERIA BIASED?*

A selection bias in the patient sample occurred because the inclusion criteria required that patients should have been on lithium only for at least three months. During the 18 years of the study, 2301 patients of the Royal Edinburgh Hospital were at some point prescribed lithium. However, most of them were excluded because: 1) they did not take lithium at all; 2) they did not take lithium

long enough (less than three months); or 3) they took lithium together with other antidepressants and antipsychotics.

### *4.4.10. IS THREE MONTHS ENOUGH TIME TO DEFINE READMISSION AS RECURRENCE?*

An issue that is still unresolved with regard to discontinuation strategies relates to the natural course of the index episode. Discontinuation designs have the potential to confuse the distinction between a relapse and a true recurrence, and consequently a clear definition is critical for any evaluation of study results (for a review of these terms see Frank *et al*, 1991 and Prien *et al*, 1991). Our definition of the end of the index episode was somewhat arbitrary. We relied upon the conservative interpretation of case notes to determine whether patients had been symptom free for at least three months following discharge. The choice of an arbitrary time limit is a compromise. If a period is too short the number of early re-admissions that were likely to have been relapses of the index admission may be increased, if too long, some genuine recurrences may be missed.

It is debatable if three months is enough time to postulate that if a readmission occurs after this period it is due to a new episode rather than a relapse of the index episode. Some authors have preferred shorter periods, for instance in the National Institute of Mental Health - NIMH (Maryland, USA), a recovery from an affective episode was defined as a minimum of eight consecutive weeks with an absence of or only mild affective symptoms (Keller *et al*; 1984; Coryell *et al*, 1987) and even four weeks have been used (Fleiss *et al*, 1976; Fieve *et al*, 1979; Peselow *et al*, 1982; Quitkin *et al*, 1984). Coppen *et al* (1971) considered an intervening period of 4 months before classifying an attack as a new episode.

Longer periods have been used based on the fact that the prophylactic effects of lithium may be felt only after six months to one year of therapy (Baastrup and Schou, 1967; Dunner and Fieve, 1974). Nevertheless, our choice of the three month period seems reasonable and it is unlikely to have invalidated our comparison between patient groups or our interpretation of the effects of lithium withdrawal.

### *4.4.11 WHEN DOES ACUTE LITHIUM TREATMENT STOP AND LITHIUM PROPHYLAXIS START?*

Therapy has been divided in three different phases: acute treatment, continuation and prophylaxis. Short-term treatment is the initiation of psychopharmacologic and psychotherapeutic treatment following a relapse or recurrence until an adequate therapeutic response is achieved. Continuation treatment refers to the consolidation of the acute treatment response. Prophylaxis or maintenance therapy describes the prevention of new episodes on a long-term basis (Thase, 1990). By definition, for a patient to be eligible for prophylactic treatment at least one previous episode has to be diagnosed. Duration of each phase, although distinguishable in theory, is often blurred in clinical practice (Prien, 1987), because of the difficulty in determining when continuation treatment ends (i.e., when the episode is over) and when preventive treatment begins (Prien and Kupfer, 1986). This study considers the continuation period to be the first three months after discharge of the index admission since the patient remains well during that period and the prophylactic period is defined as the following months of therapy after the continuation period.

### *4.4.12. IS READMISSION A GOOD CRITERION OF RECURRENCE?*

One of the major methodological weakness in lithium research is the lack of a consensus morbidity index. A number of ways have been used: 1) recurrence frequency, 2) number of hospitalizations, and 3) overall morbidity measured expressed by a simple or complex rating scale. In research, higher rates in rating scales (e.g. Hamilton) have been used but this is impractical in retrospective studies. This study included only patients who had been admitted to hospital, hence, it focused on the more severe end of the depression spectrum. The choice of readmission rather than recurrence of symptoms was chosen as the outcome measure since it is more definable in a retrospective study. This criterion of recurrence was conservative but more reliable. However, this approach does not allow any inference about the beginning of the episode since it does not take into consideration the fact that some patients have subtle warning symptoms several weeks before the full syndrome appears (Molnar *et al*, 1988) and a readmission is delayed in relation to the exact time of the episode.

The distinction between inpatient-outpatient is important since it may reflect factors such as severity of psychopathology, level of functional impairment, treatment seeking behaviour and a decision by the clinician about the need of a more intensive therapy. The decision to admit to a hospital is also clearly influenced by the availability of social support and alternative community services but the relative homogeneity of the services provided in the area served by the Royal Edinburgh Hospital will have protected us from what might be described as artefacts of patient management. Thus, it would be most surprising if the rate of hospital admission within a given patient group were not directly related to the level

of symptoms. A practical advantage of using readmission as a criterion is that it carries direct implications for the use of expensive in-patient resources.

Another possible source of bias in a retrospective study is the fact that many different psychiatrists were involved in the management of the patients and different criteria of severity might have been used as a criterion of readmission. In practical terms, reduced frequency and reduced severity of episodes run a parallel course but occasionally the decision to readmit may be taken based on different levels of illness severity (Grof *et al*, 1983). However, the relative homogeneity of clinical assessment and psychiatric practice in the Royal Edinburgh Hospital gives a partial protection against substantial differences in psychiatric assessment.

### *4.4.13. ARE RETROSPECTIVE DESIGNS USEFUL IN THE STUDY OF LITHIUM PROPHYLAXIS?*

The most important limitation of retrospective studies is that patients do not enter different treatment groups at random. The groups were defined based on a joint decision by clinician and patient and were not controlled in any way by the investigators. Therefore, bias could be introduced which might contaminate the findings. Indeed, we suspect that bias was introduced in the present study, because the patients who discontinued lithium tended to be younger, and were doing better as a group than the control population; such patients might have been expected to do well after discontinuing lithium, whereas they actually did badly. In other words, the bias introduced by non-random discontinuation could have prevented our finding an effect of lithium prophylaxis but was unlikely to account for what we did observe. However, we believe that the age difference is unlikely to have affected our overall results since the seven year difference is clinically

unimportant. In any event, age was not significantly related to recurrence in this study, a finding that agrees with other work (Carroll, 1979). Randomised studies do not have these disadvantages but may, nevertheless, recruit unusual and hence unrepresentative samples of patients, are often extremely expensive and difficult to organise because they require a multicentre basis, and may have to accept softer definitions of recurrence. Other shortcomings found in this study due to its retrospective design are:

*a) Gradual vs. abrupt discontinuation.* There is no consensus about the merits of gradual vs abrupt discontinuation in clinical trials (Greenhouse *et al*, 1991). In this particular study we are not able to determine how lithium was discontinued due to its retrospective design.

*b) Double depression.* There have been reports that a degree of chronicity in some depressed patients is observed, i.e. a moderate persistence of symptoms not severe enough to require hospitalization (Keller *et al*, 1984). This phenomenon has been called double depression (Keller *et al*, 1982) but we are unable to comment on this because of the study design.

*c) Biological and psychological predictors.* These predictors can not be properly evaluated in a retrospective study.

The advantage of retrospective studies of this sort is that they describe what actually happens in delivery of care, and so are crucial in complementing the findings from randomised trials, for instance, patients with severe personality disorders are often not eligible for participation in a long-term controlled investigation but are treated on an uncontrolled basis. If effects described in research trials fail to be translated into clinical practice, then it is important to determine why not. In a different sense, the success with which an effect can be

translated from research to practice offers one of the more meaningful ways in which a quantitative audit of treatment efficacy could be devised.

### *4.4.14. HOW GOOD IS THE LIFETABLE METHOD IN SURVIVAL ANALYSIS?*

Life-table techniques were first developed by Halley (1693) in the description of mortality. They are by no means new to medical research (Greenwood, 1926) but it was only in the 1970's that researchers begin to apply these techniques for data analysis derived from trials of treatment of affective disorders (Fleiss *et al*, 1976). Life tables are described in details elsewhere (Gross and Clark,1975; Lawless, 1982). There are two methods of analysing survival curves: parametric and non-parametric (Gross and Clark,1975; Lawless, 1982). Parametric methods, such as exponential and Weibull, make assumptions about the distribution of data considered normal whereas non-parametric methods, such as the Kaplan-Meier (Kaplan and Meier, 1958) and the actuarial life table (Fleiss *et al*, 1976), are distribution free in the sense that no specific form for the survival curve is assumed (Woolson *et al*, 1978). We adopted the non-parametric model because it is based on a more conservative approach to the analysis of data and because of previous studies using this technique.

The difference between the Kaplan-Meier estimator and the actuarial estimator of the survival curve is that the Kaplan-Meier curve is used when the exact times of recurrences are known, whereas the life table estimator is used when responses and withdrawals are only known to have occurred during an interval of time (Greenhouse and Stangl, 1989). The estimates in any method will be similar but we prefer to use the actuarial life table because we were interested in examining the two year survival.

The actuarial life table assumes that all patients are last observed in the middle of the interval. Other solutions have been proposed (Chiang 1968; Kaplan and Meier, 1958) but this one is the simplest (Fleiss *et al*, 1976). One of the advantages of the life table technique is the fact that it allows the comparison of survival curves in the presence of censorship (Rubinstein *et al*, 1981). A second advantage is that it permits the analysis of the entire curve instead of comparing each time point separately (Mantel, 1966). A third advantage is that it uses all the survival information accumulated up to the closing date of the study (Cutler and Ederer, 1958).

The mean duration of the intervals of the patients observed to relapse is usually biased and it is dependant on the observation time, therefore the number of episodes in a population increases as the duration of observation is lengthened (Zis and Goodwin, 1979). The description of a sample mean in survival analysis may be affected by some extremely long well intervals and can be misleading. This finding lead Peto *et al* (1977) to state that average times should almost never be cited. To obtain unbiased comparisons of response rates it is necessary to use a method that utilises the total length of follow-up for all patients even when the length of follow-up differs among patients, such technique is called the life table which is a more appropriate way of describing survival data (Greenhouse and Stangl, 1989). Life table methods free the investigator from the necessity of arbitrarily choosing a cross-sectional point on which to report by presenting the continuous description of the pattern of events during the whole follow-up (Keller *et al*, 1982). This method is a powerful tool in analysing data from longitudinal studies in which the outcome is binary (in this case readmission or no-

readmission), patients enter and leave the study at different times and the outcome can occur at any time during the follow-up (Fleiss *et al*, 1978).

The approach of considering all the data in life tables instead of comparing simple points deserves some comment. This approach is more appropriate because it takes into consideration the whole pattern of the curves instead of a specific point estimate. However, this chi-square is especially sensitive to differences in early failures rates (Fleiss *et al*, 1976). This is important when there is crisscrossing such as when one curve is superior in one interval equals in another and inferior in a third one. As can be observed in figures 1 and 2 this pattern did not occur, and therefore, the summary chi-square is adequate.

Limitations of the life table method are: first, the reduced precision when sample sizes are small; second, the formula used in this study to calculate the variance (Greenwood, 1926) is the most employed formula, but it underestimates the variance when the withdrawal rate is high (Chiang, 1968). In spite of these limitations, the life table method is robust for analysing survival curves (Lawless, 1982).

### *4.4.15. HOW SHOULD DROPOUTS BE ANALYSED?*

If the data from all patients were available the calculation of the response rate would pose no problem. However, in the life tale analysis, this is not often the case because a proportion of subjects do not respond, that is, they are not readmitted to a hospital, or do not complete the observed period. These incomplete observations are known as censored observations, and they occur for various reasons: some are censored simply because the study ends before the

event of interest is observed, while others are censored because subjects withdraw or are lost to follow-up. Because of censoring, the relevant data for a survival analysis consists of two components: a) the subject's status at the last point of observation, that is, whether the subject responded or was censored; b) the length of time the subject was followed. In working with these data, two assumptions were made: first, neither the treatment nor the characteristics of patients changed during the period of study, therefore censoring was not related to any of these factors and second censoring was independent of the time of response.

Because dropouts are lost to follow-up (move to other places, failed to return to appointments, etc), it is impossible to determine their clinical status at the time of dropping out , they could be better , the same or worse than individuals who remain under observation. However, for the dropouts who are withdrawn at the closing date of study, there is no reason to believe that their survival experience is not similar to individuals who remain under observation. In any case, some degree of bias is inevitable no matter how the problem is handled statistically (Fleiss *et al*, 1978). In this study, only the analysis where no assumptions are made about the clinical status of drop-outs is reported, and therefore, it was assumed that patients withdrawing from the study did so for reasons not associated with clinical status. This approach has been advocated by Lawless (1982) on the grounds that if censored observations are fairly distributed along the intervals and they are independent of lifetimes then the standard life table should behave reasonably, and also by Cutler and Ederer (1958) on the basis that there is no reason to believe that patients withdrawing from the study are different from patients observed for a longer period. The power of life table analysis depends mainly on the total number of responses observed and is little affected by the degree of censoring (Lininger *et al*, 1979).

# CHAPTER 5

# LITHIUM TREATMENT AND PROPHYLAXIS IN UNIPOLAR DEPRESSION : A META-ANALYSIS

## 5.1. INTRODUCTION

Two decades ago, due to the poor methodological design of lithium trials at that time there was little convincing evidence to support the efficacy of lithium in the treatment of unipolar depression. This was reflected by the statement of Blackwell and Shepherd (1968) who wrote "...the results obtained with lithium in depressive illness are almost uniformly bad". They suggested that any reported beneficial effects of lithium were not in reality due to lithium itself but to an expression of the natural history of the illness. They based their argument on three factors: firstly, the recurrent nature of the illness was in some doubt in patients who had suffered only a few spaced episodes; secondly, some patients while not on lithium had had periods of remission longer than the relatively short period of lithium treatment; thirdly, some patients actually appeared to become worse while they were receiving lithium treatment. Other opponents of lithium also based their scepticism of the apparent efficacy of lithium in clinical observations on the lack of controlled trials. Proponents of lithium at the time, however, opposed controlled trials as it would be unethical to withhold what was observed to be clinically effective treatment for patients at risk of suicide. Even now, the role of lithium in the acute treatment and prophylaxis of depressive illness remains less supported than its role in the management of bipolar illness and mania.

### *5.1.1. REVIEWS OF THE USE OF LITHIUM IN UNIPOLAR DEPRESSION*

The role of lithium in the acute treatment of depression is disputed. Several studies have reported positive findings while other studies have failed to demonstrate such an effect. Some of these studies have already been

described in Chapter 2 (Table 2.2 ). Reviews which support the clinical efficacy of lithium include those of Murray (1984) and Doyal and Morton (1984). Conflicting conclusions, however, were reached by Christodoulou (1968) and Schou (1968, 1976-a), and these were reinforced by official bodies. By the end of the last decade, the WHO Mental Health Collaborating Centres concluded there was not enough evidence to recommend lithium in the treatment of acute depression (WHO, 1989).

Conflicting conclusions have also been reached for lithium prophylaxis in unipolar depression, and some of these have been described in Chapter 2. In support of lithium prophylaxis, Schou (1968) concluded that lithium prevented relapses with equal efficacy in patients suffering both mania and depression and in patients with a history of depression only; Davis (1976) opined that lithium is almost equally effective in unipolar and bipolar patients; and Schou (1976-a) claimed that the evidence for a prophylactic action of lithium in recurrent depression was very strong. On the other hand, Gershon (1974) commented that the case for lithium prophylaxis is not clear and concluded that the studies he reviewed did not imply clear efficacy.

In 1979, Prien and Schou reviewed the available range of publications and reached different conclusions. The six studies included in the Prien (1979) review involved 81 lithium-treated patients and 84 placebo-treated patients. Although four studies found statistically significant differences in favour of lithium, Prien concluded that the evidence was inconclusive. Schou's review (1979-a) included five trials of lithium versus placebo in unipolar samples. Lithium reduced the percentage of patients falling ill within a year from 70% to 20% which Schou concluded to be effective.

Most of these reviews have employed a narrative design in which studies were compared critically, on a qualitative basis. Using this approach, the conclusions tend to reflect those of individual studies which are judged to be the best. This type of review usually ignores the issue of relationship strength, that is they do not assess the size of effect under study, although Davis (1976) attempted some statistical comparisons. He emphasized the distinction between effect size and statistical significance but could not try to combine the results because "different statistical indices were used and it is difficult to combine statistical tests for differences in degree of association" (Davis 1976). Schou (1976-a) also did some statistical analyses but again no combination of the results was sought. To the author's knowledge, there has been no previous review using the techniques of meta-analysis to address this problem.

Further doubts about the effectiveness of lithium prophylaxis were introduced by the reluctance of official bodies in the United States to recommend lithium use in unipolar depression. In 1975, the Neuropsychopharmacology Advisory Committee to the Food and Drug Administration of the United States and the American Psychiatric Association (APA) Task Force on Lithium Therapy concluded that there was still insufficient evidence to warrant an indication of lithium in the prophylaxis of unipolar depression (Prien, 1979). The FDA and APA committees cited two reasons for not recommending lithium for that disorder: a) the definition of unipolar depression was disputed; b) evidence for lithium's effectiveness was based on relatively small samples of patients (Prien, 1979). In that country, the reluctance of these official bodies to recognize lithium maintenance following short-term tricyclic treatment for unipolar depression has an important clinical

implication, which is that lithium is not widely employed and may even be underutilized for this disorder (Schou 1989-a). The small number of patients involved in the trials and the contradictions between the narrative reviews, e.g. Prien (1979) and Schou (1979-a) reinforce the need for a quantitative method to integrate the findings of these small trials.

### *5.1.2. AIM*

The main objective of this review is to analyze quantitatively the results of lithium trials in the acute treatment and prophylaxis of unipolar depression.

## 5.2. METHOD

### *5.2.1. META-ANALYSIS*

The aim of meta-analysis is to employ quantitative techniques to combine the results of different trials. Combining the findings across studies, that either might be too small or too limited to enable conclusions about the effect of treatment to be generalized, provides an attractive alternative to extend the evidence about the treatment's efficacy. The major difficulty in integrating studies comes from the diverse nature of designs and methods employed in the different studies. A primary emphasis can be placed upon measuring effect size rather than simply significance level. It is only by obtaining large numbers of patients that trials can convincingly measure the size of treatment effects and this is often feasible only by combining the results from several similar trials (Peto, 1978). While this is the basis for large prospective multi-centre studies, it can also be applied to the retrospective analysis of a number of small trials that

share a similar but not an identical design. It is, of course, essential that the source trials are satisfactory in the first place; treatment should be randomized and outcome both well-defined and evaluated blind to treatment. However, if these criteria are met the statistical techniques for pooling data are relatively simple and deserve to be more widely known among psychiatrists and general physicians (Yusuf *et al*, 1985). Furthermore, trials of much less satisfactory design can also be quantitatively compared. This is of interest because if treatment effects in poorly controlled clinical studies are comparable with the better trials, it allows us to do greater justice to the clinical observations of an earlier generation of psychiatrists and to make more meaningful comparisons with real clinical conditions (for a detailed discussion of the advantages and disadvantages of meta-anlysis see Appendix 5.2).

Basically, two approaches are used in meta-analysis: combination and comparison of significance levels and effects sizes (Rosenthal, 1983). Although significance level and effect size are correlated they provide distinct information (Strube and Hartmann, 1983; see Section 5.4.8.). The methods of combining and comparing statistical significance used in the analysis of uncontrolled studies are based on those described in detail by Rosenthal (1980,1983). These methods are necessary when studies report solely the significance level and the effect size must be worked out from the p level.

Effect sizes can be measured by different methods: a) the standardized difference between the treatment and control outcome means divided either by the standard deviation of the outcome in the control group (Glass, 1976) or by the pooled standard deviation of both groups (Cohen, 1977); b) percentage of overlap between treatment and control distributions (Cohen,1977); c) logistic

regression (Cox, 1970); d) correlation coefficients (Rosenthal, 1984); and e) the Mantel Haenszel method (1959). The choice of the meta-analytic procedure depends on whether the outcome is continuous or dichotomous. The first two methods are based on the means of the control and experimental group divided by the mean of the control group or the pooled variance of the control and experimental group. When data gathered from the studies are published in terms of means, these methods are very useful to integrate the findings. But, when the outcome of treatment is a binary result rather than a test score (or similar number) the Mantel Haenszel method or the logistic regression could be used. The logistic regression model has the advantage of controlling for covariates, such as age and sex. This is important when the assumption of homogeneity is rejected (which is not the case in this meta-analysis). The choice of the technique is usually not crucial since they give similar results. Only when the heterogeneity of the studies is high or the magnitude of effect is just significant may they yield different results (Streiner, 1991).

The Mantel Haenszel method was chosen to measure the effect sizes for a number of reasons: firstly, the measurement of the observed minus the expected number of failures is readily understandable and it is optimally sensitive to any real effects (Yusuf *et al*, 1985). Secondly, each treatment is compared with its own control (Sacks *et al*, 1987). Thirdly, studies are weighted by sample sizes. Therefore, from the statistical point of view the simple difference between the observed and expected (O-E) number of events is not only more understandable, but it is also more justifiable. It is both unbiased and assumption free (Peto, 1987-a).

The (O-E) divided by the variance gives a good estimate of the odds ratio where the results either favour lithium (odds ratio between zero and one) or the comparison treatment (odds ratio above one). These intervals are asymmetrical because the interval indexing the "negative" effect of lithium treatment is infinitely wide while the interval for indexing the "positive" effect of lithium association is finite. When the logarithm of the log ratio is taken, however, symmetry results. Zero becomes the value indicative of no differential risk, and the whole range of negative values (favouring lithium) is now compared with the whole range of positive values (favouring the comparing treatment) (Fleiss, 1979).

The typical odds ratio provides a useful approximation to the likely size of any effect of treatment in patients not studied. The degree to which such results can be reasonably extrapolated, however, must remain a matter of judgement rather than one of mathematical calculation (Peto, 1987-b).

In the analysis of uncontrolled studies, the z-transformation (Fisher, 1921) was used to normalize the distribution and to make the variance independent of the significance level. The transformation is reported to have a positive bias giving larger weights to larger effect sizes than to small ones. The Fisher transformation expands large effect sizes relative to small ones which causes the confidence interval around large effect sizes to be smaller than those around small effect sizes. The confidence interval around large effect sizes should be smaller because sampling error is smaller. Thus the expansion has the desired effect on confidence intervals, as was originally intended by Fisher (Hunter *et al*, 1982).

The present study illustrates the power of this method for assessing the value of lithium in the treatment and prophylaxis of unipolar depression. The magnitude of the treatment effects may be useful both in guiding the actions of clinicians and better informing patients.

*5.2.1.1. Data Collection*

An effort was made to gather data from all trials written in English, published or not, comparing lithium to other treatments in depressive illness before 1990. The following means were employed: a) a formal computer-aided search using the MEDLINE system of the recent English language medical literature to identify studies comparing lithium to other treatment or placebo in unipolar depression in the period of 1966 to 1989; b) an informal search through Index Medicus, previous reviews, quoted references in published studies and personal questioning of colleagues.

*5.2.1.2. Criteria for Inclusion*

Controlled and uncontrolled studies were reviewed separately, as suggested by Peto (1987-b). Controlled studies were required to have a prospective or discontinuation design with random assignment of treatment, double-blind evaluation of outcome and serum lithium levels within the range 0.4-1.5 mmol/l. Uncontrolled studies were included if they had some kind of group comparison. The contrast could be based on different designs, e.g. cross-over, mirror ( pre- versus post-lithium intervals), retrospective or historical controls. The following details were collected from each publication: name of the study, design, population characteristics, duration of the trial, inclusion and

exclusion criteria, treatments given, and number of drop-outs (see Table 5.1 and 5.3).

In classifying studies, terminology follows conventional usage (Consensus Development Panel, 1985). Acute treatment refers to the use of drugs in a period measured in weeks; prophylactic use is understood as the use of a drug for months or years in an attempt to prevent depressive recurrences. A recurrence is understood as a "new" episode.

*5.2.1.3. Criteria for Exclusion*

No study satisfying the entry criteria was excluded ad hoc. The criteria for exclusion which were established *a posteriori* were: a) only one publication from each study was included in the analysis. The most updated version was used when several papers were based on a single project; this is not uncommon (e.g Goodwin *et al*, 1969, 1972; Quitkin *et al*, 1978; Kane *et al*, 1982); b) some controlled studies were not included because data were described in a way that did not permit quantification of the effect size (e.g. Bennie *et al*, 1983) or they had studied too small a number of unipolar patients (e.g. Melia, 1970; Cundall *et al*, 1972; Peselow *et al*, 1982; Johnstone *et al*, 1988).

*5.2.1.4. Statistical Analysis of Controlled Studies*

Meta-analysis has the purpose of quantifying findings from different studies in terms that are strictly and formally comparable (Glass, 1977). To quantify findings a common measure of outcome must be defined. In treatment

studies, both the significance and the magnitude of effects can be determined for categorical data from 2X2 tables, e.g. treated / control x failure (no response or recurrence) / success (acute response or remained well). The Mantel-Haenszel method is the best known (1959), and lends itself particularly well to the calculation of effect sizes in clinical studies. This method is based on the calculation of the odds ratio. In this particular case, the odds ratio represents the possibility of failure (or success) on lithium versus the possibility of failure (or success) on the comparative treatment. As the raw odds ratio does not take sample size into account, a procedure developed by Mantel and Haenszel (1959) in which sample sizes are considered was used. The confidence interval of the odds ratio gives an estimate of the stability of the conclusions (Yusuf *et al*, 1985). This approach was used for controlled studies (acute treatment and prophylaxis) and uncontrolled studies (acute treatment) in which categorical data were presented. The method of calculating the odds ratios is presented in Appendix 5.1.

The chi-square of heterogeneity is also reported. It tests whether between study differences are significant. It affirmative, it demands explanation by careful post hoc examination of the data. Its method of calculation is also presented in Appendix 5.1.

*5.2.1.5. Statistical Analysis of Uncontrolled Studies*

Uncontrolled studies have tended to use a variety of methodologies from which to derive a statistical interpretation. The Mantel-Haenszel is not commonly used. Instead the declared *p* values must be used to assess significance of effects and also to make estimates of effect size (Rosenthal,

1984). Assessment of significance levels requires the calculation of individual Z scores for each study from the one-tailed significance equivalent to that declared in the study (usually two-tailed). They are combined to derive an overall probability of effect.

Effect size in these studies is calculated by transforming published statistics into a common measure such as Pearson's r. From this an estimate of average effect size can be made by a transformation of r into Fisher Z (Zr). The Pearson product moment correlation coefficient r measures the degree of association between two variables, in this case lithium and good outcome. It is often preferred for uncontrolled studies because it can be derived from the least published information. Large, medium and small effect size correspond to r = 0.5 , 0.3 and 0.1; this can be more easily understood in terms of a binomial effect size display - BESD (Rosenthal, 1984). Using the BESD, the correlation coefficient (r) is translated in the percent improvement, for instance a correlation of 0.30 is equal to 30% clinical improvement. From that a success rate can be calculated, according to the formula (success rate = $0.50 \pm r/2$). Therefore, a 30% improvement means that the success rate is increased from 0.35 to 0.65. The studies were also compared to ensure that the pattern of results was homogeneous (Appendix 5.1).

*5.2.1.6. File drawer problem*

A common criticism of meta-analysis is the possible bias introduced by the failure to publish negative results, also known as the file drawer problem. To counter this potential bias, a fail safe number can be estimated (Appendix 5.1). This is the number of studies with a null result that must be "in the file

drawers" to reduce the overall summed probability below the desired level of significance (by convention p=0.05) (Rosenthal, 1984). The fail safe N allows a reader to easily evaluate the strength exhibited in a review against the assumed completeness of the review's sampling procedure. The Z values, previously calculated, can also be used to estimate a so-called "fail safe N", or the number of unpublished statistically non-significant studies that would invalidate the overall trend of the published findings (Cooper, 1979).

*5.2.1.7. Power Calculation*

Power represents the probability of obtaining a statistically significant result if a difference in efficacy of a specified magnitude really exists. For each individual study whose sample size was above 25 subjects, the power was calculated according to the formula described by Cohen (1977; Appendix 5.1). The result was referred to Table 7.3.15 in Cohen (1977) with level of significance equals to 0.05 and one degree of freedom. When the number of the sample was below 25 subjects tables by Detsky *et al* (1985) were used.

## 5.3. RESULTS

### *5.3.1. ACUTE TREATMENT OF DEPRESSIVE ILLNESS WITH LITHIUM*

Table 5.1 summarizes the design of controlled and uncontrolled studies included in this review. It also describes the duration, admission criteria, exclusion criteria and number of drop-outs. Most studies involved only unipolar patients. Where possible, the data from bipolars have been abstracted from the studies for separate analysis. Almost all the comparisons involving lithium and placebo were of cross-over design; studies comparing lithium with another antidepressant (imipramine, desipramine or tryptophan- see Table 5.2) were prospective. There have been no adequate prospective randomized comparisons with placebo which one might wish to see in evaluating any drug for its efficacy in depressive illness. One of the best designed studies was provided by Johnstone *et al* (1988) where the primary purpose of the study was not the inclusion of unipolar patients, who were consequently not in sufficient numbers to be informative, and by Khan *et al* (1987) who employed minimisation (Taves, 1974) rather than simple randomization in allocating treatment and for ethical reasons allowed patients to drop-out on clinical grounds. The criteria for this were not defined clearly in advance, but the drop-outs dominated the pattern of response and provided the only unambiguous way of comparing lithium and placebo; the advantage of lithium compared to placebo was not statistically significant (Table 5.2).

Table 5.2 summarizes the findings in detail. The prospective studies comparing lithium with placebo, desipramine, imipramine or tryptophan showed a modest advantage for lithium but this did not reach statistical significance

either individually or in total. No individual placebo cross-over study showed a statistically significant effect favouring an antidepressant action for lithium either. The chi-squares of heterogeneity for the comparisons lithium versus antidepressants (controlled studies) and lithium versus placebo (uncontrolled studies) both with three degrees of freedom were not significant ($x^2$=0.98 and $x^2$=1.58, respectively) demonstrating a common direction of the findings. Overall patient numbers are small and the results inconclusive.

Effect size was calculated as the odds ratio (± 95% confidence interval) for each study individually and as a pooled summary statistic (Figure 5.1). Only one trial showed a clear advantage of lithium over antidepressants (Worrall *et al*, 1979). That brought the pooled odds ratio in favour of lithium. However, all studies tend to show an advantage for lithium and hence the treatments were homogeneous ($x^2$=2.45). This finding suggests that there is no difference in efficacy between lithium and other antidepressants which is sometimes interpreted positively, i.e. that lithium is "as effective" as other treatments. The 95% confidence interval is wide and reaches 1.0, or no difference level.

The result of the comparisons of lithium versus placebo in bipolar depressed patients does indicate a statistically significant effect. Overall effect size is not tightly specified because the confidence interval remains wide (0.1-0.7).

**TABLE 5.1**

STUDIES OF THE ACUTE TREATMENT OF UNIPOLAR AND BIPOLAR DEPRESSION WITH LITHIUM.

Controlled studies were prospective, randomized with double-blind evaluation. Only Khan *et al* (1987) was placebo controlled; the others compared lithium with another antidepressant. The design used in uncontrolled studies of lithium versus placebo was cross-over with either single- blind (only Noyes *et al*, 1974) or double-blind evaluation; in most of them the process of randomization is not clearly stated. In the uncontrolled trials the duration of the lithium period was usually greater than the placebo period. In Watanabe *et al* (1975) 25% of patients withdrew from the trial.

[1] Only the studies by Baron *et al* (1975) and Mendels (1976) give information for bipolar patients. In Mendels *et al* (1972) unipolar and bipolar groups could not be separated and only the first phase of the study has been included (cross-over phase omitted).

**TABLE 5.1**

CHARACTERISTICS OF THE CONTROLLED AND UNCONTROLLED STUDIES IN THE TREATMENT OF UNIPOLAR DEPRESSION.

| STUDY | DURATION | ADMISSION CRITERIA | EXCLUSION CRITERIA | DROP-OUTS Li/other |
|---|---|---|---|---|
| UNIPOLAR DEPRESSION CONTROLLED | | | | |
| Mendels *et al* (1972) | 3 weeks | Hamilton score>15 | not described | nil/nil |
| Watanabe *et al* (1975) | 3 weeks | "affective disorder" | physical only | 6/9 |
| Worrall *et al* (1979) | 3 weeks | >2 previous episodes | not described | 2/1 |
| Khan (1981) | 3 weeks | >3 depressive episodes | severe depression | 3/2 |
| Khan *et al* (1987) | 6 weeks | >1 previous episode | suicide risk | 6/8/ |
| UNCONTROLLED | | | | |
| Goodwin *et al* (1972) | Lithium>2 weeks<br>Placebo>6 days | in-patients<br>symptom list | not described | nil/nil |
| Noyes *et al* (1974) | Lithium 2 weeks<br>Placebo 4 days | 1 previous episode<br>symptom list | reactivity<br>hysterical personality | nil/nil |
| Baron *et al* (1975) | Lithium 2 weeks<br>Placebo 2 weeks | episode>4 weeks<br>symptom list<br>Feighner positive | not described | nil/nil |
| Mendels *et al* (1976) | Lithium 3 weeks<br>Placebo 1-3 weeks | severely ill<br>Hamilton =28 | not described | nil/nil |

## TABLE 5.2

LITHIUM VERSUS OTHER TREATMENTS IN ACUTE DEPRESSION.

Lithium was compared with other antidepressants in trials using only unipolar patients. Lithium was compared with placebo in cross-over trials including unipolar and bipolar depressed patients. (O - E) is the difference between the observed and expected number of failures in the lithium group. Variance (V) is given as described in Methods, p is the two-tailed probability corresponding to each normal deviate which is given by (O - E) / $\sqrt{V}$. Outcome was designated in Watanabe *et al* (1975) improved group= fairly to markedly effective, not improved group= ineffective or worse and in *Noyes et al* (1974) improved group= recovered, marked or moderate, not improved group= slight or worse.

**TABLE 5.2**

LITHIUM VERSUS OTHER TREATMENTS IN ACUTE DEPRESSION.

| STUDY | LITHIUM | | COMPARISON TREATMENT | | CALCULATIONS | | |
|---|---|---|---|---|---|---|---|
| | NOT IMPROVED | IMPROVED | NOT IMPROVED | IMPROVED | (O-E) | VARIANCE (O-E) | p |
| UNIPOLAR DEPRESSION | | | | | | | |
| CONTROLLED | | | | | | | |
| LITHIUM X OTHER ANTIDEPRESSANTS | | | | | | | |
| A) Mendels *et al* (1972) | 3 | 9 | 6 | 6 | -1.50 | 1.46 | ns |
| B) Watanabe *et al* (1975) | 4 | 22 | 3 | 16 | -0.04 | 1.47 | ns |
| C) Worrall *et al* (1979) | 9 | 13 | 7 | 6 | -1.05 | 2.08 | ns |
| D) Khan (1981) | 2 | 13 | 2 | 13 | 00 | 0.89 | ns |
| TOTAL | 15 | 48 | 12 | 35 | -2.59 | 5.90 | ns |
| UNCONTROLLED - CROSS-OVER | | | | | | | |
| LITHIUM X PLACEBO | | | | | | | |
| E) Goodwin *et al* (1972) | 8 | 4 | 10 | 2 | -1.00 | 1.17 | ns |
| F) Noyes *et al* (1974) | 9 | 7 | 5 | 2 | -0.73 | 1.21 | ns |
| G) Baron *et al* (1975) | 7 | 3 | 8 | 2 | -0.50 | 0.98 | ns |
| H) Mendels (1976) | 4 | 4 | 1 | 3 | 0.67 | 0.70 | ns |
| TOTAL | 28 | 18 | 24 | 9 | -1.56 | 4.06 | ns |
| BIPOLAR DEPRESSED | | | | | | | |
| LITHIUM X PLACEBO | | | | | | | |
| G) Baron *et al* (1975) | 1 | 7 | 5 | 3 | -2.00 | 1.00 | <0.04 |
| H) Mendels (1976) | 4 | 9 | 6 | 3 | -1.90 | 1.38 | ns |
| TOTAL | 5 | 16 | 11 | 9 | -3.90 | 2.38 | <0.01 |

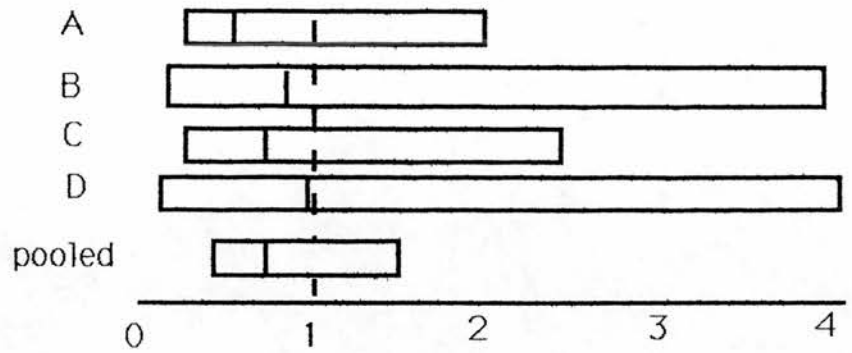
## FIGURE 5.1

The odds ratio with the 95% confidence intervals for individual and pooled data from acute treatment studies. The left side (< 1.0) favours lithium and the right side (>1.0) gives advantage to the other treatment; lithium versus other antidepressants in controlled studies of unipolar illness gives a just advantage to lithium; lithium versus. placebo in cross-over studies of unipolar illness showed no statistically significant effect; lithium versus placebo in bipolar depressed patients showed an advantage to lithium. No chi-square of heterogeneity was significant for individual group of studies.

The only significant chi-square of association was found in studies of bipolar patients ($x^2 = 6.37$ $p < 0.05$). Some studies had 95% confidence intervals which extended beyond 4.0 and are not drawn in full: Watanabe *et al* 1975 from 0.19 to 4.93; Khan 1981 from 0.12 to 7.9; Mendels 1976 from 0.25 to 26.5.

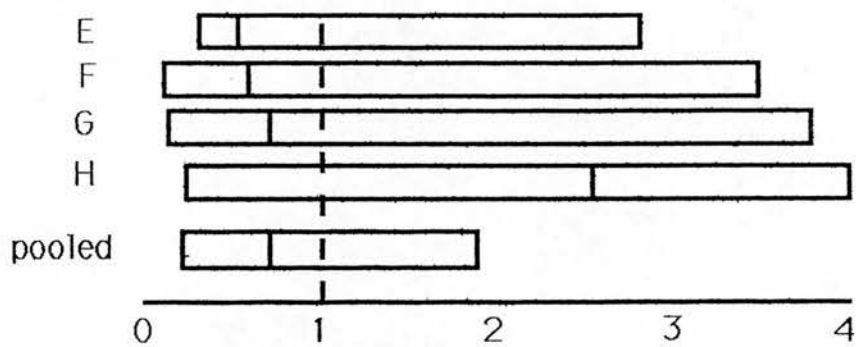
UNIPOLAR DEPRESSION

LITHIUM V. OTHER ANTIDEPRESSANTS




UNCONTROLLED - CROSS-OVER

LITHIUM V. PLACEBO




BIPOLAR DEPRESSED TYPE

LITHIUM V. PLACEBO

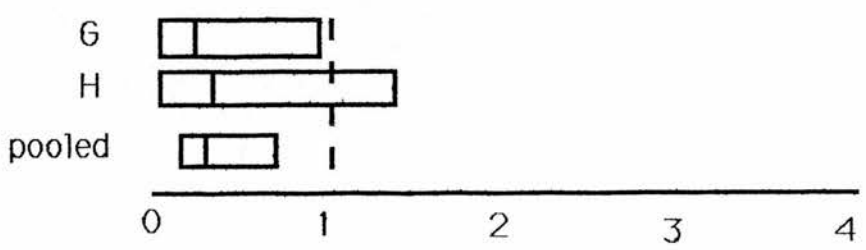



figure 5.1

### *5.3.2. PROPHYLAXIS OF DEPRESSIVE ILLNESS WITH LITHIUM*

Table 5.3 summarizes the design and clinical characteristics of the controlled and uncontrolled studies of the prophylaxis of unipolar depression with lithium. Ten studies are of randomized design and examine follow-up intervals of 5 months to 3 years. They are further analysed in Table 5.4 which summarizes outcome in terms of treatment success or failure.

#### *5.3.2.1. Lithium vs Placebo*

Most trials of lithium versus placebo have shown a statistically significant benefit from lithium. However, the largest, by Prien *et al* (1984), did not. The particular advantage of the analysis presented in Table 5.4 and Figure 5.2 is that, the effect size in this study is shown to be compatible with that of other studies and to favour lithium treatment. However, because the rates of recurrence in both groups were high, the variance and hence the confidence interval were increased. The summary statistics for the pooled data are powerfully in favour of a benefit from lithium compared with placebo (Figure 5.2). The pooled odds ratio when lithium was compared to placebo was 0.22 with 95% confidence interval 0.13 to 0.36. In other words, lithium prophylaxis reduced the odds of recurrence over about one year (the average duration of the trials) by 78 % (confidence interval 87% to 64%). This result corresponds to the sum for O-E of - 22.3, suggesting that 45 recurrences had been avoided with the use of lithium (out of a total of 137 patients treated; there were 126 untreated controls). This summary combines data from discontinuation studies with that from randomized prospective treatment (Table 5.3). If discontinuation studies are excluded, the effect size is 0.26 (95% C.I. = 0.15 to 0.47) and so remains

essentially unchanged. The chi-square of heterogeneity with eight degrees of freedom was not significant ($x^2$=13.9). The Spearman's correlation coefficients between effect size and duration of the trial (0.54) trial size (0.31), disc-prospective (0.32) and year of publication (0.39) were all non significant.

*5.3.2.2. Lithium vs Other Antidepressants*

In contrast to the results with placebo, lithium is not demonstrably superior to antidepressant treatment in preventing recurrence. The pooled odds ratio of the comparison lithium versus other antidepressants was 0.74 with 95% C.I. = 0.47 to 1.17 (Figure 5.2). The confidence interval leaves much room for debate about the relative efficacy. Some antidepressants may be less effective than others (e.g. mianserin, see Table 5.4). The chi-square of heterogeneity with seven degrees of freedom was significant ($x^2$=19.1, $p<0.02$) with some trials favouring lithium while others favoured the antidepressant. For the prophylactic controlled studies, the Spearman correlation coefficients were not significant between effect size-sample size (0.61) and effect size-year of publication (0.29). The Spearman correlation coefficient between effect size-duration of trial (0.72) just missed significance (0.06). Lithium alone has been compared with lithium plus imipramine in some studies; the results are wholly inconclusive (Table 4).

**TABLE 5.3**

CHARACTERISTICS OF STUDIES IN THE PROPHYLAXIS OF UNIPOLAR DEPRESSION WITH LITHIUM.

Glen I refers to the study of Glen *et al* (1984) comparing lithium and amitriptyline in recurrent unipolar depression; Glen II was the other half of the study in which first episodes depressives were treated with lithium, amitriptyline or placebo. Mirror design means that patients were studies before and after the introduction of lithium; in many of these trials the length of the lithium period was different from the placebo period. In Hullin *et al* (1972) unipolar and bipolar patients could not be separated. In Prien *et al* (1973) only the second phase is reported (5-24 months); the first phase (1-4 months) was omitted but showed similar results.

[1] Research Diagnostic Criteria.

**TABLE 5.3**

CHARACTERISTICS OF CONTROLLED AND UNCONTROLLED STUDIES IN THE PROPHYLAXIS OF UNIPOLAR DEPRESSION WITH LITHIUM.

| STUDY | DESIGN | DURATION | ADMISSION CRITERIA | EXCLUSION CRITERIA | DROPOUTS Li - OTHER |
|---|---|---|---|---|---|
| CONTROLLED | | | | | |
| Baastrup *et al* (1970) | discontinuation | 5 months | on Lithium > 1 year | schizoaffective | 1/4 |
| Coppen *et al* (1971) | prospective | up to 26 months | frequent episodes | not described | 2/11 |
| Hullin *et al* (1972) | discontinuation | 6 months | no admission previous 2 years, on Lithium | physical disorders | ?/? |
| Prien *et al* (1973) | prospective | 5-24 months | frequent episodes | severe illnesses, age > 60 years | 12/11 (imipramine) 20 (placebo) |
| Fieve *et al* (1976) | prospective | mean = 20.5 months (lithium) 9 months (placebo) | Feighner positive, frequent episodes | hypomania | 2/3 |
| Coppen *et al* (1976) | prospective | 12 months | on Lithium > 1 year, >3 previous episodes | not described | 5/9 |
| Coppen *et al* (1978) | prospective | 12 months | >3 previous episodes | severe psychiatric and physical illnesses | 5/8 |
| Kane *et al* (1982) | prospective | mean 11 months | RDC[1], frequent episodes, euthymia 6 months | other medication, <18 years, >65 years | ?/? |
| Glen *et al* (1984) - I | prospective | up to 36 months | RDC, >1 episode | physical illnesses, <25 years, >65 years | I) 1/3 |
| Glen *et al* (1984) - II | prospective | up to 36 months | RDC, first episode | | II) 0/1 (amitriptyline) 0 (placebo) |
| Prien *et al* (1984) | prospective | 24 months | RDC, frequent episodes, rating scales scores | other psychiatric and physical illnesses <21 years, >60 years | ?/ ?/? |

**TABLE 5.3** (CONTINUATION)

CHARACTERISTICS OF STUDIES IN THE PROPHYLAXIS OF UNIPOLAR DEPRESSION WITH LITHIUM.

| STUDY | DESIGN | DURATION | ADMISSION CRITERIA | EXCLUSION CRITERIA | DROPOUTS Li - OTHER |
|---|---|---|---|---|---|
| UNCONTROLLED | | | | | |
| Baastrup and Schou (1967) | mirror | before = 6.5 years; on lithium = 1-5 years | frequent episodes, on Lithium >1 year | not described | nil |
| Angst *et al* (1970) | mirror | before, mean =9.1 months; on lithium, mean =9.1 months | frequent episodes | not described | nil |
| Persson (1972) | Historical controls | before, 2 years; on lithium, 2 years | >1 episode | not described | 12 |
| Lepkifker *et al* (1985) | retrospective | 1-15 years | >3 previous episodes | various reasons | 15 |
| Smigan (1985) | mirror | mean 27.3 months | on lithium, frequent episodes | various reasons | 10 |
| Bouman *et al* (1986) | retrospective | before, mean =7.8 years; on lithium, mean =54.5 months | Feighner positive, frequent episodes | not described | nil |
| Souza *et al* (1990) | retrospective discontinuation | 2 years | DSM III | other psychiatric medication | nil |

## TABLE 5.4

PROPHYLAXIS WITH LITHIUM IN UNIPOLAR DEPRESSION: CONTROLLED STUDIES.

The pooled results for the comparison lithium versus placebo indicates a powerful treatment effect for lithium ($p<0.00006$) while the result obtained with the comparison lithium versus other antidepressants was not significant. Only two studies compared lithium with the combination lithium + imipramine and the pooled result favoured the combination ($p<0.02$). Glen I data are from patients with more than one previous episode, Glen II data are from patients with one previous episode. Chi-square of heterogeneity was found significant in lithium versus antidepressant treatment ($x^2 = 19.1$, d.f.=6, $p<0.01$), where different trials show different results.

(O - E) is the observed minus the expected number of failures in the lithium group. V is the variance of (O - E) , p is the two-tailed probability corresponding to each normal deviate given by (O - E) / $\sqrt{V}$.

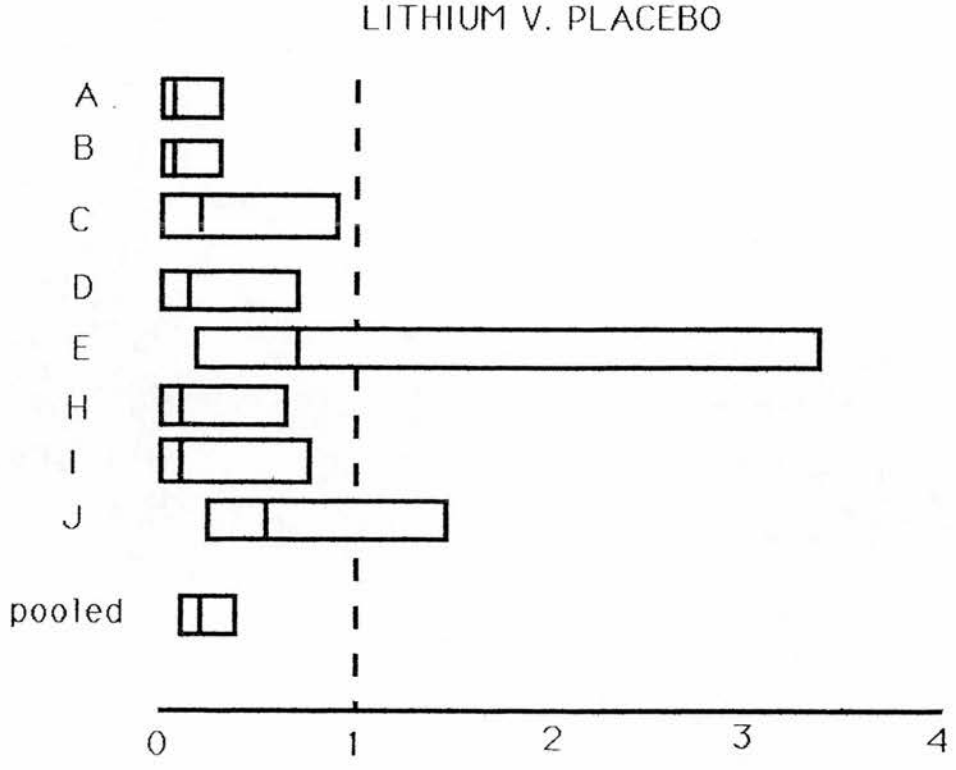
**TABLE 5.4**

PROPHYLAXIS WITH LITHIUM IN UNIPOLAR DEPRESSION: CONTROLLED STUDIES.

| STUDY | LITHIUM | | COMPARISON TREATMENT | | CALCULATIONS | | |
|---|---|---|---|---|---|---|---|
| | FAILED | WELL | FAILED | WELL | (O-E) | VARIANCE (O-E) | p |
| LITHIUM X PLACEBO | | | | | | | |
| A) Baastrup *et al* (1970) | 0 | 17 | 9 | 8 | -4.5 | 1.70 | <0.0006 |
| B) Coppen *et al* (1971) | 1 | 10 | 12 | 3 | -4.5 | 1.65 | <0.0004 |
| C) Hullin *et al* (1972) | 1 | 17 | 6 | 12 | -2.5 | 1.45 | <0.03 |
| D) Prien *et al* (1973) | 9 | 13 | 11 | 2 | -3.5 | 2.06 | <0.01 |
| E) Fieve *et al* (1976) | 8 | 6 | 9 | 5 | -0.5 | 1.73 | ns |
| H) Kane *et al* (1982) | 2 | 5 | 6 | 0 | -2.3 | 0.82 | <0.01 |
| I) Glen *et al* (1984) | 5 | 6 | 8 | 1 | -2.1 | 1.18 | <0.04 |
| J) Prien *et al* (1984) | 21 | 16 | 24 | 10 | -2.4 | 4.17 | ns |
| TOTAL | 47 | 90 | 85 | 41 | -22.3 | 14.76 | <0.00006 |
| LITHIUM X OTHER ANTIDEPRESSANTS | | | | | | | |
| D) Prien *et al* (1973) | 9 | 13 | 6 | 15 | 1.33 | 2.49 | ns |
| F) Coppen *et al* (1976) | 3 | 9 | 6 | 2 | -2.40 | 1.25 | <0.03 |
| G) Coppen *et al* (1978) | 0 | 15 | 7 | 6 | -3.75 | 1.35 | <0.001 |
| H) Kane *et al* (1982) | 2 | 5 | 5 | 1 | -1.76 | 0.86 | <0.84 |
| I-1) Glen *et al* I (1984) | 32 | 14 | 39 | 16 | -0.33 | 5.28 | ns |
| I-2) Glen *et al* II (1984) | 5 | 6 | 4 | 3 | -0.50 | 1.13 | ns |
| J) Prien *et al* (1984) | 21 | 16 | 16 | 22 | 2.74 | 4.74 | ns |
| TOTAL | 72 | 78 | 83 | 65 | -4.67 | 17.10 | ns |
| LITHIUM X LITHIUM + IMIPRAMINE | | | | | | | |
| H) Kane *et al* (1982) | 2 | 5 | 1 | 7 | 0.6 | 0.64 | ns |
| J) Prien *et al* (1984) | 21 | 16 | 12 | 25 | 4.5 | 4.63 | <0.03 |
| TOTAL | 23 | 21 | 13 | 32 | 5.1 | 5.27 | <0.02 |

## FIGURE 5.2

The 95% confidence intervals (C.I.) of the individual and pooled odds ratios in the controlled studies of prophylaxis. The pooled odds ratio of the comparison lithium versus placebo totally favoured lithium (the whole 95% C.I. is below 1.0). The comparison lithium versus other antidepressants gives a pooled odds ratio which is inconclusive (the 95% confidence interval extends from 0.5 to 1.2). The 95% C.I..of the comparison lithium plus imipramine versus lithium favours the combination but the 95% C.I. is too wide (from 1.1. to 6.1) for a firm conclusion. The 95% confidence intervals in one lithium v. other antidepressants trial (Prien *et al*, 1984) extended beyond 4.0, from 0.7 to 4.3. Glen I data is from patients with more than one previous episode, Glen II data is from patients with one depressive episode.


LITHIUM V. PLACEBO
A
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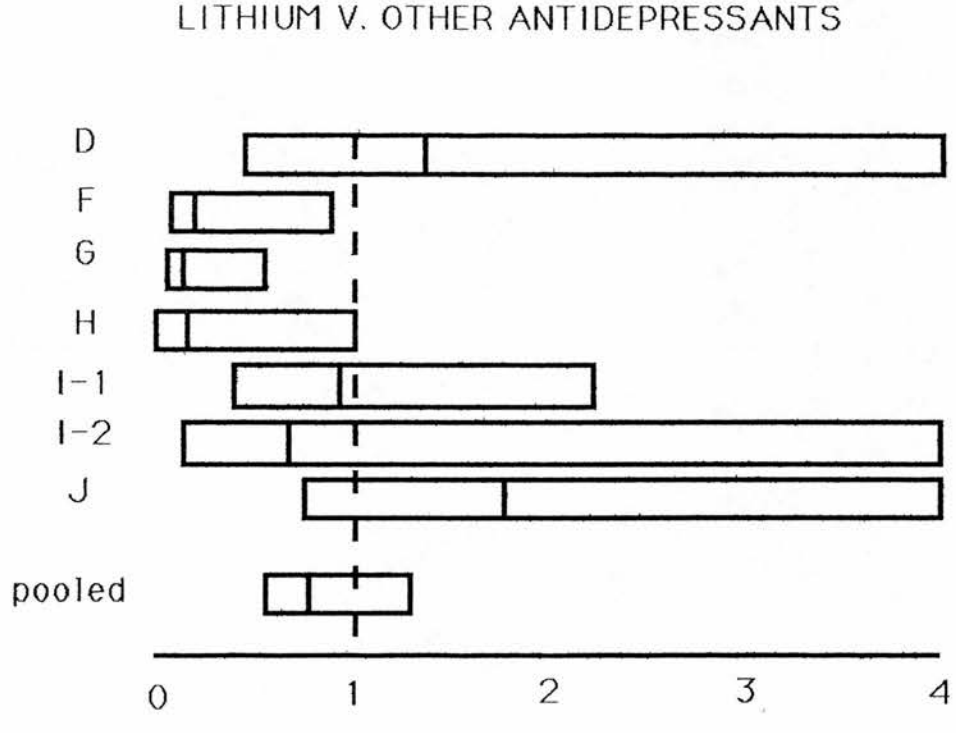
LITHIUM V. OTHER ANTIDEPRESSANTS
D
F
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H
I-1
I-2
J
pooled
0
1
2
3
4

figure 5.2

*5.3.2.3. Uncontrolled Prophylactic Trials*

Table 5.5 summarizes the findings of the uncontrolled prophylactic studies. As explained in Section 5.2.1.5, the wide differences in mode of data analysis and presentation make an approach based on the Mantel-Haenszel method impracticable. Instead, following Rosenthal (1984) significance levels were compared and combined and effect sizes estimated from the *P* values declared in each trial. Significance levels differ significantly indicating study heterogeneity (Chi square = 11.43, df = 6, $p<0.05$), but all support a similar positive treatment effect from lithium. Thus the combination of probabilities was highly significant ($Z = 6.5$). The combined effect size was found to be in the medium range, $r = 0.41$. The combined effect size of the controlled studies expressed in the same terms was $r = 0.42$. These values of r can also be understood in terms of proportional outcome ( Rosenthal, 1984). A value of $r=0.4$ corresponds to an improvement in positive outcome from 30 to 70%.

## TABLE 5.5

PROPHYLAXIS WITH LITHIUM IN UNIPOLAR DEPRESSION:
UNCONTROLLED STUDIES.

Pearson correlation coefficient (r) for the uncontrolled studies were homogeneous, and the overall correlation was r = 0.41. *P* is the reported level of significance (one-tailed); *Z* is the normal deviate (one-tailed) corresponding to each p; *n* is the number of patients studied; '*r*' is Pearson product moment correlation coefficient, given by $Z/\sqrt{N}$; '*Zr*' is the transformation of r in Fisher z, where $Zr = 1/2 \log_e ((1+ r)/(1- r))$. The 'mean' value for *r* (given in brackets) is derived from the mean for *Zr*.

## TABLE 5.5

PROPHYLAXIS WITH LITHIUM IN UNIPOLAR DEPRESSION:
UNCONTROLLED STUDIES.

| STUDY | P | Z | N | √N | r | Zr |
|---|---|---|---|---|---|---|
| Baastrup and Schou (1967) | <0.0005 | 3.3 | 22 | 4.69 | 0.70 | 0.86 |
| Angst *et al* (1970) | 0.0005 | 3.3 | 58 | 7.61 | 0.40 | 0.42 |
| Persson (1972) | 0.01 | 2.3 | 32 | 5.65 | 0.40 | 0.42 |
| Lepkifker *et al* (1985) | 0.001 | 3.1 | 33 | 5.74 | 0.54 | 0.60 |
| Smigan (1985) | 0.37 | 0.3 | 19 | 4.35 | 0.07 | 0.07 |
| Bouman *et al* (1986) | 0.26 | 0.6 | 20 | 4.47 | 0.13 | 0.13 |
| Souza *et al* (1990) | 0.001 | 3.1 | 40 | 6.32 | 0.49 | 0.53 |
| Total | | 16.0 | | | | 3.03 |
| Mean | | 2.3 | | | (0.41) | 0.43 |

### *5.3.3. FAIL-SAFE N*

The number of additional studies showing no treatment effect that would be necessary to reverse the main findings illustrated in this meta-analysis necessarily vary according to the effect size obtained in each comparison. Only one statistically non-significant study needs to be published to invalidate both the conclusion that lithium is more effective than other antidepressants in unipolar depressed patients and the finding that lithium plus imipramine is superior to lithium in maintenance treatment of unipolar depression. Three statistically non-significant studies need to be published to invalidate the conclusion that lithium is more effective when compared to placebo in bipolar depressed patients. However, for the strongest effect, lithium versus placebo in the prophylaxis of unipolar illness, 108 'negative' studies would be needed to invalidate the conclusion currently favouring lithium. It should be appreciated that a negative study for these purposes need not show an opposite effect to that currently seen; assuming random treatment effects, some would favour a treatment effect, some not.

### *5.3.4. POWER CALCULATION*

Table 5.6 shows the power of the treatment studies. In all lithium versus other antidepressants comparisons the power was low with the exception of one case (Worrall *et al*, 1979). This means that the possibility of missing a difference when such a difference truly exists, i.e. of making a type II error, was in one study over 90 percent (Watanabe *et al*, 1975). In other words, if a difference really exists in that study it would have one chance in ten of being

detected. All the cross-over trials of lithium versus placebo showed a similar pattern, in none of them was power greater than 0.20.

The power of prophylactic studies is shown in Table 7. Most of the trials comparing lithium against placebo had enough subjects to detect a difference in outcome between the groups. The only exceptions were the trials by Fieve *et al* (1976) and Prien *et al* (1984) which showed low power. The picture in relation to the comparison of lithium with other antidepressants is mixed with three studies showing power over 0.50 and four power below 0.30. One trial which compared lithium with the combination of lithium and imipramine showed a lack of power (Kane *et al*, 1982).

**TABLE 5.6**

POWER CALCULATION OF ACUTE TREATMENT LITHIUM STUDIES.

The low power to detect a significant difference was the main feature of the treatment studies. All lithium versus other depressants trials had power around 0.20 with the exception of Worrall *et al* (1979) which had enough power. In all cross-over trials the possibility of failing to detect a true difference was over 70%. In bipolar depression, one of the trials had a 70% chance of comitting a type II error.

| STUDY | N | W | POWER |
|---|---|---|---|
| *Unipolar depression: controlled* | | | |
| Lithium x placebo | | | |
| Khan *et al* (1987) | 27 | 0.20 | <20 |
| Lithium x other antidepressants | | | |
| Mendels *et al* (1972) | 24 | 0.25 | 20 |
| Watanabe *et al* (1975) | 45 | 0.01 | <10 |
| Khan *et al* (1981) | 30 | 0 | <10 |
| Uncontrolled: cross-over | | | |
| Goodwin *et al* (1972) | 24 | 0.20 | <20 |
| Noyes *et al* (1974) | 23 | 0.13 | <10 |
| Baron *et al* (1975) | 20 | 0.11 | <10 |
| Mendels (1976) | 12 | 0.26 | <20 |
| *Bipolar depression* | | | |
| Lithium x placebo | | | |
| Mendels (1976) | 12 | 0.34 | 30 |

**TABLE 5.7**

POWER CALCULATION OF LONG TERM LITHIUM STUDIES.

Power calculation of prophylactic studies showed significant differences among studies. Only two trials of the lithium versus placebo studies did not show good power (Fieve *et al*, 1976; Prien *et al*, 1984). The comparison lithium with other antidepressants exhibit four trials with inadequate power. One of the trials comparing the combination lithium plus imipramine versus lithium display a lack of power (Kane *et al*, 1972).

| STUDY | N | W | POWER |
|---|---|---|---|
| *Lithium x placebo* | | | |
| Fieve *et al* (1976) | 28 | 0.06 | <0.10 |
| Prien *et al* (1984) | 71 | 0.12 | <0.20 |
| *Lithium x other antidepressants* | | | |
| Prien *et al* (1973) | 43 | 0.12 | 0.10 |
| Glen *et al* (1984) (I) | 101 | 0.19 | 0.10 |
| Glen *et al* (1984) (II) | 18 | 0.10 | <0.10 |
| Prien *et al* (1984) | 75 | 0.15 | 0.30 |
| *Lithium x lithium + imipramine* | | | |
| Kane *et al* (1972) | 15 | 0.20 | 0.20 |

## 5.4. DISCUSSION

### *5.4.1. IS LITHIUM EFFECTIVE IN THE TREATMENT OF UNIPOLAR DEPRESSION?*

Acute treatment with lithium alone in unipolar depression has rarely been subject to satisfactory evaluation and the methodological sound trials which have been carried out have used too few patients. The absence of adequate trials which have compared the effects of lithium with the effects of placebo gives rise to understandable doubts about the efficacy of lithium alone in unipolar patients. The conventional wisdom that it is without effect may, however, be misleading. The finding of "no difference" from other established antidepressant treatments is traditionally sufficient to launch new alternative antidepressants. Since this is the position for lithium, the case in unipolars remains unproven. The confidence intervals illustrated in Figure 5.1 show that it is not possible to ascertain how effective lithium is compared either with placebo or other antidepressants in unipolar depression. There does appear to be an acute treatment effect in bipolar patients who are depressed, but the magnitude of the effect is equally uncertain.

### *5.4.2. IS LITHIUM EFFECTIVE IN THE PROPHYLAXIS OF UNIPOLAR DEPRESSION?*

Positive findings of lithium's therapeutic efficacy were remarkably homogeneous. Across different studies, be it those examining discontinuation of lithium in patients who may have been selected lithium responders (e.g. Baastrup *et al*, 1970; Hullin *et al*, 1972), or those in which lithium was being

started prospectively, the effect size was large and consistently in favour of lithium compared with placebo. Follow-up was often short, and may sometimes have included patients who were relapsing rather than recurring; but there is, overall, no reason to doubt the efficacy of lithium as an active compound versus placebo in unipolar illness.

No distinctions among different antidepressants were made but they all met current recommendations in terms of dosage and duration of treatment. Schou (1979-a) reported that one year recurrence rate among unipolar patients treated with tricyclic antidepressants was 50% higher than among those treated with lithium (35% vs 22%). In the present study, the efficacy of lithium in comparison with other antidepressants provides less ground for confidence. In contrast, the pooled effect suggests a tendency for lithium to be more effective, and individual trials strongly supported this (e.g. lithium versus mianserin, Coppen *et al*, 1976). Comparison with conventional tricyclic drugs, however, tended to show no advantage for lithium, albeit with wide margins of error. It is not possible to conclude on the basis of the available evidence whether the choice of lithium in recurrent unipolar depression is a better prophylaxis than amitriptyline or imipramine.

The trials which reported the superiority of lithium over antidepressants were those which selected patients who remained episode-free for at least six months while the studies which reported antidepressants were equally effective or superior to lithium were those which required only a two or three month period of stabilization (Prien, 1985). The implication is that lithium is more effective in patients whose inter-episode rate of depression is low (Keller and Shapiro, 1982).

The NIMH Consensus Development Conference(Consensus Development Panel, 1985) concluded that both lithium and tricyclic antidepressants had been shown to be effective prophylactic treatments, each with advantages for certain populations. It was proposed that the use of tricyclic antidepressives had three advantages: a) as most acute episodes are treated with tricyclics, continuation with the antidepressants avoids the question as to when or how to switch from the antidepressant to lithium; b) tricyclics are less toxic and have less renal and thyroid side-effects, than lithium; c) it has been claimed that tricyclics provide a greater protection against severe depression. On the other hand, it was proposed that lithium had the advantage of preventing future episodes of depression and mania. This is an important factor on the basis of the knowledge that 10 to 20% of unipolar depressed patients will subsequently develop a manic episode (Runck, 1985). Furthermore, it has been suggested that some tricyclics may, in fact, precipitate a manic episodes or rapid cycling in some patients (Bunney, 1978).

One strategy to improve prophylaxis is to combine lithium and a standard antidepressant in the maintenance regimen. The rationale behind this is the possible synergistic neurochemical effects. Even though these results supported the combination of lithium plus antidepressants the degree of certainty is very small due to the small effect size. The finding reported by Prien *et al* (1984) that both imipramine and the combination of lithium plus imipramine are more effective than lithium and placebo in preventing new episodes of depression in unipolar depressed patients is questioned in a recent re-analysis of the data (Greenhouse *et al*, 1991). The outcome could have been obtained either because the design is biased in favour of imipramine responders or

because of the abrupt discontinuation of therapy between the preliminary and maintenance phases. Further studies are need to replicate the present findings and to clarify contentious issues such as those described.

A limitation in trials assessing the effectiveness of prophylactic drugs is that frequently they only measure recurrence rates leaving out changes in severity and duration of episodes.

### *5.4.3. WERE THE FINDINGS HOMOGENEOUS?*

Some degree of variability in protocol between studies in a meta-analysis may be beneficial because this will increase generalizability, but marked heterogeneity will tend to invalidate data pooling. When heterogeneity is detected, the studies should be clustered into homogeneous groups and analysed separately (Abrami *et al*, 1988). The range of different tests to estimate the homogeneity among studies include the Mantel-Haenszel test and regression techniques (Rosenthal, 1984). In the analysis of treatment and prophylactic studies no significant statistical differences in effect sizes were found but the *p* values of the prophylactic uncontrolled trials differ significantly indicating heterogeneity of studies. Any differences found in the other cases were of degree rather than direction.

### *5.4.4. HOW GOOD IS THE RESEARCH DESIGN OF THESE STUDIES?*

The interpretation of prophylactic studies is complicated by a number of methodological characteristics, such as differences in diagnostic criteria, length of study and methods to estimate improvement. An example of the criticism

levelled at uncontrolled trials was given by Blackwell and Shepherd (1968) about the study of Baastrup and Schou (1967). They said that the comparison of the frequency of episodes in the pre lithium period with the frequency in the lithium period was based on the assumption that the frequency of episodes in the pretreatment period can be used as an index to the frequency in any subsequent period of equal length. Since manic depressive illness is characterized by episodes that occur unpredictably they claim that this assumption was invalid and the only way to clarify the situation was to conduct trials with stronger research designs.

The next research design used in lithium trials was the cross-over design. Although, most of the cross-over studies were conducted double-blind and the assignment of patients was random, they were not regarded as controlled trials because of the short-term carrying over effect; in other words, lithium may have started a chain of events that led to resolution of the illness so that the patient was indeed "improved" at the time of placebo substitution (Mendels, 1976).

Finally, a number of prospective controlled trials with double-blind evaluation and randomized assignment of patients was conducted. But, even with these good quality studies the efficacy of lithium as a prophylactic agent was inconclusive (see Chapter 2). The main reason for this was the small number of patients involved in each trial. Again, the need for an appropriate method to summarize the findings is needed. Meta-analysis has the specific purpose of combining these studies to reach a meaningful conclusion.

In the NIMH/NIH trial (Prien *et al*, 1984), as already stated, the finding that imipramine and the combination of lithium plus tricyclics are more effective than lithium and placebo in preventing recurrence in unipolar depression could have been obtained either because the two-phase design is biased in favour of imipramine responders or because of the abrupt discontinuation of therapy between the preliminary and maintenance phases (Greenhouse *et al*, 1991). In that study, over half of the patients who entered the preliminary phase were not eligible to be randomized to maintenance therapy, of these 10% did not tolerate imipramine and over 20% did not stabilize on the usual treatment of tricyclic antidepressants. Therefore, a selection bias may have happened in the preliminary phase with an over-representation of imipramine responders who were more likely to have a recurrence after imipramine discontinuation. An increase in early recurrence has been associated with abrupt withdrawal from imipramine. Therefore, patients assigned to the lithium and placebo groups who had a recurrence within the first eight weeks of maintenance therapy may, in fact , have been experiencing a drug withdrawal reaction that precipitates or displays symptoms that mimic a depressive episode (Greenhouse *et al*, 1991).

The methodological short-comings of the acute treatment studies will be discussed under specific headings:

*a) Inclusion criteria* - patients were included under different criteria. For example, Watanabe *et al* (1975) included neurotic depression and reactive depression in their sample.

*b) Duration of treatment* - this may have been too short (for example, Goodwin *et al*, 1972; Baron *et al*, 1975). Most of the controlled trials lasted for 3 weeks, but a six week trial has been proposed as an adequate period because it takes

into consideration that some patients improve between the fourth and sixth week (Quitkin *et al*, 1984). However, this alleged change in improvement which led Quitkin *et al* to detect a 25% response between weeks four and six was very small, mean (SD) Hamilton scores were reduced from 9.6 (±4.5) to 8.5 (±5.6). Furthermore, the sample was constituted of outpatients with mean Hamilton scores at trial entry under 16. Different periods of treatment were also observed - Mendels (1976) used 7 to 22 days of placebo substitution.

*c) Patients included in the analysis* - the analysis may be based on the outcome of the patients who remained in the trial, even when an appreciable number of patients dropped out (Watanabe *et al*, 1975; Khan, 1981).

*d) Polarity not stated* - Mendels *et al* (1972) did not mention how many patients of the sample were unipolar and bipolar.

*e) Doses and plasma concentrations* - failure to report doses and plasma concentrations were observed in some trials (Goodwin *et al*, 1972; Mendels *et al*, 1972).

*f) Absence of placebo group* - there was no control for spontaneous remission in some studies (Mendels *et al*, 1972).

All these methodological shortcomings threatened the internal validity of these studies.

The prophylactic trials also have methodological weaknesses:

*a) Previous use of lithium* - a bias is introduced if it is already known that these patients are good lithium responders. This pattern was observed in discontinuation trials (Baastrup *et al*, 1970; Coppen *et al*, 1976).

*b) Patient population* - the study by Prien *et al* (1984) included a greater proportion (two-thirds) of patients with substantial impairment or persistent symptoms between episodes.

*c) Blindness* - in Coppen *et al* (1971) and Prien *et al* (1973) the raters were blind but the treating doctors were not and many decisions regarding the treatment of the patients were taken by the doctor in charge.

*d) Withdrawal* - a variable number of patients withdrew from trials and they were often excluded from the statistical analysis (see Table 5.3). There is controversy about how drop-outs should be treated in the analysis. Some authors believe that the the intention-to-treat approach should be adopted, i.e. the outcome of all patients who entered the study regardless of how long they stayed in the trial should be included (Yusuf *et al*, 1985), while others favour the exclusion method, i.e drop-outs should be excluded (Levitt *et al*, 1977). As there was no unanimous approach in dealing with the drop-outs (some trials do not even mention the numbers of patients dropping out, see Table 5.3), the reported results were analysed no matter how the authors treated the drop-outs.

*e) Different follow-up periods* - were observed both between studies (from 5 months to three years) and even within studies (Fieve *et al*,1976; Kane *et al*, 1982). The different length of follow-up may obscure differences in the outcome observed on a medium and long term (months vs years) basis. The only advantage of the relatively short duration of these trials was to reduce as a possible confounding problem the worsening prognosis that may develop with disease progression (Zis and Goodwin, 1979).

*f) Rejection log* - the list of all patients considered for the study but not entered is hardly mentioned (the exception was Prien *et al*, 1984).

The argument that non blind trials should be excluded due to their obvious methodological deficiencies from the analysis of the prophylactic effect of lithium has been disputed by Stallone *et al* (1975) and Schou (1979). Stallone *et al* (1975) reported that side-effects did not help the patients to guess their medication in a double-blind procedure. The placebo effect present in the non blind discontinuation was not powerful enough to exert a detectable prophylactic action, therefore the relapse rates after double-blind and non blind discontinuation of lithium were similar (Schou, 1979-a).

### *5.4.5. MUST A META-ANALYSIS AIM TO LOCATE ALL AVAILABLE STUDIES?*

The majority of researchers believe that a complete search is fundamental in meta-analysis (Wachter and Straf, 1990). Others, however, take the opposite view and emphasize the loss of time in locating the complete set of studies (Laird, 1990). The location of 'all' studies is generally impracticable but when samples are large they become more representative and this representativeness necessarily determines the range of valid generalizations. Five retrieval methods have been described by Cooper (1982): a) computer search (such as Medline); b) abstract service (such as International Pharmaceutical Abstracts); c) descendency (indexes that identify studies pertinent to a topic); d) ascendency (references citations from research articles are tracked to find more studies); and e) invisible college networks (an informal exchange of reprints and information among colleagues). A sixth approach is to to identify major publishers of primary research studies on the review topic. The target population was all trials in which lithium was compared to other treatments. Thus, an attempt was made to collect

information from all these possible sources on the use of lithium in affective disorder. Computerized searches were used to locate published studies while the other sources of information were used to locate both published and unpublished trials. In relation to published studies located by these searches, it does not seem that bias was introduced since all trials were included either in the controlled group or in the uncontrolled group, unless it met one of the criteria of exclusion. As computerized searches are available only from 1966 onwards, if a trial was published before that period it could not have been located, but that is doubtful in this particular review. There was good agreement between computerized searches and the ascendency approach, which reinforce the belief that most, if not all, of the trials that satisfied the inclusion criteria were obtained. Unfortunately the other available sources of information for location of unpublished studies failed to locate any such trials.

Information was sought from the authors when the details of the published material were insufficient to clarify the methods or results. This occurred in some cases (Fieve *et al*, 1968; Freyhan *et al*, 1970; Worrall *et al*, 1979; Johnstone *et al*, 1988; Khan, 1981; Khan *et al*, 1987; Glen *et al*, 1984). Examples of the type of information requested were: equations instead of number of patients were mentioned as outcome measure (Freyhan *et al*, 1970), the criteria used to measure outcome (Worrall *et al*, 1979), and the numbers of unipolar patients involved in the trial (Khan, 1981); Johnstone *et al*, 1988). In all but two (Fieve *et al*, 1968; Freyhan *et al*, 1970), these supplementary were obtained. As these studies were published 20 years ago, it is probable that the researchers are retired or the data have been destroyed. Freyham's study (1970) used only seven patients in a before lithium-on lithium design, showing a slight reduction in the hospitalization rate before lithium (0.18) when

compared with the period patients were on lithium (0.22). It would be surprising if the exclusion of this study in the final analysis of the uncontrolled prophylactic studies would significantly alter the conclusions in favour of lithium. The possibility of some bias remains. However, another way to deal with this exclusion is to include this study in the fail safe number of trials necessary to revert the conclusions (see below).

### *5.4.6. HOW BIG IS THE PUBLICATION BIAS IN LITHIUM TRIALS IN UNIPOLAR DEPRESSION?*

Because of the selective reporting of studies, some studies are not easily accessible and their data may not be determined by the reviewer. Two concrete steps are used to deal with the publication bias: first, to use all available retrieval methods to locate published and unpublished studies; and second, to estimate the extent of the publication bias (Light and Pillemer, 1984). The study selection problem associated with meta-analysis is similar to the missing data problem in particular studies. Of course, a major distinction between publication bias in meta-analysis and the standard missing data problem is the fact that in the latter the number of nonrespondents is generally known whereas in the former the number of unpublished studies is not (Laird *et al*, 1988). The exact quantification of the extent of publication bias is difficult to assess because published studies may not be representative of the studies conducted, and therefore any estimate must be regarded as a rough guide.

Various sources have been attributed in causing this publication bias. First, a publication bias toward positive results has been reported (Rosenthal, 1979) while negative findings stay in the "file drawer" (Cooper, 1979). The

underreporting of negative trials is influenced by researchers, who fail to report, and editors, who refuse to publish, based on the general view that negative results never make an exciting reading. In fact, some journals have explicitly included statistical significance as one of the criteria to accept studies (Melton, 1962). Surveys among reviewers of psychology journals have confirmed the trend (Greenwald, 1975). Studies with negative results have also been regarded as having poor research design weakened by small sample sizes and type II error (Freiman *et al*, 1978).

Secondly, the study research quality may be an important factor as to whether studies are published or not. Unpublished studies may be less reliable since they may have been found unacceptable by peer reviewers and may not have been collected with the same rigour and accuracy as published results (Sacks *et al*, 1987). This view is not shared by Greenwald (1975) who reports that rarely are these differences a reflection of the methodological quality of published and unpublished research, nor by Easterbrook *et al* (1991) who found no difference in quality between unpublished and published clinical trials.

Thirdly, the risk of not publishing the study is greater if the sample size is small. Small trials with large effects tend to be published, however, large trials are likely to be published regardless of the outcome (Dickersin, 1990). It has been argued that the investment in time and effort in conducting large randomized clinical trial is so great that there is an incentive to publish the results regardless of the outcome (Begg, 1985).

Fourthly, there is evidence that unpublished studies have smaller effect sizes than published ones (Smith and Glass, 1977; Rosenthal and Rubin, 1978). Finally, the funding source may be an important source. The non publication of negative studies supported by pharmaceutical companies has been reported (Davidson, 1986). Because of concern about this issue, many journals, e.g. the Journal of the American Medical Association, require the full disclosure of the financial support of the trial (Dickersin, 1990).

Publication bias may lead to incorrect inferences. Frequently, the incorrect inferences affects only the strength rather than the direction of association. In some cases not only the magnitude but the direction is different in published studies and unpublished trials (Smith, 1980). In either case, there is a risk that publication bias will leads to the conclusion that a specific treatment is either more effective than in fact it is or, more seriously, that the treatment is effective when it is ineffective. The failure to publish an adequate account of a clinical trial is a form of scientific misconduct that may lead clinicians to make inadequate therapeutic decisions which are based on only the published literature (Chalmers, 1990).

Publication bias may not be always severe enough to invalidate meta-analyses which are based only on published articles (Light and Pillemer, 1984; Hedges, 1984). Attempts to minimize the problem of locating unpublished trials have been made, however, by establishing guidelines for the publication and reporting of the results of the studies and the creation of a registry of clinical trials. The advantages of these registers are: first, to reduce publication bias. Secondly, they should help to reduce the unnecessary duplication of studies and promote more collaboration among researchers. Thirdly, they provide a

basis for methodological research and facilitate meta-analyses of clinical trials (Dickersin, 1988).

In this meta-analysis, publication bias did occur because the search for unpublished trials was not successful. A second source of bias was introduced because only trials written in the English language were included. Finally, some studies are inadmissible because their findings are not amenable to quantitative summarization. This often precludes the inclusion of studies that are non statistical such as case studies.

In the field of clinical cancer research where thousands of studies are conducted each year many may never be published (Bangert-Drowns, 1986), but it would be surprising if the number of unpublished trials of lithium therapy is on the same scale. Even though this possibility is remote, some mechanism is necessary to protect the validity of the conclusions of a meta-analysis because of the problem of non-localization or non-inclusion. One of these instruments is "the fail safe N". Rosenthal (1984) suggested that a meta-analysis can be considered resistant to the file drawer problem if the fail safe N exceeds 5k +10, where k is the number of reported effects. Adopting this approach, the comparison of lithium versus placebo in prophylactic studies is the only one to give this degree of confidence. In other words, there is firm evidence that lithium is effective in long-term treatment of unipolar depression when compared to placebo.

There is a limitation of the fail safe N. It is an appropriate guide *only* if the assumption of a summed null relation in undiscovered studies is

acceptable. It is always possible that some studies have a *negative* pooled size effect compared with those reviewed.

In addition to Rosenthal's (1984) formula for the estimation of the fail safe N, two other methods have been suggested: an analogous procedure was designed by Orwin (1983) and the the maximum likelihood approach proposed by Iyengar and Greenhouse (1988). The advantage of Rosenthal's approach is the simplicity of calculation and its use of the combined statistical significance but it has one drawback because it does not take into consideration the sample size of the unpublished trials. Orwin's (1983) approach uses the same principles of Rosenthal (1984) and makes an attempt to calculate the sample sizes of the unpublished trials. The maximum likelihood method uses a weighted distribution to model the selection bias in the generation of the data but it has two disadvantages: the scarce empirical evidence to guide the choice of weight functions and the amount of computation. But it is probably more robust than the other two methods (Iyengar and Greenhouse, 1988). Taking into consideration the pros and cons of these methods, Rosenthal's approach was preferred due to the easy understanding of its concepts. But, at the moment, the choice of a particular model to calculate the number of unpublished studies is still a "murky business" (Hedges, 1988).

### *5.4.7. WHAT SHOULD BE REPORTED: STATISTICAL SIGNIFICANCE, POWER, CONFIDENCE INTERVALS OR EFFECT SIZES?*

Different conclusions reached by traditional reviews may be the result of differences in the importance attached to whether or not the studies produced statistically significant findings. If the probability that the result was due to chance was below a certain level, e.g. 5%, it was concluded that the effect would occur in situations similar to to those in which it had been observed. Statistical significance is a product both of the treatment's effect and sample size. A weak effect can be statistically significant if observed in a large sample or on a sensitive scale. A strong effect would fail to be significant under the opposite conditions. It must be questioned if this small but statistically significant effect is large enough to have practical significance as well, i.e. clinical significance. The conclusion based on statistical significance provides no direct information about the magnitude of the effect. The estimation of the size of the difference in response probabilities is essential. In summary, statistical significance measure reliability of the effect of treatment not its efficacy (McConaghy,1990). Measurement of effect sizes, as in meta-analysis, provided a technique which has the advantage of being independent of the number of subjects investigated (see Gardner and Altman, 1990) for a recent plea to the psychiatric community to concentrate more on this aspect of statistical procedure).

Power calculations depend on the size of the effect size and on the number of patients in the sample. The greater the effect size the smaller the number of patients necessary to detect it. The best way to ensure that a non significant difference will be obtained is to use an inadequate sample size. The

probability of type I error is always 0.05 regardless of the sample size, but the probability of of a type II error increases dramatically as the sample size decreases (Hunter *et al*, 1982). The purpose of the calculation of the power in each trial was to show that in many clinical trials, no matter how carefully conducted, if the number of subjects involved is too small it is not possible to draw firm conclusions and this highlights the need to integrate findings from different studies.

Confidence intervals also have advantages over significance tests. Firstly, the interval is correctly centred on the observed value rather than the hypothetical value of the null hypothesis. Secondly, it gives a better picture of the extent of uncertainty that surrounds results computed from small sample trials, i.e. the bigger the interval the less confidence in the result. The only way to eliminate uncertainty is either study large-sample, single studies or combine results across many small studies. Given the limited resources in many medical areas, this means meta-analysis is usually more practicable (Hunter *et al*, 1982).

### *5.4.8. HOW MUCH CHANGE IS CLINICALLY SIGNIFICANT?*

Effect sizes and statistical significance share one drawback which is that is none of them provide direct information about the clinical significance of a treatment effect (McConaghy,1990). The measurement of clinical significance as a criterion for evaluating clinical outcomes is still an unresolved problem. Clinical significance can be defined as the extent to which clinical outcomes achieve a meaningful magnitude of change (Nietzel *et al,* 1987), but there is

little consensus as to what clinical significance is, except the universal agreement that it is not merely statistical significance (Jacobson *et al*, 1984).

In short-term treatment, a binary outcome (not improved / improved) was adopted. The objection may be made that the use of a binary outcome scale in assessing trials is too crude, but this probably reflects clinical decision making. Inevitably, trying to transform continuous quantitative data, such as degrees of clinical improvement, into some sort of qualitative classification is more arbitrary than a classification where outcome is either death or survival.

In the controlled studies of prophylaxis, outcome was expressed in terms of recurrence. This meant different things in different studies; some used readmission to hospital as the criterion of failure (Hullin *et al*, 1972) while others used introduction of other treatment such as ECT or antidepressants (Fieve *et al*,1976) or a change in an index of morbidity (Coppen *et al*, 1976; Kane *et al*, 1982; Prien *et al*, 1984).

# CHAPTER 6

# TSH, T4 AND CORTISOL AFTER LITHIUM DISCONTINUATION IN BIPOLAR AFFECTIVE DISORDER

## 6.1 INTRODUCTION

### *6.1.1. THYROTROPIN (TSH) AND THYROXINE (T4) IN AFFECTIVE DISORDERS*

The association between thyroid disease and mental illness has been acknowledged since the last century. In 1825, Caleb Parry referred to fright as a cause of thyrotoxicosis. In 1888, the Clinical Society of London observed that myxoedema could result in mania, melancholia or psychosis (Clinical Society of London, 1888). In 1938, Gjessing reported that periodic catatonia improved with thyroid extract. The identification of T4 and T3 in 1926 and 1952 respectively increased the interest in this area (Gross and Pitt-Rivers, 1952; Condliffe and Weintraub, 1979), which was, however, restricted by two factors: the lack of sensitive methods to assay small amounts of complex molecules and the failure to identify a substance clearly linking the central nervous system (CNS) to the hormonal system. In the late 1970's, the identification of the thyrotropin releasing hormone (TRH) by Guillemin (1978) and Schally (1978) and the development of reliable methods of measurements provided the necessary stimulus to further psychoneuroendocrine investigations.

The hypothalamic pituitary thyroid axis by itself is a complex and highly integrated network. The hypothalamic peptide thyrotropin releasing factor (TRH) stimulates the release of TSH which regulates the production of the thyroid hormones -thyroxine (T4) and triiodothyronine (T3). The thyroid hormones exert a feedback control over the axis, which means that when their concentration falls, TSH secretion is stimulated, and when their levels are

raised TSH release is inhibited (for a comprehensive review on HPT axis see Kaplan and Sadock, 1989).

A special area of interest in these investigations is the relationship between affective disorders and thyroid function. It has long been acknowledged that hypothyroidism can mimic depression (Whybrow *et al*, 1969), but some patients with affective disorders show laboratory signs of functional disturbance of the hypothalamic-pituitary-thyroid axis without clinical manifestation of altered thyroid function (Unden *et al*, 1986). The exact mechanism of this interaction continues to be poorly understood (Baumgartner *et al*, 1988; Bauer and Whybrow, 1988; Smith and Goodwin, 1988). Hormonal changes in affective disorders have been studied using two approaches: the first one studies the unipolar-bipolar dichotomy while the second one considers the depression-mania distinction.

*6.1.1.1. Unipolar versus Bipolar Depression*

Regarding the first approach, most studies have failed to find significant differences between unipolar and bipolar illness (see Table 6.1). Takahashi *et al* (1974) did not find significant differences in T4 and TSH concentrations between 20 unipolar and 9 bipolar patients. Kirkegaard *et al* (1978) found higher T4 but not TSH in 19 unipolar depressed when compared with 12 bipolar depressed, but when the values were corrected for differences in thyrotropin binding proteins no significant differences in T4 were found. Amsterdam *et al* (1979) did not find any difference in T4 and TSH levels between 12 unipolars, 6 bipolars and 6 controls. No significant differences was found between 11 bipolar and 35 unipolar patients in T4 and TSH levels before

and after electroconvulsive therapy (Kirkegaard and Faber, 1981). Kjellman *et al* (1983) reported no differences between eight unipolars, eight bipolars and 22 normal controls in any thyroid test including T4 and TSH. One of the rare significant finding was reported by Linnoila *et al* (1982) who found that 4 unipolar depressed women had significantly higher T4 concentration than 8 controls or 9 bipolar depressed women.

A meta-analysis of these studies gives additional information on the differences between bipolar and unipolar depression (for details of the calculation of effect sizes, 95% CI and tests of heterogeneity see Appendix 6.1). The comparison between TSH concentrations of these two groups yields a mean effect size of 0.17 in favour of the bipolar group. In other words, bipolar patients were found to have higher TSH levels, however, the 95% confidence interval (CI) of -0.23 to 0.57 is too large to allow any certainty. The chi-square of heterogeneity, however, is not significant ($x^2_3 = 7.2$, NS).

The corresponding mean effect size for T4 levels is 0.33, indicating higher levels in the bipolar group, but again the 95% CI is large (from -0.10 to 0.76). Because part of the 95% CI favours the unipolar group, no definite conclusion can be drawn. The chi-square of heterogeneity ($x^2_3 = 18.1, p<0.001$) is highly significant. Possible moderating variables which might explain the heterogeneity found in some analysis of this meta-analysis are discussed in Section 6.1.3.

*6.1.1.2. Depression versus Control*

Depression has been studied to a much greater extent than mania. The picture emerging from the studies reporting on the TSH alterations in affective disorders is still unclear (see Table 6.1). The majority of the studies comparing depressed patients with controls have reported reduced TSH levels in depression (Takahashi *et al*, 1974; Kirkegaard *et al*, 1978; Linkowski *et al*, 1981; Kjellman *et al*, 1983; Orsulak *et al*, 1985; Unden, 1986). Yamagushi *et al* (1977) was the only study to report elevated TSH levels in the depressed group. The mean effect size of -0.37 (95% CI -0.20 to -0.54) reflect this finding. The whole CI remains in the area favouring a reduction of TSH levels in depression, however the degree with which this reduction is observed varied among the studies resulting in a significant heterogeneity of effect sizes ($x^2_8$= 24.2, p<0.005). Eight studies would be needed to reverse this conclusion

The pattern which emerges from the studies of T4 levels in depression is shown in Table 6.1. Some studies have shown reduced T4 levels in the depressed group when compared to a control group (Yamagushi *et al*, 1977; Kirkegaard *et al*, 1978 - bipolar; Rinieris *et al*, 1978; Linnoila *et al*, 1982 - unipolar), while others have reported an increase in T4 levels in the depressed group (Takahashi *et al*, 1974; Kirkegaard *et al*, 1978 - unipolar; Linnoila *et al*, 1982 - bipolar; Kjellman *et al*, 1983; Joffe *et al*, 1985; Unden *et al*, 1986; Rubin *et al*, 1987). A small effect size of 0.22 with 95% CI (0.08 to 0.36) favouring an increase in T4 levels was observed. The heterogeneity of effect sizes is shown by a significant chi square ($x^2_{10}$ = 94.9, p<0.001). Thus, reduced TSH, increased T4 implies peripheral activation of thyroid axis.

*6.1.1.3. The Effects of Treatment on TSH and T4 Levels*

Most studies comparing depression before and during treatment show augmented TSH concentrations after treatment (Kirkegaard *et al*, 1978; Weeke and Weeke, 1978; Linkowski *et al*, 1981; Roy-Byrne *et al*, 1984; Unden *et al*, 1986; Muller and Boning, 1988) with the exception of Kirkegaard *et al* (1975). The mean effect size was 0.17 represents a modest increase in TSH levels with treatment. As the 95% CI -0.03 to 0.37 expands over zero no firm conclusions can be drawn. The chi square of heterogeneity is not significant ($x^2_7 = 11.1$, NS).

The comparison depression before and during treatment, however, shows consistently a reduction in T4 concentrations with treatment (Whybrow *et al*, 1972; Kirkegaard *et al*, 1975; Kirkegaard *et al*, 1978; Roy-Byrne *et al*, 1984; Muller and Boning, 1988) with the exception of Weeke and Weeke (1978). The mean effect size of 0.82 (95% CI -0.61 to -1.03) reflects this fact . Although most studies favoured a reduction in T4 levels, their effect sizes were heterogeneous ($x^2_7 = 36.7$, $p<0.001$). To reverse this conclusion, 16 studies would be necessary.

*6.1.1.4. Depression versus Mania*

Alterations in the hypothalamic pituitary thyroid axis of patients with mania have also been reported, although these effects have been studied to a much less extent. One of the first reports claimed that manic patients had higher and depressive patients had lower iodine levels than normal controls (Neudstadt and Howard, 1942). TSH concentrations have been found higher

in mania compared to depression (Gold *et al*, 1979), but reduced TSH in manic patients have also been reported (Kirkegard *et al*, 1978; Muller and Boning, 1988). The mean effect size was only 0.03 with the 95% CI varying from -0.46 to 0.52). In other words, this result is wholly inconclusive. The chi square of heterogeneity was significant ($x^2_2 = 13.7$, $p<0.001$).

Most studies have reported reduced T4 levels in depression when compared to mania (Rybakowski and Sowinski, 1973; Kirkegaard *et al*, 1978; Rinieris *et al*, 1978; Linnoila *et al*, 1982) with the exception of Muller and Boning (1988). As a result the mean effect size of 0.51 (95% CI from 0.15 to 0.87) favours a reduction of TSH levels in depression. The effect sizes were heterogeneous ($x^2_4 = 20.8$, $p<0.001$). Eleven studies would be necessary to reverse this finding.to a non significant value.

The TRH stimulation test has aimed to probe the HPT axis in patients with affective disorders (Loosen, 1987). A decreased or blunted TSH response to TRH in 25-70% of depressed patients has been reported.(Kaplan and Sadock, 1989). Gold *et al* (1979) proposed that it was possible to distinguish unipolar and bipolar illness by means of the TSH response to thyrotropin stimulating hormone (TRH), based on their finding that unipolar patients had an abnormally low TSH response to TRH in comparison with bipolar subjects. This finding was based on small groups (both unipolar and bipolar groups had less than ten patients). Other studies using bigger samples, however, have not replicated this result; similar TSH response to TRH in unipolar and bipolar patients were shown by Takahashi using 18 unipolars and 8 bipolars (1974), Kirkegaard *et al* with groups of 19 unipolars and 12 bipolars (1978), Amsterdam *et al* comparing 12 unipolars and 6 bipolars (1979), Bjorum *et al* in 21 bipolars and 35 unipolars

(1979), and Mendlewicz *et al* comparing 31 unipolars and 27 bipolars (1979). To date, there is not enough evidence to establish thyroid function test as a diagnostic instrument which can separate unipolar and bipolar disorders.

Another aspect of the relationship of mania and thyroid function is the TRH-induced TSH response in manic patients which has also been studied with conflicting results (Kirkegaard, 1981; Loosen and Prange, 1982). An exaggerated (McLarty *et al*, 1975; Tanimoto *et al*, 1981) and reduced (Takahashi *et al*, 1974; Kirkegaard *et al*, 1978; Gold *et al* 1977,1980) TSH response to TRH has been reported in manic patients. The doses and procedures used in these studies are too different to allow a quantitative synthesis.

Triiodothyronine (T3) levels in endogenous depression have been found to be normal (Kiekegaard and Faber, 1981; Roy-Byrne *et al*, 1984) or decreased (Weeke and Weeke, 1978; Linnoila *et al*, 1979). A lower T3 level is consistent with the euthyroid sick syndrome which is characterized by low T3, increased reverse T3 and normal T4 concentrations (Chopra *et al*, 1983). This syndrome has been reported to occur in some depressive patients (Joffe *et al*, 1985). Some features of the syndrome, such as low free T3 and increased reverse T3, have been proposed to represent a biological difference between bipolar and unipolar illness (Linnoila *et al*, 1979,1982; Orsulak *et al*, 1985; Joffe *et al*, 1985). It is not widely accepted, however, that affective illness is commonly marked by the euthyroid sick syndrome (Bauer and Whybrow, 1988). It seems that the most frequent abnormality in iodothyronine economy is a *relative* increase in T4 levels during the acute episode which tend to decrease

after recovery without clear alterations in T3 concentrations (Bauer and Whybrow, 1988).

In summary, some trends can be observed from these studies. Firstly, there is no reliable evidence that TSH and T4 levels can differentiate unipolar and bipolar depression. Secondly, TSH concentrations in depressed patients is reduced and T4 levels are raised when compared with controls and other medically ill patients. Thirdly, antidepressant treatment frequently induces a consistent reduction in T4 concentrations. The effects of treatment on TSH levels are more variable, but an increase in its levels is frequently detected. Fourthly, T4 levels in depression seems to be lower than in mania but the data on TSH concentrations is inconclusive. Finally, T4 and TSH concentrations are usually within the normal range even when a significant difference in T4 or TSH concentrations is reported. Thus, the evidence to date suggests that if any reduction does take place, it is within the reference limits.

**TABLE 6.1**

T4 and TSH levels in affective disorders (M = male, F = female).

| STUDY | N | DIAGNOSIS | TSH LEVELS (mean ± SD) µU/ml | | P VALUES | COHEN'S D | T4 LEVELS (mean ± SD) µg/100ml | | P VALUES | COHEN'S D |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Before | After treatment | | | Before | After treatment | | |
| Whybrow *et al* (1972) | 6 M | unipolar depression | - | - | - | | 6.6 ± 2.2 | 5.3 ± 1.2[1] | 0.01 | -0.80 |
| | 10 F | | | | | | 7.2 ± 2.8. | 6.1 ± 2.1 | 0.01 | -0.44 |
| Rybakowski and Sowinski | 6 | mania | - | - | - | - | 4.6 ± 1.3 | - | - | -1.15 |
| (1973) | 9 | depression | | | | | 3.4 ± 1.0 | | | |
| | | normal | | | | | 6.6 ± 1.5 | | | |
| Takahashi *et al* (1974) | 36 | depression | 1.6 ± 1.8 | | NS | -0.79 | 12.1 ± 2.4 | | NS | 0.45 |
| | 23 | nondepressed medically ill | 3.2 ± 3.0 | | | | 11.1 ± 1.9 | | | |
| | 9 | bipolar | 2.2 ± 1.8 | | NS | -0.40 | 12.9 ± 2.6 | | NS | -0.36 |
| | 20 | unipolar | 1.5 ± 1.7 | | | | 12.0 ± 2.4 | | | |
| Salvadorini and Saba (1973) | 10 | depression | 4.1 ± 0.5 | - | - | - | - | - | - | - |
| | | control (range) | (3.5 - 8.0) | | | | | | | |
| Kirkegaard *et al* (1975) | 9 | depression -no relap | 2.2 ± 1.9 | 1.7 ± 1.3 | NS | -0.43 | 9.4 ± 2.8 | 8.9 ± 2.7[2] | NS | -0.19 |
| | 10 | depression - relapse | 1.9 ± 2.0 | 1.3 ± 1.2 | NS | -0.38 | 11.0 ± 1.9 | 9.6 ± 1.2 | 0.01 | -0.93 |
| | | normal | 1.9 ± 1.7 | | | | | | | |
| Nicholson *et al* (1976) | 24 | manic depressive psychosis | - | - | - | - | ↑ in 3 | - | - | - |
| Gold *et al* (1977) | 23 | a-affective disorder | a x b (no | - | + | - | no difference[+] | - | + | - |
| | 10 | b-normal volunteers | difference)[+] | | | | | | | |
| | 9 | c-bipolar mania | 8.8 ± 1.4 | | 0.10 (c x d) | 2.02 | | | | |
| | 7 | d-bipolar depression | 12.3 ± 2.2 | | | | | | | |
| Yamaguchi *et al* (1977) | 51 | depression | 2.8 ± 5.7 | | NS | 0.07 | 8.1 ± 4.2 | | NS | -0.07 |
| | 20 | control | 2.4 ± 3.5 | | | | 8.4 ± 2.6 | | | |
| Kirkegaard *et al* (1978) | 19 | a-unipolar depression | 1.7 ± 1.6 | - | NS (a x d) | 0.11 | 8.8 ± 1.7 | - | NS (a x d) | 0.52 |
| | 12 | b-bipolar depression | 1.7 ±1.6 | | NS (b x d) | 0.11 | 7.6 ± 1.0 | | NS (b x d) | 0.28 |
| | 14 | c-mania | 2.2 ± 1.5 | | NS (c x d) | 0.17 | 8.0 ± 1.4 | | NS (c x d) | 0 |
| | 60 | d-controls | 1.9 ± 1.8 | | NS (a x b) | 0 | 8.0 ± 1.5 | | 0.05(a x b)[4] | 0.85 |
| | | | | | (b x c) | | | | (b x c) | |
| McLarty *et al* (1978) | 30 M | affective disorders | - | - | - | - | 99 ± 19* | - | - | 0.18 |
| | 91 F | affective disorders | | | | | 95 ± 23 | | | |
| | | normal (range) | | | | | (55 - 144) | | | |
| Rinieris *et al* (1978) | 25 | a-primary depression | - | - | - | - | 6.5 ± 1.7 | - | 0.01 (a x b) | 0.88 |
| | 15 | b-mania | | | | | 8.0 ± 1.8 | | 0.001 (a x c) | 1.17 |
| | 240 | c-controls | | | | | 8.7 ± 1.9 | | NS (b x c) | 0.37 |
| Weeke and Weeke (1978) | 11 | untreated depression | 0.66 ± 1.32** | | - | 0.33 | 9.5 ± 1.5** | | | 0.90 |
| | 8 | treated depression | | 1.35 ± 2.96** | | | | 10.0 ± 2.3** | | |
| Amsterdam *et al* (1979) | 6 | unipolar disorder | + | - | + | - | + | - | + | - |
| | 6 | bipolar disorder | | | | | | | | |
| | 6 | controls | | | | | | | | |
| Linnoila *et al* (1979) | 12 | unipolar depression | 2.1 ± 2.1 | - | - | - | 7.8 ± 1.3 | - | - | - |
| | | normal (range) | (1.6 - 6.0) | | | | (4.7 - 10.5) | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Kirkegaard and Faber (1981) | 80 | endogenous depression | 1.7 ± 1.5 | 1.8 ± 1.6[2] | NS | 0.06 | 119 ± 23 | 112 ± 27[2] | 0.01 | 0.63 |
| | 35 | b-unipolar illness | | | NS (b xc)[5] | | | | NS (b xc)[5] | |
| | 11 | c-bipolar illness | | | | | | | | |
| Linkowski *et al* (1981) | 8 | a-unipolar illness | 2.0 ± 0.42 | 3.0 ± 0.42[3] | NS (a x c) | 2.32 | [5] | - | [5] | - |
| | 4 | b-bipolar illness | 2.6 ± 0.62 | 2.6 ± 0.62[3] | NS (b x c) | 0.76 | | | | |
| | 9 | c-normal controls | 3.0 ± 0.52 | | NS (a x b) | 1.6 | | | | |
| Gold *et al* (1981) | 100 | depressed/anergic normal (range) | a in 5[5] | - | - | | no difference[5] | - | [5] | - |
| Linnoila *et al* (1982) | 4 | a-unipolar depression | - | - | - | - | 111 ± 18 | - | 0.05 (a x d) | - |
| | 9 | b-bipolar depressed | | | | | 80 ± 20 | | 0.05 (a x b) | |
| | 4 | c-bipolar manic | | | | | 97 ± 24 | | NS (b x d) | |
| | 8 | d-controls | | | | | 87 ± 15 | | NS (b x c) | |
| Kjellman *et al* (1983) | 32 | a-depressive disorder | 2.6 ± 0.8 | - | 0.01 (a x d) | 0.73 (a x d) | 95 ± 20 | - | NS | 0.40 (a x d) |
| | 8 | b-unipolar | 3.1 ± 1.0 | | | 0.44 (b x c) | 86 ± 15 | | | 0.19 (b x c) |
| | 8 | c-bipolar | 2.7 ± 0.4 | | | | 88 ± 16 | | | |
| | 22 | d-controls | 3.3 ± 1.0 | | | | 88 ± 14* | | | |
| Sternbach *et al* (1983) | 44 | depression | a in 3 | - | - | - | I in 1 | - | - | - |
| Calloway *et al* (1984) | 68 | primary depression | - | - | - | - | I in 24 | - | - | - |
| Roy-Byrne *et al* (1984) | 50 (40 bi, 10 uni) | major affective disorder | 3.4 ± 1.2 | 3.7 ± 1.3[4] | 0.01 | 0.25 | 8.21 ± 1.62 | 5.78 ± 0.98 | 0.005 | 1.84 |
| Joffe *et al* (1985) | 10 | a-depression | - | - | - | - | 9.1 ±0.29 | - | 0.05 (a x b) | 1.17 (a x b) |
| | 11 | b-euthymic | | | | | 8.7 ± 0.42 | | NS (b x c) | 1.50 (b x c) |
| | 10 | c-normal volunteers | | | | | 9.3 ± 0.44 | | NS (a x c) | 0.57 (a x c) |
| Nemeroff *et al* (1985) | 28 | depression (DSM-III) (reference) | 3.3 ± 2.1 (a in 1) (≤ 8.5) | - | - | - | 8.2 ±2.0 (lin 1,a in 2) (4.5 - 11.5) | - | - | - |
| Orsulak *et al* (1985) | 32 | unipolar depression | 3.2 ± 0.8 | - | NS | 0.06 | - | - | - | - |
| | 46 | controls | 3.3 ± 1.4 | | | | | | | |
| Kirkegaard and Faber (1986)* | 17 | a-unipolar cured | 1.4 (0.6-5.4)[6] | 1.4 (0.6-4.4)[26] | NS | - | 106 (48 -183)[6] | 82 (53 -186)'[26] | 0.02 (a x a') | - |
| | 19 | b-unipolar depressed | 2.1 (0.6-4.2)[6] | 1.7 (0.6-4.5)[6] | | | 98 (58 -145) | 96 (53 -144) | 0.05 (a' x c) | |
| | 38 | c-controls | 2.1 (0.6-5.5)[6] | | | | 100 (72 -156)[6] | | | |
| Unden *et al* (1986) | 31 | major depression | 2.7 ± 0.5 | | 0.001 | 1.07 | 89 ± 15 | - | NS | 0.30 |
| | 30 | controls | 3.6 ± 1.1 | | | | 85 ± 13 | | | |
| Rubin *et al* (1987) | 40 | endogenous depression | 2.4 (1.8 -3.1)[6] | - | 0.03 | - | 8.0 ± 2.3 | - | NS | 0.09 |
| | 40 | controls | 2.8 (2.2 - 4.1)[6] | | | | 7.8 ± 2.2 | | | |
| Baumgartner *et al* (1988) | 31 | major depression | - | - | - | - | 80[2] | 65[2] | 0.001 | - |
| | 75 | controls | | | | | 79[2] | | | |
| Muller and Boning (1988) | 15 | a-mania | 8.1 ± 1.7 | 11.5 ± 1.6 (') | 0.02 | 2.13 (a x a') | 88 ± 35* | 67 ± 31 (')* | NS | 0.65 (a x a') |
| | 13 | b-depression | 7.8 ± 2.1 | 10.0 ± 1.7 (') | 0.05 | 1.20 (b x b') | 102 ± 38* | 74 ± 27 (')* | 0.01 | 0.88 (b x b') |
| | | | | | | 0.16 (a x b) | | | | 0.40 (a x b) |

Treatment : [1] = imipramine or tryptophan, [2] = ECT, [3] = amitriptyline, [4] = carbamazepine.

[5] no difference reported, but no means nor 'p' values given.

[2] values abstracted from graph.

@ no difference when correcteded for thyroxin binding proteins.

* nmol/l, ** concentrations at 2 pm.

[6] median (range).

### *6.1.2. CORTISOL IN AFFECTIVE DISORDERS*

The hypothalamic-pituitary adreno-cortical (HPA) axis functions in a similar way as the hypothalamic pituitary thyroid axis. Corticotropin releasing factor (CRF), a hypothalamic peptide, stimulates the release of adrenocorticotropin (ACTH) from the anterior pituitary which causes the adrenal cortex to secrete cortisol. The prevailing plasma cortisol concentration may influence the activity of the HPA system at pituitary, hypothalamic, and limbic cortical levels. Such negative feedback control results in stimulation of the system when plasma cortisol is low, and inhibition when plasma levels are high. The system has a circadian rhythm, with most cortisol being secreted in the morning. The regulation of CRF is complex and involves various neurotransmitters and neuromodulators (noradrenaline, acetylcholine and serotonin). A wide variety of nonspecific stresses can influence the system activity. Affective disorders are one of the best known factors that can alter cortisol secretion (for comprehensive reviews on HPA axis see Streeten *et al*, 1984; Pepper and Krieger, 1984).

The pituitary adreno-cortical axis has been the most extensively studied endocrine system in psychiatry. In depression, cortisol hypersecretion is probably the best established biochemical abnormality (Board *et al*, 1957; Gibbons, 1964; Sachar *et al*, 1973; Carroll *et al*, 1976). Between 25 to 75% of patients with endogenous depression shows hyperactivity of the hypothalamo-pituitary-adrenal cortical (HPA) axis reflected by increased circulating corticotropin and cortisol concentrations, increased cerebrospinal fluid cortisol levels, increased urinary free cortisol disinhibition of nocturnal secretion of

cortisol, loss of the normal circadian variation and cortisol resistance to dexamethasone (Rubin *et al*, 1987).

Reports studying the cortisol status in the dichotomy of unipolar-bipolar depression has produced inconsistent results. An absence of bipolar-unipolar difference in mean urinary free cortisol has been observed (Rubinow *et al*, 1984). But another study found that bipolar endogenous depressed patients have a significantly higher prevalence of cortisol hypersecretion compared with unipolar patients, schizophrenics and normal controls (Asnis and Lemus, 1987).

In mania, conflicting findings are reported on the status of cortisol. Earlier studies have shown lower levels of adrenal activity during the manic than during the depressive phase of the illness (Rizzo *et al*, 1954; Fox *et al* 1958; Gibbons and McHugh, 1962; Bunney *et al*, 1965), but more recent studies have reported normal (Sachar *et al*, 1972) and elevated (Platman and Fieve, 1968; Stokes *et al*, 1984; Rubinow *et al*, 1984; Christie et al, 1986) levels of cortisol in the manic phase. Generally, this disorder has been the focus of less attention and fewer studies have been carried out than in depression (Copolov and Rubin, 1987).

Cortisol levels in depression have also been studied by challenge tests, such as the dexamethasone suppression test (DST; Carroll *et al*, 1976). This endocrine function test utilizes the ability of dexamethasone to suppress the endogenous secretion of corticotropin and consequently of corticosteroids. A positive DST test occurs when dexamethasone fails to inhibit cortisol secretion. This finding has been observed in many endogenous depressive patients. The DST is probably the most utilized and studied biological test in psychiatry, but

the initial enthusiasm for the test has given way to more prudent and cautious utilization due to doubts about its real sensitivity. The sensitivity of this test for melancholic depression (positive finding in a true case) is between 30-70% depending on the number of measurements (Carroll *et al*, 1981; APA, 1987). The overall specificity for that condition (negative result in a patient without melancholic depression) is about 80%.

A close relationship between HPA and HPT has been proposed (Rubin *et al*, 1987). Because of the effect of glucocorticoids on the TRH test, the blunted TSH response to TRH in depressives may be secondary to the increase in HPA activity (elevated plasma cortisol) that occurs in about 50% of patients with major depression. Two studies support this possibility (Loosen *et al*, 1978; Rush *et al*, 1983). Other studies, however, have failed to confirm this finding (Kirkegaard and Carroll, 1980; Extein *et al*, 1981; Larsen *et al*, 1985).

All the methodological aspects described in Section 6.1.3 have posed great difficulty in making meaningful interpretations of the results. However, some conclusions may be drawn from the available data. Firstly, an increase in cortisol levels is observed in many patients with depression, but this increase is not characteristic of depression and it occurs in varying proportions. Secondly, cortisol levels have not been shown to distinguish the dichotomy unipolar-bipolar reliably. Thirdly, there is some evidence that the cortisol levels in manic patients are greater than those observed in depressed subjects. Fourthly, the initial claim that a blunted TSH response to TRH might be linked to an increase in HPA activity has not been confirmed.

### *6.1.3. METHODOLOGICAL ASPECTS*

These conflicting findings in the study of hormonal change in affective disorders may be explained by several methodological issues. Firstly, the diagnosis factor may account for some of the variance of the results. Examples of possible contributory factors are: the ratio of unipolar vs bipolar patients; the inclusion of psychotic (versus neurotic or reactive) depressives, endogenous depressives, major depressives or depressives not otherwise classified; the proportion of depressed, manic or euthymic patients; the different stages of chronicity and the different stages of episode or remission. Secondly, different comparison groups were used: nondepressive medically ill groups (Takahashi *et al*, 1974), less severely ill (Kirkegaard and Faber, 1981) and healthy controls (e.g. Rubin *et al*, 1987). Thirdly, the sample size varied widely between studies and in some studies the samples consisted of small numbers (see Table 6.1). Fourthly, different methods of assay with different coefficients of variation were used. Finally, there is the question of circadian rhythms. T4,TSH and cortisol have their own circadian rhythms. Measurements made in the morning are not comparable to measurements made during other periods of the day. Another possible explanation for the difference between studies may be the fact that in the studies where a significant reduction in TSH concentrations were found multiples samples were taken, whereas in those studies in which no difference was found the TSH values were taken from single samples (Rubin *et al*, 1987). Finally, the use of prophylactic medication, such as lithium or tricyclics, may act as confounding variables. Ideally, the patient sample studied should be homogeneous and completely free of confounding variables in order to assess the changes induced by the illness itself and not those triggered by these variables.

### *6.1.4 THE EFFECTS OF LITHIUM ON TSH, T4 AND CORTISOL LEVELS*

Long-term lithium therapy has been associated with changes in thyroid function in a series of ways. In 1968, the first accounts of lithium effect on thyroid was made by Sedvall *et al* (1968) who demonstrated an antithyroid effect of lithium in rat and man and by Schou *et al* (1968) who reported that 12 of 330 patients treated with lithium developed goitres. Lithium is concentrated in the thyroid gland. In vivo and in vitro studies have shown thyroid/serum lithium ratios ranging from 2.5 to 5 (Lazarus *et al*, 1986). The effects of lithium have been studied using different parameters of thyroid function, such as iodine uptake and peripheral hormone measurements.

The effects of lithium on thyroid iodine uptake have been controversial. In rat, acute administration of lithium has been reported to reduce (Berens *et al*, 1970) and to increase (Hullin and Johnson, 1970) iodine uptake. Chronic administration of lithium has been shown to stimulate (Berens and Wolff, 1975) and to inhibit (Hullin and Johnson, 1970) iodine uptake. In man, Sedvall *et al* (1968) reported increased iodine uptake while Burrow *et al* (1971) showed no effect.

Several studies have reported on the acute effects of lithium therapy on TSH and T4 concentrations (Table 6.2). In terms of TSH concentrations, the mean effect size of the differences between the concentrations before vs on lithium (expressed in standard deviation units) was found to be 0.84 (95% CI from 0.24 to 1.06) in favour of an increase in TSH levels with lithium. The chi square of heterogeneity was not significant ($x^2_{10} = 8.9$, NS). To reverse this

conclusion 33 negative studies would be necessary. T4 concentrations are reduced with lithium. This fact is reflected by the mean effect size of 0.27 with 95% CI varying from 0.05 to 0.59. The chi square is not significant ($x^2_{12}$ = 13.0, NS). 35 studies would be necessary to reverse this conclusion. In summary, the majority of these studies have demonstrated an increase in TSH concentrations and a decrease in T4 levels with lithium treatment, but rarely beyond the normal range.

Alterations in the thyroid status have also been shown with chronic lithium therapy (Table 6.3). In terms of TSH concentrations, the mean effect size is 0.51 (95% CI 0.09 to 0.93). The chi square of heterogeneity, however, is just significant ($x^2_2$= 7.5, $p<0.05$). T4 concentrations are normally reduced with the exception of Maarbjerg *et al* (1987). The mean effect size is 0.04 (95% CI -0.06 to 0.14). No definite conclusion can be drawn because the 95% CI spreads around zero. The chi square of heterogeneity is not significant ($x^2_{12}$ = 11.7, NS). In summary, the long term effects of lithium show a similar pattern as in studies of acute effects of lithium (elevation of TSH levels and reduction of T4 concentrations).

Most reports showed a direct inhibitory effect on thyroid secretion which may result in abnormal laboratory findings (reduction in plasma levels of T4, increase in serum TSH concentrations and a blunted TSH response to TRH stimulation) in euthymic patients or goitre formation and clinical hypothyroidism in severe cases (Transbol *et al*, 1978) while other studies have found no significant reductions in T4 concentrations or increases in TSH (McLarty *et al*, 1975; Lazarus *et al*, 1981). Animal studies have shown a decrease in TSH values with lithium therapy (Ruzsas *et al*, 1980; Bagchi *et al*, 1982). This

decrease has not been replicated in any study using human samples. The alterations induced by lithium are usually within the accepted range but lithium prophylaxis has been associated with a reduction in thyroid function in 4 to 30% of bipolar patients (Hullin, 1978; Amdisen and Andersen, 1982). Rapid-cycler bipolar patients have also been reported to show an increased incidence of clinical hypothyroidism during lithium therapy (Bauer and Whybrow, 1990).

Normalization of plasma cortisol concentrations has been associated with successful treatment with antidepressants and electroconvulsive therapy (Carroll *et al*, 1976; Christie *et al*, 1982). Long-term lithium therapy also induces alterations in cortisol secretion. Early works have shown that lithium administration either increases plasma cortisol (Platman and Fieve,1968; Noyes *et al*, 1971) or does not change cortisol values (Brooksbank and Coppen, 1967; Sachar *et al*, 1970), but more recent studies have demonstrated that prolonged administration of lithium in fact diminished plasma cortisol content (Meltzer *et al*, 1984; Smigan and Perris, 1984; Muehlbauer and Mueller-Oerlinghausen,1985). It is probable that lithium acts at the level of the hypothalamus, pituitary and adrenal glands or at all three to modulate adrenal function (Lazarus, 1986) but as many variables (e.g. severity of depression, presence of psychotic symptoms) influence the regulation of the hypothalamo-pituitary-adrenal cortical (HPA) axis interpretation of the results is difficult (Meador-Woodruff and Greden, 1988).

Lithium prophylaxis has provided a typical example of the complex relationship between illness management and drug characteristics because it is largely used in the long-term management of affective disorder patients and it affects thyroid and adrenal function. The administration of lithium induces

changes in many hormonal systems, and it is reasonable to think that when this drug is withdrawn multiple neuromodulatory systems may have been altered. The first report linking lithium to goitre (Schou *et al*, 1968) mentioned that two or three months after discontinuation of lithium the goitres decreased in size and disappeared completely. Since then several studies employing the design of before vs on lithium have been published to evaluate the thyroid effects of lithium therapy (Emerson *et al*, 1973; McLarty *et al*, 1975). This design has the disadvantage to confuse effects of illness itself.

Discontinuation trials, however, are reported less often in the literature. One example is the study of Spaulding *et al* (1972) who administered lithium for 5 days to euthyroid and thyrotoxic patients followed by a discontinuation period of 5 days. In affective disorders, however, only uncontrolled trials have been reported (Schou, 1968; Sedvall, 1968; Noyes *et al*, 1971). Consequently, the hormonal changes affecting the pituitary-thyroid and pituitary-adrenal axes in bipolar patients after lithium discontinuation which were reported in these earlier studies, need confirmation using stronger designs. These hormonal changes might be associated with the withdrawal syndrome previously described (Mander and Loudon, 1988). In other words, changes in thyroid hormones and cortisol may be relevant in explaining the increased relapse rate after the discontinuation of lithium. The examination of this relationship defined the objective of the present study.

TABLE 6.2

Short term effects of lithium on T4 and TSH levels in affective disorders (M = male, F = female).

| STUDY | N | DIAGNOSIS | DURATION OF THERAPY (months) | TSH LEVELS (mean ± SD) µU/ml Before Li | TSH LEVELS (mean ± SD) µU/ml on Li | P VALUES | COHEN'S D | T4 LEVELS (mean ± SD) µg/100 ml Before Li | T4 LEVELS (mean ± SD) µg/100 ml on Li | P VALUES | COHEN'S D |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Burrow *et al* (1971) | 9 | mood disorders | 0.75-1 | 1.1 ± 1.8 | 3.1 ± 2.4 | NS | 1.0 | 4.3 ± 1.2 | 3.9 ± 1.2 | NS | -0.35 |
| Lazarus and Bennie (1972) | 13 | manic depressives | 3 | 1.9 ± 1.0 | 2.3 ± 1.1 | 0.05 | 0.4 | 6.3 ± 1.9 | 5.4 ± 1.4 | NS | -0.54 |
| Halmi and Noyes (1972) | 6 | volunteers | 0.43 | - | - | - | - | 8.2 ± 1.2 | 6.0 ± 0.9 | 0.01 | -2.18 |
| Emerson *et al* (1973) | 27 | manic depressives | 1-3 | 3.3 ± 1.0 | 5.0 ± 1.0 | 0.01 | 1.68 | 8.1 ± 1.5 | 8.0 ± 1.0 | NS | -0.07 |
| Lauridsen *et al* (1974) | 8 | volunteers | 0.7 | 1.7 ± 1.7 | 2.0 ± 1.8 | NS | 0.18 | 7.7 ± 1.3 | 7.7 ± 1.2 | NS | 0 |
| Rifkin *et al* (1974) | 12 | EUCD[4] | 1.4 | - | - | - | - | 4.6 ± 0.6 | 3.9 ± 1.0 | NS | -0.80 |
| Villeneuve *et al* (1974) | 56 M | manic depressives[1] | 0.9-1.8 | - | - | - | - | 7.1 ± 1.2 | 6.9 ± 1.7 | NS | -0.13 |
| | 93 F | | | | | | | 6.8 ± 1.6 | 6.8 ± 2.0 | | 0 |
| Child *et al* (1976)[5] | 4 | volunteers | 1.4 | 4.0 ± 0.6 | 4.8 ± 0.8 | 0.05 | 1.3 | 9.5 ± 2.0 | 9.0 ± 1.6 | NS | -0.32 |
| Blomqvist *et al* (1977) | 5 | affective disorders | 0.23 | 2.1 ± 1.9 | 3.0 ± 3.8 | NS | 0.32 | 122 ± 17[2] | 97.8 ± 15[2] | - | -1.68 |
| Bakker (1982)[5] | 7 | euthyroid patients | 1.4 | 2.1 ± 2.6 | 4.2 ± 4.7 | 0.05 | 0.58 | - | - | - | - |
| Smigan *et al* (1984) | 51 | affective disorders | 4 | 2.5 ± 1.5 | 3.2 ± 2.0 | 0.02 | 0.68 | 101 ± 24[2] | 92.9 ± 24[2] | 0.05 | -0.34 |
| Perrild *et al* (1984) | 8 M | volunteers | 0.93 | 0.8 ± 0.3 | 1.1 ± 0.3 | 0.01 | 1.0 | 92 ± 12[2] | 80 ± 12[2] | 0.02 | -1.06 |
| | 8 F | | | 1.1 ± 0.6 | 1.4 ± 0.5 | 0.05 | 0.26 | 94 ± 18[2] | 71 ± 7[2] | 0.05 | -1.80 |
| Nelson *et al* (1988) | 10 | volunteers | 0.5 | 1.8 ± 1.0 | 4.8 ± 3.0 | 0.001 | 1.4 | - | - | - | - |
| Bochetta *et al* (1991) | 129 | affective and schizoaffective disorders | 2-3 | [3] | - | [3] | - | [3] | - | [3] | - |

[1] patients with other diagnoses included.

[2] nmol/l.

[3] no difference reported, but neither means nor 'p' values were given.

[4] EUCD = emotionally unstable character disorder

[5] values abstracted from graph.

**TABLE 6.3**

Long term effects of lithium on T4 and TSH levels in affective disorders (M = male, F = female).

| STUDY | N | DIAGNOSIS | DURATION OF THERAPY | TSH LEVELS (mean ± SD) μU/ml | | P VALUES | COHEN'S D | T4 LEVELS (mean ± SD) μg/100ml | | P VALUES | COHEN'S D |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (months) | Before Li | on Li | | | Before Li | on Li | | |
| Lindstedt *et al* (1973) | 334 | manic depressives | 'chronic' | ↑ in 2 | - | - | - | ↓ in 2 | - | - | - |
| Emerson *et al* (1973) | 27 | manic depressives | mean = 8 (1-19) | 3.3 ± 1.0 | 8.2 ± 4.7 | 0.001 | 1.48 | 8.1 ± 1.5 | 7.2 ± 0.5 | 0.05 | -0.79 |
| Villeneuve *et al* (1974) | 56 M | manic depressives[1] | 14-14.9 | - | - | - | - | 7.1 ± 1.2 | 6.9 ± 1.9 | NS | -0.12 |
| | 93 F | | | | | | | 6.8 ± 1.6 | 6.7 ± 1.2 | | -0.06 |
| McLarty *et al* (1975) | 17 | patients before lithium | mean = 21 | 3.5 ± 2.2 | | | | 100 ± 22[2] | | | |
| | 21 | patients on lithium | (1-67) | | 17.1[8] | - | - | | 88 ± 33[2] | NS | -0.44 |
| Lindstedt *et al* (1977) | 53 | patients on lithium | > 24 | ↑ in 8 | - | - | - | ↓ in 2 | - | - | - |
| Transbol *et al* (1978) | 105 | a-blood donors | mean = 80 | 2.3 ± 1.0 | | | | 101 ± 21[2] | | | |
| | 66 | b-MD on lithium with high TSH | | | 23.0 ± 31.0 | 0.001(a x b) | - | | 83 ± 38[2] | 0.01 (a x b) | - |
| | 20 | c-MD on lithium with normal TSH | | | 2.3 ± 0.9 | | | | 97 ± 20[2] | | |
| Eotterman *et al* (1979) | 88 | patients on lithium | mean = 27 | | 2.9[8] | 0.05 | - | | 6.8[8] | NS | - |
| | 40 | patients on antidepressants or neuroleptics | | 1.97[8] | | | | 7.6[8] | | | |
| Lazarus *et al* (1981) | 73 (58 bi, 15 uni) | manic depressives | mean = 37 (6-95) | - | ↑ in 11[4] | - | - | | 105 ± 23 | (3) | - |
| | | normal mean (range) | | | | | | 102.5 (55-150) | | | |
| Amdisen and Andersen (1982) | 237 | patients on lithium | > 6 | ↑ in 18[4] | - | - | - | ↓ in 10[4] | - | - | - |
| Bakker (1982)[5] | 13 | euthymic patients | 14-17 | 2.2 ± 0.7 | 2.4 ± 0.7 | NS | 0.29 | - | - | - | - |
| Smigan *et al* (1984) | 51 | manic depressives[1] | 12 | 2.5 ± 1.5 | 3.0 ± 1.5 | - | 0.31 | 101 ± 24[2] | 100 ± 24[2] | - | -0.02 |
| Myers *et al* (1985) | 133 | affective and schizoaffective disorders | 6 | ↑ in 12[4] | - | - | - | ↓ in 12[4] | - | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Maarbjerg *et al* (1987)[2] | | manic depressives | | | | | | | | | |
| | 430 | a-before lithium | | 2.0[6] | | | | 91 ± 23[2] | | | |
| | 202 | b-on lithium 6 months | | | 3.0[6] | NS | - | | 87 ± 26[2] | NS (a x b) | -0.16 (ax b) |
| | 162 | c-on lithium 12 months | | | 2.5[6] | NS | - | | 94 ± 27[2] | NS (a x c) | 0.13 (a x c) |
| | 37 | c-on lithium 48 months | | | 2.0[6] | NS | - | | 104 ± 32[2] | 0.001 (a x d) | 0.52 (ax d) |
| Perrild *et al* (1990) | | manic depressives | | | | | | [3] | - | [3] | - |
| | 19 | a-no lithium | | 1.5 (0.3 -9.0)[6] | - | | | | | | |
| | 24 | b-on lithium 1-5 years | | | 2.1 (0.3 -28)[6] | NS | - | | | | |
| | 50 | c-on lithium >10 years | | | 1.8 (0.3 -9.5)[6] | NS | - | | | | |
| Bochetta *et al* (1991) | 129 | affective and schizoaffective disorders | > 60 | | ↑ in 24[7] | [7] | - | [7] | - | [7] | - |
| | 21 | patients not on lithium | | ↑ in 2[7] | | | | | | | |

MD = manic depressives.

[1] patients with other diagnoses included.

[2] nmol/l.

[3] no difference reported, but neither means nor 'p' values were given.

[4] no means nor 'p' values were reported.

[5] values abstracted from graph.

[7] significant difference reported but no means nor 'p' values were given.

[6] median (range).

[8] no SD reported.

### *6.1.4. AIM*

The objective of this study is to investigate the neuroendocrine changes involving thyroxine (T4), thyroid stimulating hormone (TSH) and cortisol before and after lithium discontinuation in bipolar patients and to test whether they are related to the withdrawal syndrome observed in these patients.

## 6.2. METHODS

### *6.2.1. SUBJECTS*

Fourteen bipolar patients (nine females, five males) were diagnosed by DSM-III (APA, 1980) and identified through the lithium registry of the Royal Edinburgh Hospital (R.E.H.). Permission of supervising consultants was sought. All data regarding intake of lithium in Edinburgh are recorded by the R.E.H. lithium registry. Standardization of lithium serum level estimations is high because only one laboratory is involved. The inclusion criteria required that patients should be clinically euthymic on lithium prophylaxis for at least eighteen months, euthyroid at study entry and not taking any other psychotropic drugs. Patients were carefully examined and those with physical illnesses, family history of thyroid disease and physical complications of lithium treatment were excluded. They were also excluded if they scored more than 2 on a 23 item questionnaire about depression and mania. Written informed consent was obtained from all patients after full explanation of the nature of the study. Table 6.4 describes the demographic and clinical characteristics of the sample studied. They were mostly middle aged and had been on prophylactic lithium on average for almost a decade.

*6.2.2. STUDY DESIGN*

The study consisted of three phases, each lasting four weeks. During the first phase, patients were established on lithium carbonate (Camcolit® , 400-2000 mg) and baseline clinical ratings were obtained. Patients were seen weekly for the whole period of the study . During the second and third phase, a randomised double-blind procedure was followed: subjects were separated in two groups, the first received lithium for 4 weeks followed by placebo for 4 weeks, the second the reverse. At study entry, patients underwent physical examination and laboratory thyroid-adrenal function assessment, which included determination of serum levels of T4 ,TSH and cortisol. The same process was repeated after one month of lithium discontinuation. Patients were seen every week for clinical assessment and a family member was contacted if they were unable to attend. Blood was taken between 9 and 12 a.m. at the end of each phase of the study or at the discontinuation of the trial, for example following relapse.

Patients were classified as relapsed if: a) DSM-III criteria for mania were fulfilled; b) they scored an increase over 5 from baseline on a symptom check list; and c) they scored over 20 on the Manic Modified Rating Scale (Blackburn *et al*, 1977), applied on days 1 and 30 of the trial. Subjects who withdrew from the trial who did not meet all three criteria were considered to have remained well (full details are given in Mander and Loudon (1988).

*6.2.3. HORMONES ANALYSIS*

Within 2 hours of collection, all the blood samples were centrifuged and the plasma was stored at -40$^0$ centigrade prior to the analysis. A high sensitive time-resolved fluoroimmunometric assay was used to measure TSH (DELFIA®), with coefficients of variation (CoVs) at 4.9 and 21.6 mU/l were 3.4 and 4.0% respectively. DELFIA (Dissociation-enhanced lantanide fluoroimmunoassay - DELFIA$^R$, Pharmacia, Milton Keynes, U.K) is a solid phase, two-site immunofluorometric assay (IFMA) which employs two monoclonal antibodies directed against different antigenic determinants of the TSH molecule (Paterson *et al*, 1985). One antibody is bound to a solid matrix while the other is radiolabelled. Simultaneous binding of both antibodies to TSH results in the formation of a radiolabelled insoluble "sandwich", the concentration of which is directly proportional to the quantity of TSH present in the sample (Seth *et al*, 1984). The procedure of the Delfia measurement is described in detail by Kalhola *et al* (1985). T4 was analysed using the same technique, that is competitive time resolved fluoroimmunoassay (DELFIA), with coefficients of variation (CoVs) at 27, 107, and 155 nmol/l of 7.6, 3.6 and 3.5% respectively.

Total cortisol concentrations were determined by radioimmunoasay using a modification of the method of Seth and Brown (1978) and an antiserum (Scottish Antibody Production Unit) raised in sheep cortisol-3-O-carboxymethyloxime-bovine serum albumin. The cross-reaction of this antiserum as characterized by the Scottish Antibody Production Unit was: cortisol 100%, corticosteroid 0.18%, cortisone 0.07%, 21-deoxycortisone 0.30%, 11-desoxicorticosterone 0.03%, 11-deoxycortisol 0.58%, 17 alpha hydroxyprogesterone 2.1%, dexamethasone 0.33%. Antisheep-goat serum

(Scottish Antibody Production Unit) at a final tube dilution of 1/83 was used as the second antibody. The sensitivity of the assay for cortisol (90% B/Bo) was 11.6 nmol/l (0.42 ug/100ml). The intra-assay coefficient of variation were 2.2%(low pool, 153 nmol/l; 5.54 ug/100 ml), 2.8% (middle pool, 311 nmol/l; 11.3 ug/100 ml), 3.2% (high pool, 560 nmol/l; 20.3 ug/100 ml). The low, medium and high pools had corresponding interassay coefficient of variation (CoVs) of 4.6, 3.0 and 6.3%.

### *6.2.4. STATISTICAL ANALYSIS OF THE DATA*

Data were analyzed using SPSS programs. Demographic data were compared by means of chi square. A Paired t test was used to compare of neuroendocrine function of patients on and off lithium. Correlations between changes in thyroid and cortisol indexes after lithium discontinuation with demographic and clinical variables were determined by Pearson product moment correlations. Because of their skewed distribution TSH levels were normalized by log transformation for calculation of statistical differences. A Two tailed significance test was adopted.

## 6.3. RESULTS

### *6.3.1. VARIATIONS OF TSH LEVELS*

A significant reduction ($t= 2.94$, $p < 0.01$) in plasma level of TSH from 2.0± 0.1 to 1.2 ± 0.9 mU/l was observed after lithium discontinuation (Figure 6.1). Patients with higher TSH levels during lithium therapy also had higher baseline TSH concentrations after lithium withdrawal. Only one patient showed a TSH level during lithium prophylaxis above 4.0 mU/l, a criteria adopted by Bocchetta *et al* (1991) to define subclinical hypothyroidism. Thus, despite significant variations in TSH levels, all measurements can be classified as within the normal range (Figure 6.1). No association could be demonstrated between TSH levels after lithium discontinuation and lithium levels, duration of treatment, age, sex and cortisol concentrations. TSH was negatively associated with T4 levels ($r= -0.73$, $p < 0.01$).

### *6.3.2. VARIATIONS OF T4 LEVELS*

Figure 6.2 describes the effects of lithium withdrawal on serum levels of T4. After one month of discontinuation, there was a significant increase ($t= -4.4$, $p<0.001$) in serum T4 concentrations from 92.1 ± 16.3 to 112.9 ± 31.1 nmol/l. The increase in T4 was observed systematically in all but one patient. The pattern of increase was similar to the decrease in TSH, i.e. those patients with higher T4 concentrations during lithium therapy also had higher T4 levels after lithium discontinuation. The measurements made while patients were on lithium and after lithium discontinuation were all within the normal range. Despite the significant variations in T4 levels, patients could not be described

as being hypothyroid according to the criteria of Evered *et al* (1973) during lithium treatment. T4 concentrations were not associated with lithium levels, duration of treatment, cortisol concentrations and sex, but were correlated with age ($r= -0.67$, $p < 0.01$) and TSH concentrations after lithium withdrawal ($r= -0.73$, $p < 0.01$). There was no difference in the pattern of thyroid function after the discontinuation between patients who had been on lithium for more than 100 months and those who had been on lithium for less time.

### *6.3.3. VARIATIONS OF CORTISOL CONCENTRATIONS*

Figure 6.3 shows the effects of lithium discontinuation on plasma concentrations of cortisol. A non-significant reduction ($t= 0.92$, $p= 0.3$) in cortisol level was found after lithium withdrawal. No association could be demonstrated between cortisol levels and lithium dosage, duration of treatment, age, sex, T4 and TSH concentrations.

## TABLE 6.4

Demographic and clinical characteristics of patients discontinuing lithium. Values are mean ± standard deviation.

| | |
|---|---|
| Age at trial (years) | 52.7 (16.4) |
| Sex (M,F) | 5, 9 |
| Illness duration (years) | 9.8 (4.7) |
| Episode frequency (per year) | 0.2 (0.2) |
| Duration of lithium therapy (years) | 9.7 (4.9) |
| Last lithium level before discontinuation (nmol/l) | 0.72 (0.1) |

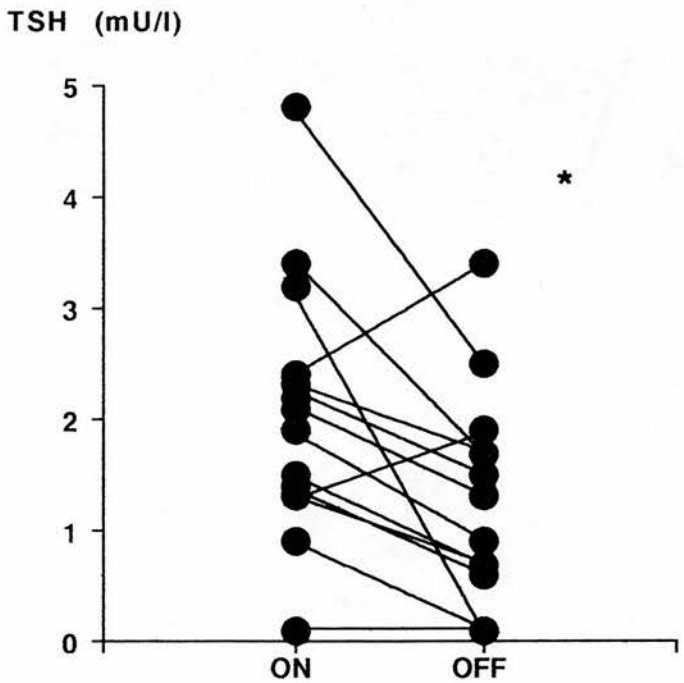



Figure 6.1. Plasma TSH levels in bipolar patients before and after lithium discontinuation (* $p<0.01$).

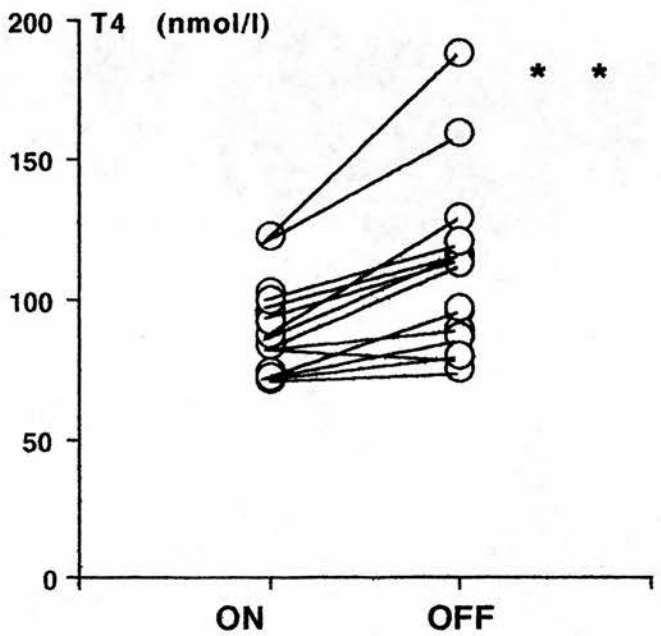



Figure 6.2. Plasma T4 levels in bipolar patients before and after lithium discontinuation. (**p<0.001)

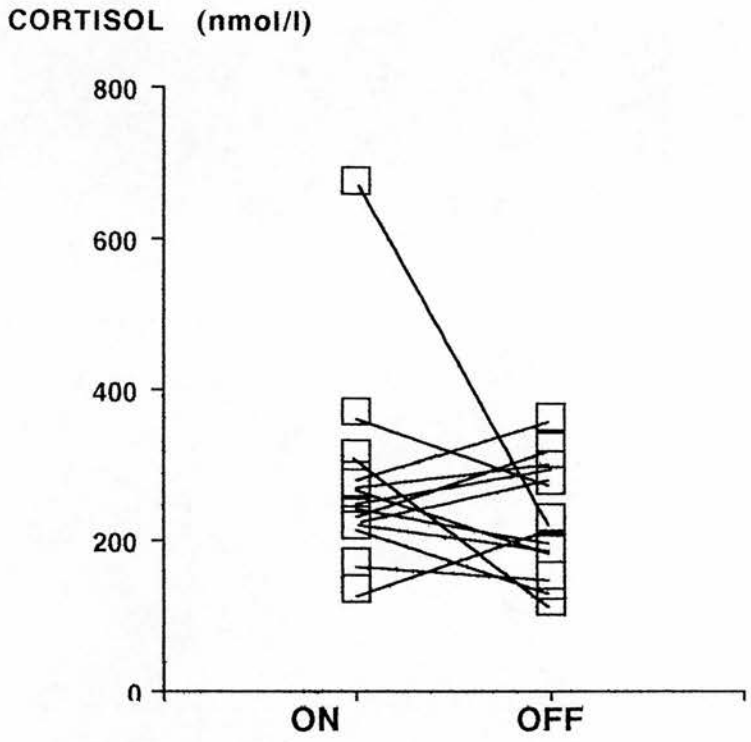



Fig 6.3. Plasma cortisol levels in bipolar patients on/off lithium.

### *6.3.4. RELAPSE VS REMAINED WELL GROUPS*

Table 6.5 shows the hormonal measurements of seven patients who had relapses shortly after placebo substitution (13-19 days) and who then had their lithium immediately restarted, compared with seven other patients who remained well after lithium discontinuation. As no significant differences were observed in TSH, T4 and cortisol between these two sub-groups, patients relapsing after lithium discontinuation could not be differentiated from those remaining well on the basis of these measures. Relapse was not associated with any variable (lithium dosage, duration of treatment, age and sex).

## TABLE 6.5

Plasma T4, TSH and cortisol concentrations (mean ± s.d.) in relapsed and remained well groups of bipolar patients before and after lithium discontinuation.

| HORMONE | BEFORE DISCONTINUATION | | AFTER DISCONTINUATION | |
|---|---|---|---|---|
| | RELAPSED | WELL | RELAPSED | WELL |
| T4 (nmol/l) | 84 (9) | 100 (19) | 102 (19) | 123 (39) |
| TSH (mU/l) | 1.9 (0.3) | 2.1 (1.6) | 1.4 (0.9) | 0.9 (0.9) |
| CORTISOL (nmol/l) | 315 (176) | 240 (40) | 222 (70) | 261 (80) |

## 6.4. DISCUSSION

### *6.4.1. HOW WAS TSH ALTERED BY DISCONTINUATION OF LITHIUM?*

The present study confirms the findings of previous studies which found a decrease in thyroid function during lithium therapy characterized by an increase in TSH plasma levels (Lazarus and Bennie, 1972; Emerson *et al*, 1973; Lazarus *et al*, 1981; Smigan *et al*, 1984) and refutes others which proposed that lithium inhibits the TSH release mechanism (Ruzsas *et al*, 1980) and those which found serum TSH concentration significantly lower in lithium treated animals (Bagchi *et al*, 1982). Thyroid stimulating hormone levels have also been found to be significantly decreased in patients who had a dosage reduction of lithium (Coppen *et al*, 1983). Significant decrease in TSH levels were also observed by Klein *et al* (1981). The decrease in plasma TSH levels observed after lithium withdrawal was statistically significant, however, the mean TSH levels before and after lithium discontinuation were within the normal range. It is interesting to note that mean TSH was in the top range of normal values. These findings would suggest that these patients had enough thyroid reserve to cope with prolonged lithium therapy. A positive association between TSH levels and duration of lithium therapy has been found (Child *et al*, 1976). This study, however, did not find any significant correlations between TSH values after lithium withdrawal and clinical and demographic variables.

Since lithium is concentrated in the hypothalamus and the pituitary, it is difficult to be sure if these findings are the result of a primary antithyroid action of lithium or whether they reflect direct action of lithium in the hypothalamus or pituitary or both (Lazarus, 1986). The increase in TSH concentration after

initiation of lithium therapy and its decrease after lithium discontinuation as demonstrated in this study indicates that the cause of hypothyroidism is further down the pituitary-thyroid axis, i.e. it suggests that the thyroid gland may not be able to produce and/or release the normal amounts of hormone or conversely that the peripheral degradation is altered (Smigan *et al*, 1984). Additional evidence for the thyroid being the prime target of lithium is provided by St Germain (1988) who claimed that alterations in TSH secretion in euthyroid individuals treated with lithium may result primarily from the direct effects of this agent on the thyroid.

### *6.4.2. HOW WAS T4 ALTERED BY LITHIUM THERAPY?*

The present study is in agreement with those which found a decrease in thyroid function during lithium therapy characterized by a reduction in T4 (Sedvall *et al*, 1968; Halmi and Noyes, 1972; Amdisen and Andersen, 1982). Consequently it is at odds with Goodnick (1985) who found no significant changes in thyroid function after three weeks of lithium discontinuation and also with Maarbjerg *et al* (1987) who found an increase in T4 with prolonged lithium therapy. The increase in serum T4 levels observed after lithium withdrawal was statistically significant, however, the mean T4 levels before and after lithium discontinuation were within the normal range. It is interesting to note that the mean T4 concentration was in the lower segment of the normal range. It has been recognized that small variations in basal thyroid function, even with the normal range may be of potential importance (Bauer and Whybrow, 1988).

Lazarus and Bennie (1972) reported a positive association between duration of lithium therapy and thyroid status. Transbol *et al* (1978) found an

association between laboratory signs of hypothyroidism and females patients over the age of 40. This study did not find any significant association between T4 levels after lithium discontinuation and clinical or demographic variables. The only exception was a negative correlation found between changes in T4 values and age.

These findings would suggest that these patients had enough thyroid reserve to cope with prolonged lithium therapy. The suppressive effect of lithium on the thyroid is similar, but hardly identical, to the suppressive effect of high iodine concentrations (Wolff, 1979), and that, as with iodine, most subjects compensate ("escape") sufficiently the lithium induced thyroid inhibition (Fyro *et al*, 1973; Amdisen and Andersen, 1982). They also lend support to the suggestion that patients who have low thyroid reserve (high TSH concentrations off lithium) are those who may develop clinical hypothyroidism or sustained abnormal thyroid function tests with prophylactic lithium (Shopsin, 1970; Berens and Wolff, 1975; Bagchi *et al*, 1982).

Which affective disorders patients are susceptible to develop hypothyroidism in affective disorder patients and how the high prevalence of hypothyroidism function tests can accord with the relatively low clinical occurrence of hypothyroidism are still unresolved questions. Positive findings have been associated with certain patient characteristics or study design. Some investigators found females over 40 years old to be more susceptible to alterations in thyroid function induced by lithium (Transbol *et al*, 1978). Differences in sex ratio in different studies have been suggested as a possible cause for the conflicting results regarding the effects of lithium on thyroid metabolism (Emerson *et al*, 1973). Hypothyroidism affects females more

frequently than males; a female/male ratio of 5:1 has been reported in 39 individual case reports (Lazarus, 1986). Duration of lithium prophylaxis and temporal adaptive mechanisms may account for some of this discrepancy. Some patients may lack the ability to escape after a certain time on lithium (Emerson *et al*, 1973; Fyro *et al*, 1973). This hypothesis was not confirmed by Smigan et al (1984) who did not find an increase of hypothyroidism with increasing duration of treatment. The presence of thyroid antibodies is also proposed as a predisposing factor (Lazarus *et al*, 1981; see also section 4.4.14). To date, no clear evidence is available to answer these questions satisfactorily.

It is still not clear exactly how lithium alters thyroid physiology and different mechanisms have been proposed to explain the effects of lithium on the thyroid gland. The first is inhibition of secretion or action of thyroid stimulating hormone (TSH). Secondly, inhibition of iodine concentrating mechanism has been proposed (Lazarus and Bennie, 1972). Lithium reduces the radioactive iodine uptake in the rat thyroid in vivo and in vitro. These high uptakes reflect an increased iodine retention within the thyroid gland. It is considered that the overall effect of lithium on depression of iodine coupling reactions is not great, at least in relation to other aspects on thyroid metabolism, e.g. secretion of hormone (Berens and Wolff, 1975). The third hypothesis is inhibition of hormone synthesis (Wolff, 1979). Fourthly, inhibition of hormone release from the gland has been proposed (Bhattacharya and Wolff, 1976). Finally, inhibition of peripheral degradation of thyroxine or diversion of the peripheral monodeiodination of T4 to rT3, an inactive metabolite, instead of T3 which is 4 to 5 times as active as T4 has been proposed (Lazarus *et al*, 1981; for reviews see Cooper and Simpson, 1974; Jefferson,1990). The inhibition of

secretion of hormone release is considered to be the main effect, at least from a functional point of view (Sedvall *et al*, 1968; Lazarus, 1986).

The mechanism of the lithium induced impairment of thyroid function has also been ascribed to autoimmune thyroiditis (Emerson *et al*, 1973) but antithyroid antibodies titers were not measured in this study. At present, the role of thyroid antibodies in lithium induced hypothyroidism remains controversial. The incidence of the antibodies in lithium treated groups has been found to be similar to untreated groups (Lindstedt *et al*, 1977). Further studies did not confirm a strong relationship between the levels of thyroid antibodies and the hypothyroidal effect of lithium therapy (Ghose *et al*, 1977; Deniker *et al*, 1978; Smigan *et al*, 1984). Other studies suggested that lithium does not induce antithyroid autoimmune disease but it may have an immuno-modulatory effect on existing autoimmune disease (Hassman and MacGregor, 1988).

Because of its hypothyroid effect lithium was suggested as a possible therapeutic agent in the treatment of thyrotoxicosis (Temple *et al*, 1972; Lazarus *et al*, 1974). For early treatment, lithium can be used alone or in conjunction with antithyroid drugs but it does not have much advantage over iodine (Lazarus, 1986). Lithium should not be used for long-term therapy of thyrotoxic patients, however, unless it is combined with thionamide medication, because an "escape phenomenon" (re-emergence of symptoms after 2 weeks of lithium therapy) has been described due to iodine pooling (Bakker, 1982). Hyperthyroidism following lithium withdrawal or dosage reduction has been reported in patients with pre-existing Graves' disease (Wilson and Jefferson, 1985).

Although this study did not find severe alterations in thyroid status in patients on lithium, hypothyroidism must be regarded as a serious complication when compared with other side-effects of lithium. The calculated incidence for goitre development was 4% per year per 100 patients on continuous lithium (Kushner and Wartofsky, 1988) and a reduction in thyroid function is reported to be in the range of 4 to 30% (Hullin, 1978). Furthermore, hypothyroidism in lithium patients may be misinterpreted as depression making diagnosis difficult (Lindstedt *et al*, 1977; Turnbridge, 1979). Due to the possible harmful effects of lithium on the thyroid, it has been proposed that thyroid function tests should be performed periodically. Different schedules of checks have been proposed for patients on lithium prophylaxis, such as every 2 to 3 months (Kushner and Wartofsky, 1988), or every year (Maarbjerg *et al*, 1987).

### *6.4.3. HOW WAS CORTISOL ALTERED BY THE DISCONTINUATION OF LITHIUM?*

During lithium prophylaxis, cortisol levels are frequently reduced (Meltzer *et al*, 1984; Smigan and Perris, 1984; Muehlbauer and Mueller-Oerlinghausen, 1985), consequently after lithium discontinuation they were expected to rise. But, in fact, cortisol concentrations showed a small fall; the reduction, however, was not significant. This finding is in agreement with Noyes *et al* (1971) who found a reduction of the excretion of 17-OHCS in the first 24 hours after lithium discontinuation which was reversed upon reintroduction of lithium. Cortisol directly suppress TSH release from the pituitary (Morley, 1981). In this study, however, no correlation between the cortisol levels and plasma concentrations of TSH and T4 were found.

### *6.4.4. CAN HORMONAL CHANGES EXPLAIN EARLY RELAPSE?*

In a longitudinal study, Kirkegaard *et al* (1975) found that a reduction in T4 levels and an increase in TSH response was associated with no relapse in ten patients who had been on therapy for a mean of 12 months, but in seven patients who relapsed in the first 3 months of therapy these parameters were not significantly modified. The changes induced by lithium in the hormonal status of affective disorders patients suggested a possible association between hormonal changes and the occurrence of early relapse after the discontinuation of lithium. In this trial, patients were observed for only one month after lithium discontinuation due to ethical requirements. A longer period, e.g. 3 months, would be desirable to ruled out completely any association between relapse and hormonal status. The small number of the sample also makes a reliable interpretation of the results difficult, but considering the accepted normal levels of hormonal measurements, there is no strong evidence for a hormonal influence in the seven relapses observed within one month of lithium discontinuation. Thus, the possibility of a withdrawal syndrome in bipolar illness being induced by changes in the hormonal concentrations of TSH, T4 and cortisol was not confirmed.

### *6.4.5. ARE LITHIUM RESPONSE AND ENDOCRINE EFFECTS RELATED?*

It is widely accepted that increased thyroid function facilitates treatment response in depression, e.g. the potentiation of tricyclic therapy by T3. Lithium therapy, however, is associated with decreased thyroid hormone levels. To solve this apparent contradiction, it was proposed that the relative decrease in

thyroid indices rather than the absolute hormone concentrations achieved with treatment is the important factor associated with treatment response (Joffe *et al*, 1984). This study gives indirect support to this hypothesis.

It has been postulated that in peripheral tissues, such as liver and kidney, nearly all nuclear T3 is derived directly from plasma T3 (Silva *et al*, 1978). On the other hand, animal studies have shown that in the cerebral cortex of the rat approximately 80% of T3 is produced locally (Crantz *et al*, 1982). Although these studies were performed in rats, the physiochemical properties of their thyroid hormones and nuclear T3 receptors are remarkably similar to those in human tissue (Oppenheimer, 1979). Administration of T3 raises plasma T3 but by negative feedback regulation, suppresses T4 production and consequently by decreasing plasma T4 induce relative hypofunction in the brain (Joffe *et al*, 1984). Therefore, the effects of T3 supplementation appear consistent with the findings of lithium prophylaxis, where reduction in plasma T4 are greater than decreases in plasma T3 (Dunner and Fieve, 1978).

A number of possible interactions between lithium, affective disorders and the endocrine system have been proposed (Johnson, 1988): a) the endocrine effects may be totally unrelated to the mechanism underlying recovery from affective disorder; b) lithium may influence endocrine functions by exactly the same mechanism as that involved in the clinical efficacy; c) the endocrine changes may be related to changes taking place in the central nervous system in complex interactive ways; d) endocrine functions may be more closely bound up with the mechanisms and etiology of psychopathological states than has been acknowledged previously. At the moment, it is still unclear how this relationship occurs.

### *6.4.6. ARE CHANGES IN THYROID FUNCTION SPECIFIC TO LITHIUM?*

The antithyroid effects observed with prophylactic lithium occurs with other psychiatric treatments. Long-term imipramine has produced loss of weight of thyroid gland in animals (Prange and Lipton, 1962) and in men (Baumgartner *et al*, 1988). Reichlin *et al* (1959) found increased thyroxine turnover during the last ten days of combined chlorpromazine-sleep therapy. Diphenylhidantoin was found to have a significant depressant effect on thyroidal hormones, but phenobarbitone had no significant effect (Liewendahl *et al*, 1978; Yeo *et al*, 1978). Carbamazepine decreased peripheral hormone levels while increasing thyrotropin levels (Roy-Byrne *et al*, 1984). Electroconvulsive therapy has also been shown to decrease thyroid function tests (Kirkegaard and Faber, 1981). As was seen with lithium, the hormonal changes in the majority of patients using these drugs are within the normal range. It remains to be elucidated whether the changes in thyroid function induced by these different drugs share a common mechanism or are the result of the illness itself.

### *6.4.7. HOW IS HYPOTHYROIDISM CLASSIFIED?*

Evered *et al* (1973) and Wenzel *et al* (1974) proposed definitions of thyroidal hypothyroidism from subclinical (grade 3) to overt (grade 1) considering the TSH response to TRH stimulation, basal TSH level and T4 and T3 concentrations. In grade 1, the only altered parameter is the TSH response to TRH stimulation which is increased. In grade 2, both the TSH response and the basal TSH level are increased. In grade 3, all three are disturbed, there is

an increase in TSH response and basal TSH, and the concentrations of T4 and T3 are reduced.

Inherent to the definition of hypothyroidism is the adoption of a specific laboratory criteria to determine the normal range of hormone concentration. Alexander *et al* (1962) defined the limits of the normal range as the best separation determined by inspection of the figures obtained from normal individuals and those found in patients with diseases associated with abnormally low or high values. The finding that thyroid function test in affective disorders falls within the normal limits is not new. Boumann *et al* (1950) reported that the results of the serum bound iodine test of 6 manics and 16 depressives were within the normal range but significantly different from those of normal controls. The interpretation of the "normal" range in measurements of peripheral TSH and T4 is difficult due to different definitions of normal values. The normal range of TSH has been defined as: less than 10 mU/L (Levy *et al*, 1981), less than 3 mU/L (Larsen, 1982), less than 6 mU/L (Morley and Schafer, 1982), $3.5 \pm 2.0$ mU/L (Wartofsky and Burman, 1982), 0.5-7.0 mU/L (Orsulak *et al*, 1985), 0.16 - 5.9 mU/L (Kirkegaard *et al*, 1990). The range of the normal limits of T4 has also been defined differently: $110 \pm 23.1$ nmol/L (Turnbridge *et al*, 1977), 72-156 nmol/L (Kirkegaard *et al*, 1990), 140 nmol/L (Joyce, 1991). Clearly the results obtained in this study are within the accepted normal range and they do not indicate any abnormality in their laboratory tests of these patients.

Subtle changes in thyroid economy may be associated with profound changes in behaviour, yet not change significantly hormonal levels measured in the periphery or be reflected only by changes within the "normal range", which

may be defined too broadly. Thus, the disturbances in the thyroid may be best understood as existing on a continuum and the traditional designation of hypo-, hyper, and euthyroid state exists as arbitrary, non physiological, and not directly relevant to a specific symptom or metabolic requirements of a target tissue (Reus, 1988). Rates of changes in hormonal levels may be more important than the levels themselves (Prange *et al*, 1977). According to this approach, different definitions of normal values in measurement of TSH have been proposed for patients on lithium (0-11 mU/L) versus patients not on lithium (0-8 mU/L; Lindstedt *et al*, 1973).

The TSH response to TRH stimulation was not performed in these patients. This test would give a more comprehensive picture of the HPT axis after lithium withdrawal. The TSH response, however, seems to change with symptomatology in some depressed patients, i.e. there is a normalization of the TSH blunting with clinical improvement (Kaplan and Sadock, 1989). As all subjects were required to be euthymic at study entry the use of this test is limited for this sample. In addition, the relevance of TSH response in manic relapse has not been fully investigated (Kaplan and Sadock, 1989), and also small changes in T4 concentrations have been reported to magnify TSH response considerably (Vagenakis *et al*, 1974).

In terms of TSH and T4 concentrations, none of the patients during the two phases of this study could be categorized as abnormal using these classification. The changes that occurred in the HPT axis were *relative* rather than absolute. If these relative hormonal alterations have any role in the relationship between thyroid function in affective disorder patients and lithium discontinuation, this could not be detected.

### *6.4.8. ARE HORMONAL CHANGES INDUCED BY LITHIUM REVERSIBLE?*

Two cases of permanent hypothyroidism after lithium discontinuation have been reported (Perrild *et al*, 1978), however other studies have failed to confirm this irreversibility of lithium effects on HPT axis (Schou 1968; Sedvall *et al*, 1968; Shopsin, 1970; Lindstedt *et al*, 1973 ). Lithium withdrawal appears to have reversed the alterations in T4, TSH and cortisol levels which were induced by its long-term treatment. This is in accordance with previous studies (Schou 1968; Sedvall *et al*, 1968; Shopsin, 1970; Lindstedt *et al*, 1973). The plasma levels of TSH and cortisol after chronic lithium treatment were found to be lower than after acute treatment (Nelson *et al*, 1988; Christie *et al*, 1989). Additional evidence of the reversibility of the effects of lithium on the thyroid gland is provided by two studies: first, Spaulding *et al* (1972) who observed that the slope of the protein bound $^{125}I/^{131}I$ returned to normal after the five day discontinuation period; and second, Bakker (1982) who demonstrated that basal TSH and TSH response to TRH were reversible in 8 euthyroid patients who had their lithium stopped. Laboratory studies also confirm the reversibility of lithium effects. Tsuchiya *et al* (1990) reported that in porcine thyroid cells when lithium was removed from the medium, iodine uptake in the cells treated with lithium chloride (LiCl) returned to the levels in the cells treated with lithium TSH alone and cell viability measured by trypan blue was not changed by LiCl treatment.

# CHAPTER 7

# THE ROLE OF DIETARY INOSITOL ON THE THYROIDAL AND OTHER SIDE-EFFECTS OF LITHIUM

## 7.1. INTRODUCTION

Lithium-induced hypothyroidism and other adverse effects may jeopardize long-term treatment as a result of discontinuation of the therapy. In order to prevent the side-effects of lithium in patients for whom long-term lithium usage is recommended, a different strategy was followed - the addition of inositol to the diet without discontinuation of lithium. The mechanism of action of lithium remains poorly understood (Wood and Goodwin, 1987), although, a second messenger system based on phosphoinositides (PI) located in the cell membrane has been proposed as the primary target for lithium (Berridge *et al*, 1982, 1989). Supplementation of the diet with inositol, which does not cross the blood brain barrier, might reverse the actions of lithium in target organs or tissues. If the effects of the addition of inositol to the diet was to mimick the peripheral effects of lithium discontinuation, two important conclusions could be drawn: first, the involvement of PI cycle in the action of lithium in men would be confirmed; secondly, a potentially important therapy to prevent the peripheral side effects of lithium would be available. The aim of this study was to examine the influence of inositol on thyroid function in patients receiving lithium.

In addition to the thyroid side effects, patients receiving prophylactic lithium may present with other adverse effects, such as dry mouth, nausea, nocturia, thirst and tremor. Reported incidences of patients showing these side effects have varied from 66% (Johnston *et al*, 1979) to 90% (Vestergaard *et al*, 1988). In some cases, these side effects are responsible for the discontinuation of lithium (Bech *et al*, 1976). Thus, the effects of inositol on these adverse effects were also evaluated in this study.

*7.1.1. INOSITOL*

In 1812, Vasquelin published the first account of a lipid which contained phosphorus (Hawthorne and Pickard, 1979). Inositol was first reported as a lipid constituent by Anderson and Roberts in 1930 (Hawthorne, 1982). In 1942, Folch and Woolwey described a brain phospholipid containing inositol. Folch subsequently introduced the term phosphoinositide (Hawthorne, 1982). In 1953, the exocrine pancreas was the first tissue in which phospholipid metabolism was found to be stimulated by agonists, in this case acethylcholine (Hokin and Hokin, 1953).

There are nine hexahydroxycyclohexanes, and they were originally described collectively as 'inositols'. To avoid confusion of the generic term with the only inositol which is found in the naturally occurring phosphoinositides, the *myo*-prefix was added *(myo*-inositol) and the various isomers have been termed cyclitols (Hawthorne, 1982; Agronoff, 1987). In animal cells, there are three myo-inositol containing phosphatides: phosphatidylinositol myo-inositol (PI), phosphatidylinositol 4-monophosphate (PIP), and phosphatidylinositol 4,5-bis-phosphate ($PIP_2$). *Myo*-inositol is a cyclic hexitol with molecular weight of 180 daltons which characterizes the class of phosphoinositides. Phosphoinositides constitute 2 to 8% of the lipid cell in eukariotic cells; PI accounting for 80 to 90% of the total inositol lipids while polyphosphoinositides (PIP and $PIP_2$) represent 10 to 20% (Hokin, 1985).

In 1971, Allison and Stewart were the first to report that the acute administration of lithium resulted in a 30% decrease in the level of *myo*-inositol. This decrease of myo-inositol was possible through the inhibition of the enzyme

*myo*-inositol-1-phosphatase, which was first studied in yeast by Chen and Charalampous (1966). In 1974, Naccarato *et al* showed that lithium completely inhibits *myo*-inositol -1- phosphatase of the rat mammary gland. The first demonstration of phosphatidylinositol metabolism in pituitary cells was made by Hokin *et al* (1958).

Receptor stimulation triggers the cleavage of phosphatidylinositol 4,5-bis-phosphate by phospholipase C giving rise to diacylglycerol and inositol 1,4,5-triphosphate, which are the second messengers for a series of intracellular processes. Diacylglycerol activates protein kinase C by enhancing its affinity for calcium which stimulates protein phosphorylation (Nishizuka, 1984) and inositol releases calcium from intracellular stores (Michell, 1975; Downes and Michell, 1982; Berridge, 1984). Phosphatase enzymes sequentially remove phosphate groups from inositol triphosphate, giving rise to free inositol which is then converted to phosphatidylinositol bisphosphate to reinitiate the phosphatidylinositol cycle (for a detailed review of inositol metabolism see Michell, 1975; Downes and Michell, 1982; Hokin, 1985; Berridge, 1987).

The formation of inositol in the thyroid has not not been systematically studied. Most studies have used cells of the central nervous system to study the metabolism of inositol, and four possible routes of formation of intracellular inositol have been described in central nervous system (see Table 7.1). First, by hydrolysis of phosphatidylinositol (Berridge *et al*, 1989). Secondly, by synthesis de novo from glucose-6-phospate (Eisenberg, 1967). In rabbit brain about 1% of the free *myo*-inositol was synthesized in vivo from glucose during a period of 3 hours (Spector and Lorenzo, 1975) but, even if glucose uptake is

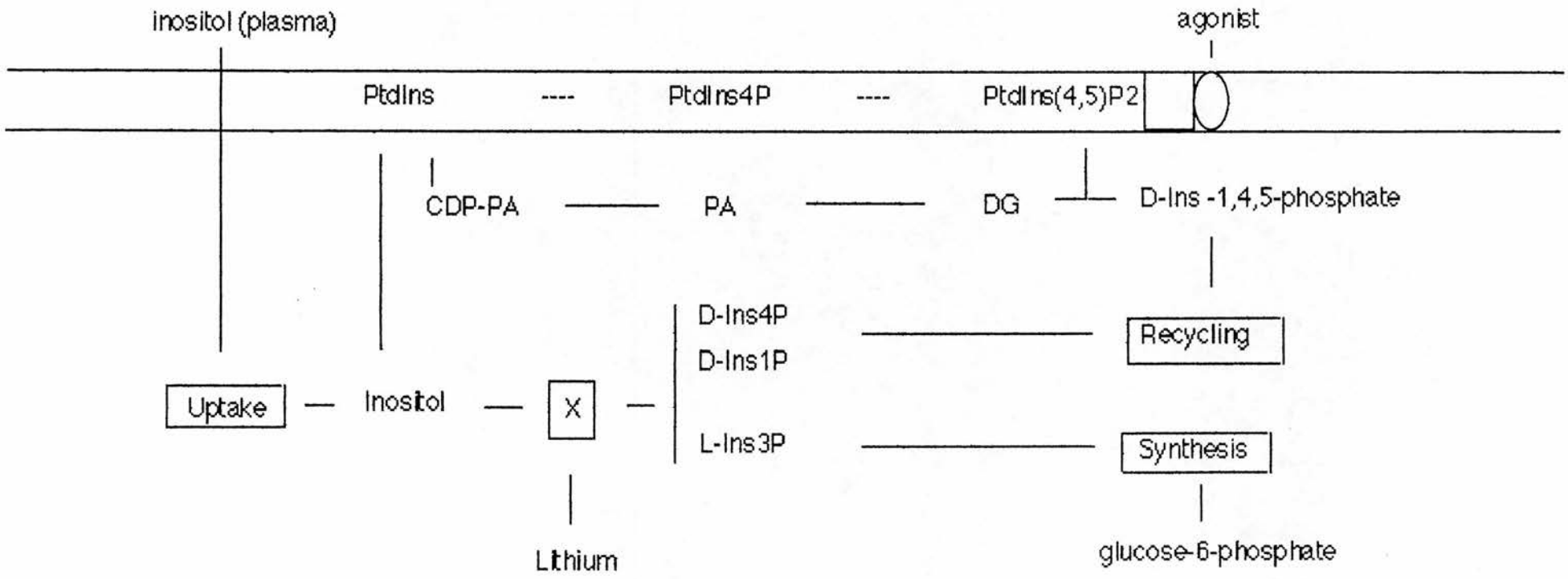
enhanced, it did not cause further appreciable increases in the concentration of phosphatidylinositol (Scott *et al*, 1966). The metabolic pathway of inositol from glucose-6-phosphate involves in the final step the transformation of inositol-1-phosphate to myo-inositol by the same enzyme *myo*-inositol-1-phosphatase that is blocked by lithium (Berridge *et al*, 1989). Thirdly, by epimerization of inositol to *scyllo*- and *neo*-inositol (Hipps *et al*, 1977; Sherman *et al*, 1978; Wong *et al*, 1987). In several brain regions, the 'in vivo' concentration of myo-inositol is 20 times higher than of *scyllo*-inositol (Sherman *et al*, 1968) and the concentration of *scyllo*-inositol is 20 times higher than of *neo*-inositol (Sherman *et al*, 1971). Consequently, epimerization represents a minor pathway as a source of inositol. Finally, transport from blood to the brain cells via the blood brain barrier. Uptake of *myo*-inositol into the brain is highly controlled (Spector and Lorenzo, 1975) and only 3% of plasma inositol is taken into the brain (Margolis *et al*, 1977; Lewin *et al*, 1976; Barkai, 1981).

In the CNS, inositol is mainly synthesized from glucose via *myo*-inositol-1-phosphate or by the hydrolysis of phosphatidylinositol (Margolis *et al*, 1971; Spector and Lorenzo, 1975), while in the peripheral nervous system myo-inositol is taken up exogenously (Greene *et al*, 1982). The importance of phosphoinositide hydrolysis in the CNS is highlighted by the differences in D- and L- enantiomer accumulation. Sherman *et al* (1981) demonstrated that the myo-inositol which accumulates in the brain of lithium treated animals is predominantly the D-enantiomer, and therefore the one which is derived from hydrolysis of phosphatidylinositol, as opposed to being derived from the *de novo* synthesis pathway which gives rise to the L-enantiomer (see Figure 7.1.). It remains unknown which pathway is the most important for the formation of the intracellular pool of inositol in the thyroid.

## FIGURE 7.1

Summary of inositol cycle. The sources of inositol (uptake, recycling and synthesis) are illustrated. Abbreviations are as follows: PtdIns - phosphatidylinositol. PtdIns4P - phosphatidylinositol-4-phosphate. PtdIns (4,5)P2 - phosphatidylinositol-4,5-bisphosphate. DG - diacylglygerol . PA - phosphaditic acid. CDP-PA - cytidine diphosphate diacylglycerol. D-Ins4P , D-Ins4P , L-Ins3P - inositol monophsphates. "X" - inhibition of the enzyme myo-inositol-1-phosphatase by lithium.

FIGURE 7.1


inositol (plasma)
agonist
PtdIns
----
PtdIns4P
----
PtdIns(4,5)P2
CDP-PA
PA
DG
D-Ins -1,4,5-phosphate
D-Ins4P
D-Ins1P
Recycling
Uptake
Inositol
X
L-Ins3P
Synthesis
Lithium
glucose-6-phosphate
CELL

### *7.1.2. THE EFFECTS OF LITHIUM ON c-AMP AND INOSITOL METABOLISM*

Traditionally research in psychopharmacology has focused on individual neurotransmitters. Lithium research has not been an exception to this pattern. The mechanism of action of lithium has been studied in terms of modification of noradrenergic, dopaminergic, and serotoninergic functions. Efforts using this approach have been fruitless, however. More recent research has focused on second messenger systems, adenylate cyclase activity and phosphatidylinositol metabolism (Wood and Goodwin, 1987; Baraban *et al*, 1989). Therefore, the mood stabilizing actions of lithium might be effective not because of the alterations induced in noradrenergic or serotoninergic metabolism per se, but because lithium alters the postsynaptic signal generated in response to such endogenous neurotransmitters (Risby *et al*, 1991). This approach has been more promising. Two hypotheses have been formulated: the adenyl cyclase and the inositol hypotheses.

The adenyl cyclase hypothesis, as proposed by Sutherland and Robinson (1966) suggests that c-AMP is a universal intracellular second messenger or mediator for the action of most mammalian hormones. Lithium inhibits adenyl cyclase (Dousa, 1970; Ebstein *et al*, 1976; Newman *et al*, 1983). Moreover, agents that stimulate cAMP accumulation inhibit agonist-stimulated accumulation of inositol phosphates (Campbell *et al*, 1990; Hall *et al*, 1989). Lately, a specific mechanism for "cross-talk" between cAMP and phosphoinositide has been proposed with still poorly defined functions (Baraban *et al*, 1989). Because stimulation of the alpha 1 adrenoreceptor inhibits inositol phospholipid breakdown (Kendall *et al*, 1985), it has been

argued that in reducing noradrenaline stimulated cAMP production (Ebstein *et al*, 1980) lithium could be acting through its inhibition of alpha 1 adrenoreceptors rather than beta adrenoreceptor (Godfrey *et al*, 1989).

The inositol hypothesis of the mechanism of action of lithium may be summarized as follows: lithium inhibition of inositol-1-phosphatase depletes inositol and reduces phosphatidylinositol turnover, and thus dampens cellular responses to neurotransmitters (Berridge *et al*, 1989). Transmitters affected would include all those known to act via the phosphatidylinositol cycle, including norepinephrine, serotonin, acetylcholine, histamine, and several peptides. As a result cells overstimulated by processes postulated as causal in mania or depression would be brought to a more normal functional level (Menkes *et al*, 1986). There is some experimental evidence for the inositol hypothesis. At therapeutic concentrations, lithium inhibits the activity of the enzyme inositol-1-phosphatase (Hallcher and Sherman, 1980). Lithium inhibition of inositol 1-phosphatase is noncompetitive (Berridge *et al*, 1989) suggesting that the more active the cell, the more it might be affected (Cornish-Bowden, 1986). Long-term lithium therapy decreases rat brain inositol levels and increases inositol-1-phosphate content (Allison *et al*, 1971, 1976).

Since lithium affects both adenylate cyclase and phosphoinositide, alternative hypotheses involving these two systems have been put forward in order to explain the effects of lithium. The first hypothesis concerns the guanine nucleotide-binding proteins (GTP proteins), which transduce signals from receptors to second messenger systems (for a review of GTP proteins see Gilman, 1987). Lithium within the therapeutic range inhibits adrenergic and cholinergic increase in GTP binding proteins in rat cortex by interfering with Gs

and Gp (Avissar *et al*, 1988). A second hypothesis relating affective disorders and the effects of lithium involving the second messenger systems was formulated by Wachtel (1989). It proposes that affective illnesses arise from the imbalance of the two major intraneuronal signal amplification systems - adenylcyclase (AC) and phospholipase (PLC). Depression would result from a hypofunction of adenyl cyclase and hyperfunction of the phospholipase system, and mania would result from opposite effects. The therapeutic effect of lithium would be due to the dampening of an over-active AC system in mania and to the dampening of the PLC system in depression (Wachtel, 1989).

### *7.1.3. LITHIUM, INOSITOL, c-AMP AND THE THYROID*

The interaction of cyclic-AMP, phosphoinositol, thyroid stimulating hormone (TSH) and lithium in the thyroid is complex. TSH exerts two primary effects on the thyroid: the stimulation of adenylate cyclase and the enhanced turnover of phosphatidylinositol (Gerard *et al*, 1982). TSH stimulates the incorporation of $^{32}P$ into phospholipids, especially phosphoinositol (Freinkel, 1957; Scott *et al*, 1966; Schneider, 1972). In the absence of TSH, monophosphatidylinositol which contains only 10% of the lipid $^{31}P$ accounted for about half of the lipid $^{32}P$ while phosphaditylcholine which contains half of the lipid $^{31}P$ accounted for about a third of the lipid $^{32}P$. In the presence of TSH, a greater proportion of the incorporated radioactivity was diverted to monophosphatidylinositol (Scott *et al*, 1966). This enhanced incorporation $^{32}P$ into phospholipids is independent of adenylcyclase since (i) dibutyryl cyclic AMP is unable to mimic this effect (Gerard *et al*,1982), (ii) it occurs at concentrations of TSH which are too low to stimulate adenylate cyclase activity (Burke, 1970-a), (iii) it is not affected by drugs such as theophyline and

prostaglandin $E_2$ which are known to increase the level of cyclic AMP in thyroid tissue.(Burke, 1969, 1970-b; Zor *et al*, 1969). Cyclic-AMP has also been found, however, to induce independently an increase in $^{32}P$ incorporation into phospholipids (Burke, 1969). TSH also enhances the incorporation of inositol $^{14}C$ into thyroid lipids (Freinkel, 1960; Jungalwala *et al*, 1971).

TSH increases the rate of formation of cyclic AMP by activation of adenylcyclase both in homogenates (Pastan and Katzen, 1967) and slices of bovine thyroid (Gilman and Rall, 1966), but treatment of thyroid membranes with phosphatidylinositol depresses the stimulation of adenylate cyclase by TSH and also inhibits TSH binding to plasma thyroid membranes (Omodeo-Sale *et al*, 1978; Aloj *et al*, 1979).

The role of lithium in the function of the thyroid needs further clarification. Lithium inhibits TSH stimulation of adenyl cyclase in the thyroid, and this action has been implicated in the reduction of $^{131}I$ accumulation in that organ (Wolff *et al*, 1970). Lithium inhibition of thyroid stimulating hormone sensitive to adenylate cyclase may be related to the hypothyroidism induced by the drug (Burke, 1970-a; Wolff *et al*, 1970). The effects of lithium on the phosphatidylinositol metabolism of the thyroid have not been systematically studied. Due to their easy availability, some studies have examined the effects of lithium on the phosphatidylinositol metabolism of the rat's pituitary tumour cells (GH3). In those cells, thyroid releasing hormone (TRH) and lithium stimulated the hydrolysis of phosphatidylinositol (Drummond and Raeburn, 1984).

Additional evidence for a role of phosphatidylinositol in thyroid function comes from the differences in the way that cyclic AMP and inositol respond to acute and chronic TSH stimulation. It has been suggested that TSH causes a coordinated increase in the formation of phospholipids and RNA and that dibutyryl cyclic AMP mimics the more rapid effects of TSH on transport and metabolic functions but does not influence the slower responses to the hormone (Kerkof and Tata, 1969). Thus, it may be hypothesized that cyclic AMP is more involved in the acute stage of TSH stimulation while phosphaditylinositol may have more influence on chronic TSH effects, such as those blocked by prophylactic lithium. Furthermore, because it does not enter the brain to any great extent, inositol is unlikely to interfere with the therapeutic effects of lithium. It may reduce some of its adverse effects, however. Of these, those on the thyroid are most worrying and necessitate expensive and frequent monitoring.

### *7.1.4. AIM*

The objective of this study was to evaluate the effects of adding inositol to the diet of clinically stable bipolar patients on prophylactic lithium upon thyrosine (T4) and thyroid stimulating hormone (TSH) concentrations and on other peripheral side-effects of lithium and to compare with those found of a group of normal controls not taking lithium.

## 7.2. METHODS

### *7.2.1. SUBJECTS*

Eleven bipolar patients (8 males, 3 females) diagnosed according to DSM-III criteria (APA, 1980) were compared with nine normal controls (6 males, 3 females) before and after adding inositol to their diet. Patients were recruited from the Lithium Register of the Royal Edinburgh Hospital or were referred by supervising consultants while normal controls were recruited from the University staff and community. To be eligible for this study the following criteria were applied:

a) patients should be stable on lithium for at least one year.

b) on entering the study, both patients and controls should be euthymic and euthyroid.

c) controls should not have any previous or family history of psychotic illness.

Any subject who had a known physical illness or a family history of thyroid disease was excluded from the trial. Four patients were on lithium only while the other seven were on lithium plus imipramine (1), amitriptyline (1), phenelzine (1), chlorpromazine (2), temazepan (1), or temazepan and clonazepan (1). No subject was taking any medication during the trial. Written informed consent was obtained from all subjects after being given a full explanation of the nature of the study.

*7.2.2. STUDY DESIGN*

This was a pilot study involving a single-blind design. On the first and last two days of the trial sucrose was administered to the subjects while in the intervening sessions inositol was administered. Inositol was started at a doses of 2 g/day and it was increased by 2 g on every second day, so that after one week subjects were taking 8 g/day. Plasma samples, taken before and seven days after adding inositol to the diet, were analysed for free thyroxine and thyroid stimulating hormone. Subjects were weighed prior to the addition of inositol.

*5.2.3. RATING SCALES*

Symptom severity and mood were assessed by the Beck Depression Inventory (BDI; Beck *et al*, 1961), Personal Feeling Scale (PFS; Wessman and Ricks, 1966) and Visual Analogue Mood Scale (Zeally and Aitken, 1969).

The BDI is a 21-item scale containing descriptive symptoms which were found to discriminate depressed from non depressed psychiatric patients. These symptoms refer to characteristic clinical aspects of depression, for example pessimism, social withdrawal suicidal wishes. For each symptom, there are four or five statements in the first person ranging from a mild or neutral statement up to one indicating a particularly severe degree of that particular symptom. Each statement is assigned a score of 0, 1, 2, or 3 to indicate the degree of severity of the symptom. The total score obtained on the BDI is the sum of the individual scores for each item. The maximum score on the BDI is 63. This inventory was found to have good internal reliability and was

validated in clinical settings. Beck *et al* (1961) reported correlations of BDI scores with physicians' ratings of 0.65 to 0.67 and reliability was found to range from 0.86 to 0.93. A correlation of 0.82 between the BDI and the Hamilton Rating Scale for Depression - HRSD (Hamilton, 1960) has been reported by Williams *et al* (1972). These correlations were highest near recovery and lowest at the acute stage of illness (Paykel *et al*, 1973). Possible explanations for this finding are the distorting effects of illness on self perception, lack of insight and response sets.

The aim of the PFS was to provide subjects with a comprehensive and exact vocabulary of affect and feeling that would be suitable for repeated self reports (Wessman and Ricks, 1966). It consists of a list of sixteen descriptive scales. Each scale has 10 statements ranging from extreme feelings at one end of the continuum, through more neutral feelings, to extreme contrasting feelings at the opposite end. In each scale, the subject is asked to choose the statement that best describe his or her mood at that time.

The Visual Analogue Mood Scale is a self recorded scale and contains the following topics - how well, how depressed and how elated subjects feel. These variables are recorded by marking a point on a 100 mm line to indicate how intense the feeling was (0=minimum, 100=maximum). Lines are scored using a millimetre rule and the mean mood and the standard deviation are calculated. The Visual Analog Mood Scale has been shown to be reliable, valid and clinically useful as a repeated measurement of mood (Aitken, 1969; Folstein and Luria, 1973).

Frequent side-effects of lithium therapy (dry mouth, nausea, nocturia, thirsty, tremor) were estimated by a completion of a side-effects check-list using the following scale: not at all (0), mild (1), moderate (2) and severe (3) based on how disabling the patient perceived the side effect to be.

*5.2.4. PROCEDURE*

All the scales were administered on the third and tenth days of the trial. All subjects were tested in the morning, between 9 and 11 AM after an overnight fast. Access to these data to the subjects was not permitted during the trial period.

*7.2.5. HORMONE ANALYSIS*

All blood samples were centrifuged within 2 hours of collection and the plasma was stored at $-40^0$ centigrade prior to the hormonal analysis. Both TSH and T4 were analysed using a high sensitivity time-resolved fluoroimmunometric assay (DELFIA®). The coefficients of variation (CoVs) for TSH at 4.9 and 21.6 mU/l were 3.4 and 4.0% respectively and for T4 were at 27, 107, and 155 nmol/l of 7.6, 3.6 and 3.5% respectively. DELFIA (Dissociation-Enhanced Lantanide FluoroImmunoAssay - DELFIA®, Pharmacia, Milton Keynes, U.K) is a solid phase, two-site immnunofluorometric assay (IFMA) which employs two monoclonal antibodies directed against different antigenic determinants of the TSH molecule (Paterson *et al*, 1985). One antibody is bound to a solid matrix while the other is radiolabelled. Simultaneous binding of both antibodies to TSH or T4 results in the formation of a radiolabelled insoluble "sandwich", the concentration of which is directly proportional to the

quantity of TSH or T4 present in the sample (Seth *et al*, 1984). For a detailed description of the procedure of the Delfia measurement see Kalhola *et al* (1985) and Methods of the previous chapter.

### *7.2.6. STATISTICAL ANALYSES OF THE DATA*

Data were analyzed using SPSS programs. The groups were compared on the basis of sex by means of chi square and on the basis of age and weight by t tests. A multivariate analysis of variance (MANOVA) was performed to analyse data regarding hormonal levels, rating scales and side effects before and after the addition of inositol. This statistical method allows the comparison of the control and patient groups on all outcomes simultaneously. TSH levels were normalized by log transformation for analysis purposes. A two tailed level of significance was used throughout the study.

## 7.3. RESULTS

### *7.3.1. DEMOGRAPHIC AND CLINICAL VARIABLES*

Table 7.1 describes the demographic and clinical characteristics of the sample studied. No significant differences were observed for any demographic variable between the patient and control groups. The only clinical variable showing a significant difference between the patient and control groups was weight ($t=2.4$, $p<0.02$), with patients being heavier than controls. Weight gain has been associated with chronic administration of lithium in 20 to 60% of patients (Vendsborg *et al*, 1976; Vestergaard *et al*, 1988), and is also seen with antidepressants (Fernstom and Kupfer, 1988) and neuroleptics (Amdisen, 1964). As all patients were taking one or more of these drugs they were expected to be heavier.

### *7.3.2. TSH AND T4 MEASUREMENTS*

Table 7.2 shows the means (S.D.) of the T4 and TSH levels found in the patient and control group before and during inositol administration. In terms of thyroidal side-effects, adding inositol to the diet would be expected, according to the hypothesis outlined above, to have a similar effect as stopping lithium. The findings after one week of inositol, however, did not support this hypothesis. There were no significant differences in hormonal concentration between subjects ($F=0.74$, $df=18$, $p=0.4$) nor in the interaction of hormone measurement by time ($F=0.78$, $df= 18,1$, $p=0.38$) nor in the interaction of group by hormone measurement by time ($F=0.02$, $df= 18,1$, $p=0.88$). Figures 7.2-A and 7.2-C show T4 and TSH levels in both groups before the supplementation with

inositol. Figures 7.2-B and 7.2-D display T4 and TSH concentrations, respectively, in both groups after the addition of inositol. On entering the study, all subjects had T4 and TSH levels within the normal range and this continued after one week of inositol.

### *7.3.3. RATING SCALES AND SIDE EFFECTS CHECK-LIST SCORES*

Table 7.2 shows the means (S.D.) of the scores obtained in the rating scales and side effects check-list by the patient and control groups before and during inositol administration. In terms of rating scales, there was no significant difference between subjects ($F=0.06$, $df=17$, $p=0.81$), but a trend was observed to indicate that the performance of the patient and control group differed on different scales ($F=2.5$, $df= 4$, $p=0.09$).

In terms of side effects, some subjects showed more side effects than others ($F= 5.12$, $df=17$, $p=0.03$), but there was no significant difference in the interaction group by side effect ($F= 1.08$, $df= 4$, $p=0.37$). The interactions of group by side effect by time and of side effect by time were both non significant ($F=1.01$, $df=4$, $p=0.42$ and $F=1.33$, $df=4$, $p=0.3$)

## TABLE 7.1

Demographic and clinical variables of the patient and control groups to whom inositol was administered for one week. All values are mean ± S.D.

| VARIABLE | PATIENT | CONTROL |
|---|---|---|
| Age at trial (years) | 55.0 (18.4) | 51.3 (18.3) |
| Sex (M:F) | 3:8 | 3:6 |
| Weight (kilos) | 80.9 (10.7) | 68.5 (12.0) |
| Illness duration (years) | 9.8 (5.8) | - |
| Episode frequency (per year) | 0.4 (0.3) | - |
| Duration of lithium therapy (years) | 8.6 (5.7) | - |
| Last lithium level before adding inositol (nmol/l) | 0.66 (0.19) | - |

## TABLE 7.2

Plasma T4 and TSH concentrations, scores obtained with self-rating scales and check-list of the most frequent side effects in the patient and ccontrol group before and during administration of inositol. All values are mean ± SD.

| | PATIENTS | | CONTROLS | |
|---|---|---|---|---|
| | Before Inositol | On Inositol | Before Inositol | On Inositol |
| **Hormone** | | | | |
| T4 (nmol/l) | 91 (25) | 89 (26) | 83 (18) | 81 (18) |
| TSH (mU/L) | 3.0 (1.7) | 2.7 (1.1) | 2.0 (1.1) | 1.9 (0.9) |
| **Rating Scale** | | | | |
| Beck | 8.1 (7.5) | 7.0 (7.7) | 2.2 (2.4) | 1.5 (2.1) |
| PFS | 10.8 (1.8) | 11.7 (2.2) | 12.6 (1.4) | 13.4 (1.8) |
| VAS Depressed | 22 (20) | 18 (18) | 7 (6) | 7 (5) |
| VAS Elated | 65 (23) | 73 (25) | 48 (31) | 73 (25) |
| VAS Well | 77 (15) | 81 (18) | 91 (9) | 87 (13) |
| **Side Effect** | | | | |
| Dry mouth | 0.9 (0.8) | 0.7 (0.9) | 0.1 (0.3) | 0.2 (0.7) |
| Nausea | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.3) | 0 |
| Nocturia | 1.2. (0.7) | 0.9 (0.9) | 0.7 (0.9) | 0.6 (0.7) |
| Thirst | 0.9 (0.8) | 0.7 (1.0) | 0.2 (0.4) | 0.1 (0.3) |
| Tremor | 0.7 (1.0) | 0.7 (1.0) | 0 | 0 |

Beck - Beck Depression Inventory

PFS - Personal Feeling Scale

VAS - Visual Analogue Scale

VAS was measured by lines of 100 mm where 0=minimum and 100=maximum.

Side effectswere rated from 0 (no symptom) to 3 (severe symptom).

## FIGURE 7.2

Serum T4 concentrations in bipolar patients and normal controls before (7.2-A) and after adding inositol to the diet (7.2-B). This figure also shows TSH levels in the same group of subjects before (7.2-C) and during the administration of inositol (7.2-D). Mean ± S.E. are illustrated through horizontal lines.

(1 = patients, 2 = controls).

FIGURE 7.2-A

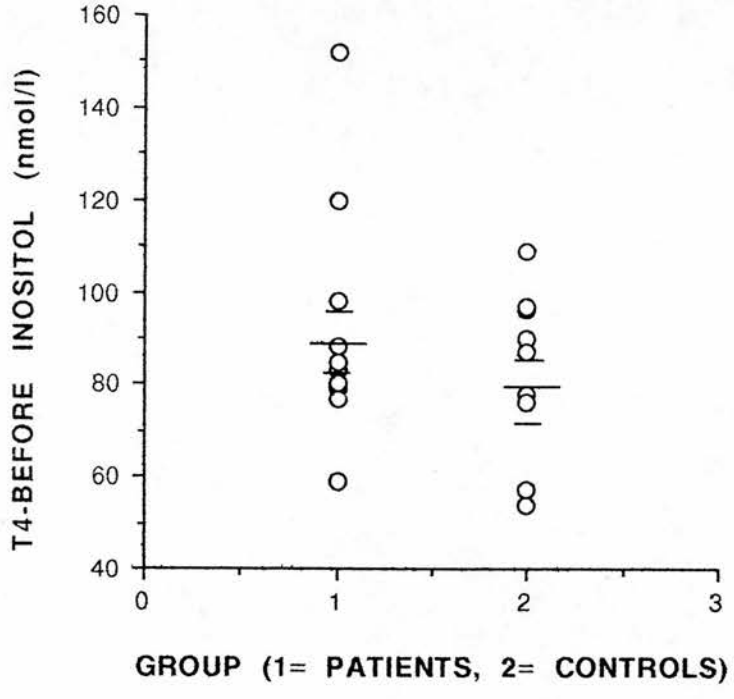

T4-BEFORE INOSITOL (nmol/l)
160
140
120
100
80
60
40
0
1
2
3
GROUP (1= PATIENTS, 2= CONTROLS)

FIGURE 7.2-B

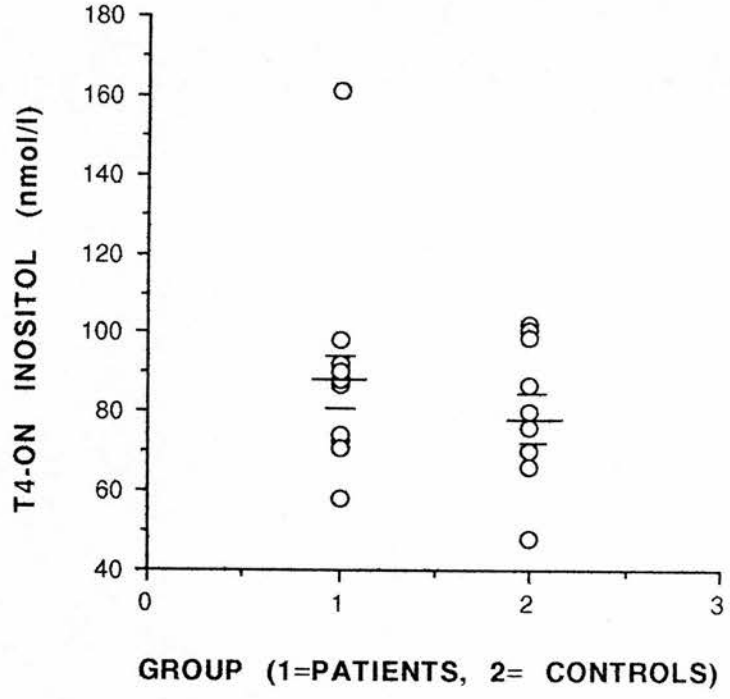

T4-ON INOSITOL (nmol/l)
180
160
140
120
100
80
60
40
0
1
2
3
GROUP (1=PATIENTS, 2= CONTROLS)

FIGURE 7.2-C

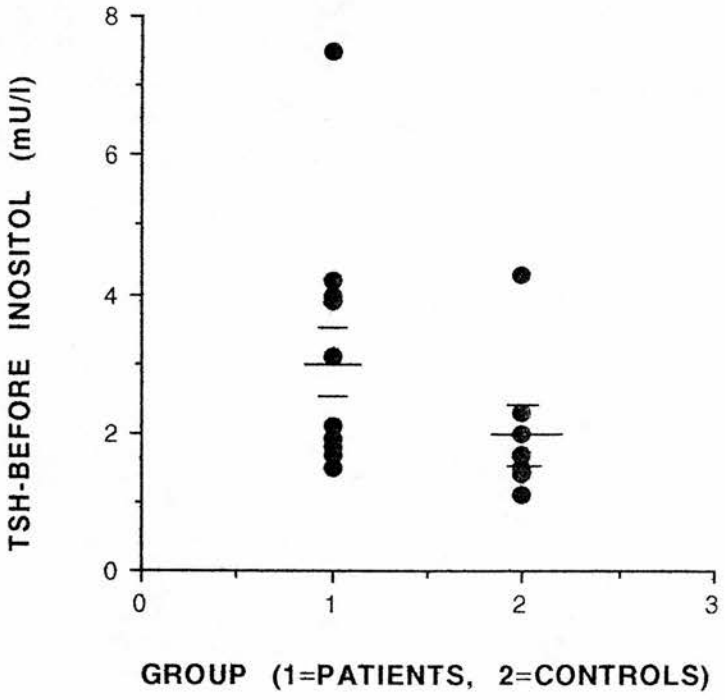
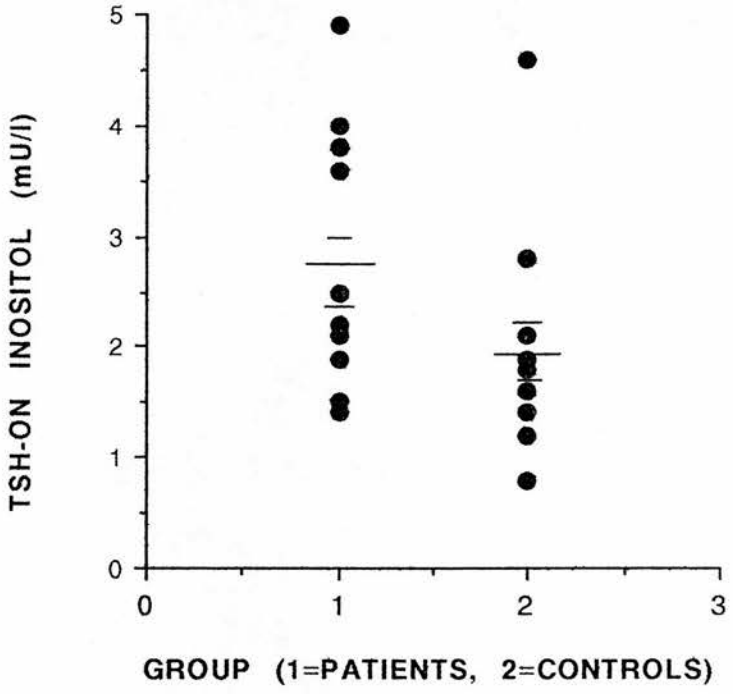

TSH-BEFORE INOSITOL (mU/l)
8
6
4
2
0
0
1
2
3
GROUP (1=PATIENTS, 2=CONTROLS)

FIGURE 7.2-D



## 7.4. DISCUSSION

### *7.4.1. HAS INOSITOL ANY ROLE IN REDUCING THYROIDAL SIDE EFFECTS?*

The results obtained from the addition of inositol to the diet of bipolar patients with the aim of reducing the side-effects of lithium were disappointing. The findings of this study do not support the view that dietary inositol can change, in any significant way, TSH and T4 concentrations. A high level of free myo-inositol may be essential to allow resynthesis to balance receptor mediated degradation (Berridge, 1984). The addition of inositol aimed to provide extra amounts of the substance to the thyroid and it was expected that changes would occur in T4 and TSH levels similar to those found with the withdrawal of lithium (increase in plasma thyroxine and decrease in TSH, for details see previous Chapter). However, the addition of inositol has failed to alter significantly the thyroidal status of either patients or controls. A more pronounced effect of inositol might have been observed if subjects had a marked reduction in thyroid function. As this was a pilot study, however, it was ethically advisable to evaluate the effects of dietary inositol, if any, in an euthyroid population.

Dietary inositol, given at a dose of one gram a day for two weeks, improved diabetic neuropathy in seven patients (Salway *et al*, 1978). Inositol increased the amplitude of evoked action potentials of the median, sural and politeal nerves by an average of 76%, 160% and 40% respectively but there was no significant change in the conduction velocities (Salway *et al*, 1978). This was the main guide to what dose of inositol to employ.

There is ample evidence that several of the biological effects of lithium can be reversed by the addition of *myo*-inositol (Zawalich *et al*, 1989; Kofman and Belmaker, 1990; Zhu and Fu, 1990). Downes and Stone (1986) observed that the enhancement of CMP-phosphatidase levels by carbachol in the presence of lithium could be reverses by adding back myo-inositol. The teratogenic effects of lithium on developing *Xenopus laevis* embryos can be completely blocked by replenishment of inositol (Taylor, 1988; Busa and Gimlich, 1989). The ability of lithium to attenuate muscarinic agonist-induced desentization in rat hippocampal slices was reversed by the addition of 1 mM myo-inositol (Pontzer and Crews, 1990). However, not all studies support the view that the addition of inositol reversed the effects of lithium. Kendall and Nahorski (1987) found that buffering the cellular inositol pool by in vitro preincubation with 2.5 mM myo-inositol did not prevent the inositol depletion by lithium. However, the effects of lithium in the intact brain may be different. Taken together, these findings would suggest that the *in vivo* effects of lithium may involve more complex mechanisms than the simple depletion of cellular inositol. The incorporation of many labelled precursors, including inositol, *in vitro* into phosphatidylinositol of thyroid tissue is enhanced by the addition of thyrotropin (Jungalwala *et al*, 1971). During lithium prophylaxis a sustained elevation of thyrotropin is observed. The necessary level of thyrotropin *in vivo* to influence inositol incorporation, however, may be above the normal range of TSH found in long-term lithium treated patients or controls in euthyroid state.

The concomitant administration of other drugs may have altered the human thyroid metabolism. Only four out of the eleven patients were on lithium alone, the other seven were on lithium plus a variety of other drugs (see

Methods). These drugs have not been clearly associated with the hypothalamic pituitary thyroid axis (McLarty *et al*, 1978; Prange, 1985) nor has any statistically significant difference in thyroidal status between patients on lithium only and lithium plus other psychotropic drugs been found (Lazarus *et al*, 1981).

To date, there is no good evidence to support the importance of the transport of inositol from blood to the thyroid for hormonal secretion. It appears that in the thyroid gland, the newly synthesised phosphatidylinositol stimulated by TSH is synthesised *de novo* rather than utilizing released diacylglycerol because the total incorporation of glycerol is unchanged. However, the proportion of glycerol going to phosphatidylinositol rises at the expense of other phosphoinositides, so no conclusive interpretation can be drawn from these findings (Michell, 1975).

In summary, organs that are known to have a synthetic capacity, such as the thyroid, are often also known to be capable of inositol transport, thus the degree of dependence on one means of inositol supply or another is often unclear (Wong *et al*, 1987). Cells or tissues sensitive to lithium are those that , for one reason or another, are unable to buffer internal inositol stores by uptake of external inositol (Berridge *et al*,1989). An unresolved issue is which mechanism does the thyroid gland mainly depend on.

### *7.4.2. CAN INOSITOL ALTER SCORES ON RATING SCALES?*

The finding that euthymic patients show a trend to score more poorly than controls in the BDI and PFS may be due to illness factors, since patients tend to

perceive themselves in a more pessimistic way and describe a poorer mental state (Paykel *et al*, 1973).

Another aspect that deserves comment refers to the use of self rating scales in this study. One criticism, at least, can be made about self rating scales, that is, they must have enough insight and be willing to give correct answers. Despite their deficiencies, self rating scales are widely used in psychiatric assessment, because they are economical in terms of research time and can be used repeatedly (Hamilton, 1987).

### *7.4.3. HAS INOSITOL ANY ROLE IN THE TREATMENT OF OTHER SIDE EFFECTS OF LITHIUM?*

Discontinuation of lithium therapy can be necessitated by the presence of other side effects (Van Putten, 1975; Jamison *et al*, 1979). The effects of inositol supplementation was also evaluated in relation to the most frequent complaints - dry mouth, nausea, nocturia, thirst and tremor (Bone *et al*, 1980; Vestergaard, 1983). In the patient group, dietary inositol failed to reduce the intensity of any of these side effects .

Inositol did not seem to alter the subjective sensation of thirst and nocturia in patients receiving long-term lithium therapy. Thirst is a common adverse effect of lithium. King *et al* (1985) found that 67% of patients complain of thirst despite the low levels of lithium on which they had been maintained, but reported incidences rates have varied from 35 to 70% (Vestergaard, 1983).

During lithium therapy, gastrointestinal symptoms, such as nausea, coincide with the absorptive rise of serum lithium concentration (Schou *et al*, 1970). The incidence of nausea in long-term lithium therapy is estimated to be about 10-30% (Bech *et al*, 1976; Campbell *et al*, 1991), but nausea has been reported to be more frequent in non euthymic patients (Bone *et al*, 1980). Dry mouth is present in 10 - 25% of patients receiving long-term lithium therapy (Christodoulou *et al*, 1977; Ghose, 1977). Both symptoms were unaltered by the administration of inositol.

Tremor is one of the most frequent side effects, with reported frequencies varying from 33 to 65% (Vestergaard, 1983). Inositol did not significantly alter this adverse effect in the patient group. Three aspects of lithium therapy have been associated with tremor:

1) Lithium levels - tremor has been found in 45% of the patients with levels of 0.85 mmol/l, and in only 15% of patients with levels of 0.68 mmol/l (Vestergaard *et al*, 1988). Our patient group had mean lithium concentrations of 0.66 mmol/l which can be considered in the lower range, and consequently it could be classified in the low incidence group.

2) Duration of lithium therapy - a reduction in the frequency of tremor has been observed with prolonged lithium treatment (Schou *et al*, 1970), but this finding has been disputed (Volk and Muller-Oerlinghausen, 1986). Tremor was not reported by significant numbers in the patient group, however.

3) Simultaneous intake of lithium and other medications - it has also been associated with tremor. It has been reported that tremor is more frequent in patients taking lithium and antidepressants simultaneously (Schou, 1983). The addition of inositol does not seem to influence tremor in patients taking lithium alone or with antidepressants, but the small numbers of patients taking either

lithium (4) or both medications (3) in this study does not allow further conclusions to be drawn.

### *7.4.4. WERE SIDE EFFECTS ADEQUATELY ASSESSED?*

The conversion of adjectives which describe severity into a set of numbers in arithmetical progression is a procedure which may be unacceptable to statistical purists (Hamilton, 1987). It not only implies that the intervals between one grade and the next are equal but they are also equal to the interval between absent (counting as 0) and mild (counting as 1). However, these procedures have been shown to be reliable (Hamilton, 1987). To assess side effects, two methods have been used: observer scales and self rating scales. In this study, side effects were not estimated by objective means; for instance, the subjective complain of thirst was not confirmed by water intake and nocturia was not confirmed by a 24-hour urine volume. One of the limitations of subjective rating scales is that an assumption is made that different patients will rate a symptom in a similar way. There has been agreement between scores obtained by observer rating scales and self rating scales, at least in depression (Williams *et al*, 1972). Thus, as a first step in the assessment on the effects of dietary inositol, these self-rating scale questionnaires seemed appropriate.

### *7.4.5. WAS ONE WEEK OF INOSITOL LONG ENOUGH FOR ITS EFFECTS TO BE SEEN?*

Patients were evaluated after only one week of inositol administration. This period may be too short to observe any significant changes in the thyroidal

and other side effects of lithium therapy. Addition of inositol for longer periods might be necessary to observe any inositol action on the side-effects of lithium.

### *7.4.6. WERE THE INOSITOL DOSES SUFFICIENT?*

The doses of inositol might have not been high enough to induce alterations in the thyroid status or to affect the adverse effects of chronic lithium administration. Based on the present knowledge, the doses of inositol used should have been sufficient, since the normal dietary intake is only 300-900 mg/day in man (Clements *et al*, 1973). While the extent to which dietary inositol is absorbed is still uncertain, it is apparent that large inositol loads result in significant elevations of plasma inositol which persist for several hours in man (Clements *et al*, 1973).

Good results have also been obtained in the treatment of diabetic neuropathy with one gram of inositol for a fortnight (Salway *et al*, 1978). In diabetics rats, the effects of inositol are contradictory; 1% inositol improved motor conduction, but this improvement was abolished and experimental neuropathy was exacerbated by a diet containing high concentration of inositol (Salway *et al*, 1978). Consequently, there was a paradox whereby low concentrations of inositol were associated with impaired nerve conduction and high levels of inositol were harmful. The implication for this study is that the dose, instead of being low, might have been too high.

# CHAPTER 8

# LITHIUM AUGMENTATION IN ANTIDEPRESSANT RESISTANT PATIENTS: A QUANTITATIVE ANALYSIS

## 8.1. - INTRODUCTION

The concept that pharmacotherapy is an effective treatment for major depression dates back from 1960's (Kraines, 1967). Some patients, however, fail to respond to standard antidepressant treatment. Treatment resistant depression (TRD), as this phenomenon is known, is a common and well-known clinical problem (Nierenberg and White, 1990). While between 70% and 80% of depressed patients respond within 3 weeks to a tricyclic antidepressant and a further proportion may respond within another 3 to 4 weeks to a second-line antidepressant (Klein *et al*, 1980; Nolen *et al*, 1988), between 10% to 30% of patients with a major depressive illness do not respond to antidepressants given at an adequate dose and for an adequate period of time (Keller *et al*, 1984; Nolen *et al*, 1988). For those patients who fail to respond to standard antidepressant treatment, different strategies have been proposed: a) optimization of the current regimen; b) substitution of a different treatment for the current drug; c) combination of two different treatments, each having different mechanisms of action; and d) augmentation of the therapeutic effects of the current drug by a second drug ( for comprehensive reviews see Extein, 1989; Goodwin, 1990). Augmentation differs from combination because it is based on the assumption that the second drug will interact in a specific way with the first drug to magnify the first drug effects. Unlike combination there is no assumption that the second drug will have any independent therapeutic effect (Extein, 1989). Therefore the interaction is greater than the sum of its parts (potentiation) rather than equal to the independent effects of each drug (additive).

Pharmacological augmentation of the effects of either re-uptake inhibitors or MAOIs is an attractive second-line approach to the management of treatment-resistant depressed patients. To achieve it, a variety of agents have been proposed including L-tryptophan (Pare, 1963), stimulants (Wharton *et al*, 1971), triiodothyronine (Goodwin *et al*, 1982) and reserpine (Price *et al*, 1987). Positive results, however, have been most extensively reported with lithium (Price, 1989).

### *8.1.1 LITHIUM AUGMENTATION*

Himmelhoch *et al* (1972), were the first to describe the benefits of adding lithium and antidepressants in the treatment of refractory depression. Tranylcypromine was added to 21 tricyclic (TCA) unresponsive depressives. A modest response was observed with the use of lithium alone, but when mono amine oxidase inhibitor (MAOI) was added a fuller response evolved. Lingjaerde (1973) showed, in a placebo controlled trial, that lithium enhanced the antidepressant effects of TCA in depressive patients (resistant or not). Van Putten and Sanders (1975) found that lithium improved the psychiatric status of 35 resistant cases. Neubauer and Bermingham (1976) obtained good results in 20 endogenous depressives when lithium was given either alone or in combination with TCA.

The first trial of lithium augmentation in resistant patients which attracted real interest was published by de Montigny *et al* (1981). This trial was not the first to report the augmenting effect of lithium but it highlighted the rapidity of its action. It had widespread impact and certainly helped to established lithium as the most studied potentiating agent in tricyclic antidepressant (TCA) resistant

depression (Schou, 1990). In their study, Montigny *et al* reported that, of 35 unipolar depressives treated for three weeks with a TCA, all eight initial non responders showed a dramatic improvement within 48 hours of the addition of lithium. Six of the eight patients maintained this improvement even though lithium had been discontinued. The importance of this trial warrants further discussion. Firstly, the improvement with the addition of lithium may also have reflected a delayed effect of TCA since 3 weeks is not sufficient time for the TCA treatment to achieve its full therapeutic effect. A placebo effect was discounted since the patients felt hopeless that another treatment would be of any help. Secondly, the lithium and antidepressant interaction was considered to be synergistic rather than an independent effect of lithium acting as an effective antidepressant. This conclusion was unwarranted since the patients had not been treated with lithium alone. This initial report was later confirmed by another study (de Montigny *et al*, 1983). In this second study, 39 unipolar depressed patients, unresponsive to TCA, had an average symptom reduction of 62 %. The authors speculated that the mechanism of TCA effects might involve enhancement by lithium of the serotonergic transmission (see Section 8.4.2). Initially, the justification for lithium augmentation was an empirical one, but improved understanding of the mechanism of action of antidepressants gave a better rationale for its use (de Montigny and Aghajanian, 1978).

There have now been 49 case reports and open studies (as listed in Schou, 1990; Thase *et al*,1989; Dinan and Barry, 1989) with some 387 patients being given lithium in addition to a tricyclic or MAOI. No less than 243 (62.7%) responded, to a greater or lesser extent, to the addition of lithium, often within 48 hours as de Montigny *et al* (1981) had claimed. However, these findings are derived from studies that are methodologically weak. While they

may have been clinically convincing, they cannot be taken as conclusive without controlled evaluation of lithium augmentation.

### *8.1.2. REVIEWS ON THE AUGMENTATION OF LITHIUM*

The initial enthusiasm for lithium augmentation has been tempered by the small number of controlled studies. To date there have only been seven double-blind, placebo controlled trials of lithium augmentation in patients resistant to a standard course of an antidepressant. Although traditional qualitative reviews of the literature (Schopf, 1989; Schou,1990) have supported the benefits of this approach, they also highlight the difficulty of drawing firm conclusions based on the results of several small studies, none of which is conclusive in itself and some of which are actually negative. These reviews also concluded that the controlled studies carried out so far have produced contradictory findings and call for further research in the area. Since the efficacy of this approach to treatment-resistant depression is of considerable clinical importance, and trials of an adequate size are difficult to perform, there is a need to extract as much quantitative information from the existing data as is possible. As described (Chapter 5), quantitative analysis can combine the results of different trials of similar methodology to improve the quantitative basis of our understanding of a given treatment effect, and it shifts the focus to effect size rather than significance levels in evaluating therapeutic efficacy.

### *8.1.3. AIM*

The objective of this study was to review the controlled trials of lithium augmentation in treatment resistant depression using quantitative techniques.

## 8.2. METHOD

### *8.2.1. META-ANALYSIS*

The importance of meta-analysis as a valid method to review and integrate findings of different studies has been described in detail in Section 5.2.1.

#### *8.2.1.1. Data Collection*

An attempt was made to gather data from all controlled trials of lithium augmentation in treatment resistant depression. The relevant references were obtained using a computer-aided search and an informal search through Index Medicus, recent journal reviews and published studies. Direct contact with authors was made when details of interest were not available from the published data (see Sections 5.2.1.1 and 5.4.6 for a comprehensive description and discussion of these methods).

#### *8.2.1.2. Inclusion Criteria*

Only controlled studies were analysed and consequently, trials included in the review were required to have random assignment of subjects to lithium or placebo and double-blind evaluation. In addition, all studies included in this analysis defined treatment resistant patients as those not responding to a minimum of 150 mg /day of a tricyclic antidepressant (or an equivalent antidepressant) given for 3 weeks or more. Patients were required to have a

minimum lithium level of 0.4 mmol/L at the time of assessment of treatment response (Blier and de Montigny, 1985; but see Section 8.4.9.6.). In spite of the small number of subjects, a study by Kantor *et al* (1986) was included in order to analyse the maximum number of patients.

*8.2.1.3. Exclusion Criteria*

Two controlled studies were excluded. The first was by de Montigny *et al* (1983) due to its use of a lithium rather than placebo control group, and the second was by de Cournoyer *et al* (1984) which did not lend itself to this type of analysis on account of its cross-over design and lack of sufficient raw data to allow inclusion of the results of the first phase of the trial. In the study by Stein and Bernadt (1988) the lithium levels in the double blind placebo-controlled phase were $\leq$ 0.4 mmol/l. It was worth analysing, however, because of the relatively large number of patients studied. Effect sizes were, therefore, calculated with and without this study.

*8.2.1.4. Statistical Procedures, File Drawer Problem and Power Calculation*

See Section 5.2.

## 8.3. RESULTS

Table 8.1 gives details of patient entry criteria and lithium duration, lithium dose and serum lithium levels of the controlled trials analysed in this meta-analysis. Either lithium or placebo was added to an antidepressant in all studies. Most studies reported on unipolar patients, except for Schopf *et al* (1989) where a third of patients were bipolar. All patients met either DSM III or research diagnostic criteria (RDC) for major depressive disorder/episode. There was a wide range of Hamilton Rating Scale for Depression (HRSD) scores suggesting that the studies included patients with a wide spectrum of illness severity. Whilst most patients had been on antidepressants for three weeks or more, illness duration at the time of study entry is often unclear, with the exception of the Zusky *et al* (1988) and Schopf *et al* (1989) trials which gave a mean duration of six months. In Table 8.1 "Duration" refers to the period during which the trial was double-blind and placebo controlled. This period was different in most cases from the full duration of the trial which was 24 days in Heninger *et al* (1983), 21 days in Zusky *et al* (1988) and 14 days in Schopf *et al* (1989).

Table 8.2 shows the findings of these studies. Schopf *et al* (1989) and Stein and Bernadt (1988) defined 'responders' as patients with a ≥50% drop in HRSD and Kantor *et al* (1986) used a ≥40% drop in HRSD. Heninger *et al* (1983) used a decrease of 2 or more points on the Short Clinical Rating Scale (SCRS; a 15 point nurse rated 'psychopathology' scale) as their measure of response, while Zusky *et al* (1986) defined 'responders' as those with a HRSD score of 7 or less. Only half the studies were said to be 'significant' ($p < 0.05$) but all the studies (except Stein and Bernadt,1988) showed a positive treatment

effect as indicated by negative (O-E) values. Indeed, when pooled significance intervals were considered, these results were unlikely to have occurred by chance ($p < 0.001$).

Figure 8.1 illustrates both individual and pooled effect sizes and confidence intervals. The pooled odds ratio is 0.14 with a 95% confidence interval ranging from 0.05 to 0.44. The pooled (O-E) value is -6.5 which means that 13 out of 34 patients or nearly 40% were 'responders' when treated with lithium.

The chi square of heterogeneity was 2.5 (NS), indicating that the studies did not significantly differ in the results obtained. When the study of Stein and Bernadt (1988) was included, the chi square of heterogeneity was 8.5 giving a *p* value of 0.005, thereby highlighting its methodological differences from the rest of the studies. The pooled odds ratio increased to 0.29 with inclusion of this study while the 95% confidence intervals became 0.12 - 0.73 which was a significant increase in width, as would be expected.

The number of unpublished studies reporting negative results necessary to reverse the conclusion that lithium is effective in augmentating the antidepressant response in TRD would be 13 studies. If the study of Stein and Bernadt (1988) is included, this would be reduced to 9 studies.

The power of the three studies which did not find significant differences between lithium and placebo groups was calculated. The statistical power of the studies of Kantor *et al* (1986), Zusky *et al* (1988) and Stein and Bernadt

(1988) were 0.17, 0.30 and 0.23, respectively. Thus, the possibility of missing a true difference in these studies was at least 70% (in Zusky *et al*, 1988).

An updated version of the study by Stein and Bernadt (1992), using de Montigny criteria of improvement, found a greater number of patients responding when a higher dose of lithium was administered, demonstrated by the fact that 15/34 (44%) patients responded to lithium 750 mg as compared to 6/34 (18%) who responded to lithium 250 mg. The mean lithium levels in the 250 mg group was 0.25 nmol/l and in the 750 mg group was 0.70 nmol/l. Their conclusion was that lithium 750 mg is significantly better than lithium 250 mg and that lithium 250 mg is no better than placebo.

**TABLE 8.1**

Controlled studies of lithium augmentation.

| STUDY | Patient Entry Criteria | Duration of Antidepressant Treatment | Duration* (days) | Li Doses (mg/day) | Li Serum Levels (mmol/l) |
|---|---|---|---|---|---|
| Heninger *et al* (1983) | Unipolar:14/15<br>Mean HRDS:34 ±10 | ≥3 weeks | 12 | 900-1200 | 0.5-1.1 |
| Kantor *et al* (1986) | Mean HRDS:23±4 | 3 weeks | 2 | 900 | not available |
| Zusky *et al* (1988) | Mean HRDS≥12<br>Mean HRDS:23±9<br>Episode duration:9 months | | 14 | ≥300 | ≥0.4 in 2nd week |
| Schopf *et al* (1989) | Mean HRDS≥15<br>Unipolar:18/27<br>Mean HRDS:20±5<br>Episode duration:8 months | ≥3 weeks | 7 | ≥800 | 0.6-0.8 |
| Stein and Bernardt (1988) | Mean HRDS:25±5 | ≥1 month | 21 | 250 | Mean level 0.23 |

*Duration refers to the period during which the trial was double-blind and placebo controlled

**TABLE 8.2**

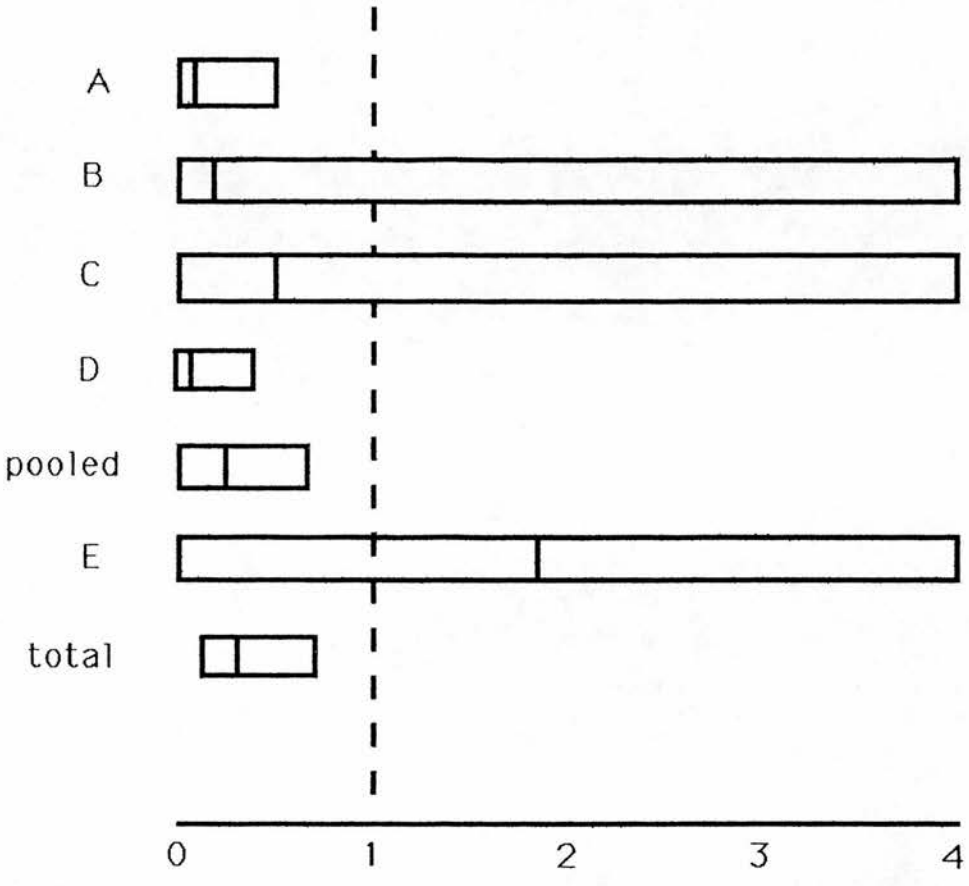
Results of controlled studies of lithium augmentation.

| STUDY | LITHIUM | | PLACEBO | | O-E | V | P |
|---|---|---|---|---|---|---|---|
| | responders | non-responders | responders | non-responders | | | |
| A) Heninger *et al* (1983) | 5 | 3 | 0 | 7 | -2.3 | 0.88 | <0.014 |
| B) Kantor *et al* (1986) | 1 | 3 | 0 | 3 | -0.4 | 0.24 | NS |
| C) Zusky *et al* (1988) | 3 | 5 | 2 | 6 | -0.5 | 0.92 | NS |
| D) Schopf *et al* (1989) | 7 | 7 | 0 | 13 | -3.3 | 1.34 | <0.005 |
| | | | | | | 3.38 | <0.001 |
| **Pooled** | 16 | 18 | 2 | 29 | -6.5 | | |
| E) Stein and Bernadt (1988) | 2 | 14 | 2 | 14 | 0.8 | 1.27 | NS |
| **Total** | 18 | 32 | 4 | 43 | -5.7 | 4.65 | <0.008 |

**FIGURE 8.1**

The odds ratio with the 95% confidence intervals for individual and pooled data from lithium augmentation studies. The left side (< 1.0) favours a positive effect of lithium augmentation and the right side (>1.0) favours no effect. Some studies have 95% confidence intervals which extended beyond 4.0 and are not drawn in full (Kantor *et al* (1986) from 0.004 to 11.6; Zusky *et al* (1988) from 0.07 to 4.51; Stein and Bernadt (1988) from 0.22 to 15.8). 'Pooled' refers to pooled results (a) to (d).

FIGURE 8.1



## 8.4. DISCUSSION

### *8.4.1. IS LITHIUM EFFECTIVE IN POTENTIATING ANTIDEPRESSANT RESPONSE?*

These findings suggest that lithium augmentation is effective in treatment resistant depression. The pooled effect size is large and Figure 6.1 illustrates the difference in emphasis between a statistical analysis based on significance levels and one based on effect sizes. Thus, 'negative' studies (Kantor *et al*, 1986, Zusky *et al*, 1988, and Stein and Bernadt, 1988) are not statistically significant but equally are not necessarily negative (in terms of effect size) as would be reported in traditional reviews (Schopf, 1989 and Schou, 1990). As highlighted in Chapter 5 the difference is not trivial because it leads to opposite conclusions; that lithium is ineffective (because 'not significant'), or that it may be effective (as shown by a favourable effect size) but the confidence interval is too great to allow certainty. The uncertainty is also highlighted by the results obtained in the analysis of heterogeneity between studies. No heterogeneity in the studies' results was observed when four studies were combined ($x^2$=2.5, NS). However, when the study by Stein and Bernadt (1988) was included in the analysis, the chi square of heterogeneity was significant ($x^2$=8.5, NS). This is a quantitative way of identifying aberrant studies.

The findings reported here are in agreement with previous narrative reviews (Schopf, 1989; Schou,1990) which found a positive effect of lithium in the potentiation of the antidepressant response in TRD patients. In summary, this meta-analysis supports the practice of lithium augmentation in TRD. The odds of remaining ill are reduced by 56% to 95% with lithium augmentation.

There remains considerable uncertainty over the duration of treatment necessary to promote and sustain the treatment response.

### *8.4.2. WHAT IS THE MECHANISM OF ACTION OF LITHIUM AUGMENTATION*

The exact mechanism of lithium's augmentation remains unclear. De Montigny *et al* (1983) have suggested that lithium augmentation may result from the cumulative enhancement of serotonergic transmission mediated by post synaptic actions of tricyclic and presynaptic actions of lithium. Long-term administration of tricyclics drugs induces a sensitization of postsynaptic serotonin receptors in rat forebrain regions (de Montigny and Aghajanian, 1978).

Short-term administration of lithium seems to enhance serotonergic transmission via a mechanism which is different from that in the tricyclics. Several studies suggest that acute treatment with lithium causes a presynaptic increase of the serotonergic function (Blier and de Montigny, 1985; Wood and Goodwin, 1987) due to an increase in tryptophan uptake and its conversion to serotonin (Knapp and Mandell, 1973). Moreover, long-term treatment increases 5-HT release (Treiser *et al*, 1981). Lithium could enhance the presynaptic sensitized 5-HT neurons by tricyclics. Since lithium addition failed to modify TCA drug plasma levels it is unlikely that the improvement was due to a pharmacokinetic interaction (de Montigny *et al*, 1983). Thus, it was suggested that the rapid responses observed in depressive resistant patients after receiving lithium was due to a dual effect enhancing serotonergic transmission: a) sensitization of postsynaptic serotonin receptors with prior tricyclic administration and b) subsequent presynaptic enhancement with short-

term lithium administration (de Montigny *et al*, 1983). Lithium has been shown to enhance post-synaptic behavioral responses (Goodwin *et al*, 1986).

Patients with affective disorders showed a different 5-HT homoeostatic response to lithium treatment compared with healthy volunteers (Price *et al*, 1989). The prolactin response of the 5-HT function was increased by short term lithium treatment in both groups whereas depressive patients on long-term lithium treatment showed no difference (Glue *et al*, 1986; Price *et al*, 1989). A more recent study, however, has shown that the addition of lithium to patients taking tricyclics resulted in an increase in the prolactin response to L-tryptophan after both four days and four weeks of treatment (Cowen *et al*, 1991). In addition, several strategies to decrease brain 5-HT produced relapses in depressed patients who improved with antidepressants (Treiser and Cascio, 1981). The reduction of plasma tryptophan in a diet free of the amino acid precursor of serotonin (Delgado *et al*, 1990), and the administration of parachlorophenylaline, which decreases 5-HT synthesis by inhibiting the activity of tryptophan hydroxylase (Shopsin *et al*, 1976), resulted in a rapid recurrence of depressive symptoms. Thus, a sustained serotonin function seems to be essential for a continued antidepressant effect (Ontiveros *et al*, 1991). However, the antidepressant induced serotonin receptor sensitization itself remains subject for continuing debate. No consistent alterations of serotonin turnover following long-term antidepressant administration either in animals or in depressed subjects was found (Charney *et al*, 1981).

Lithium also affects other neurotransmitter functions which may be involved in the lithium augmentation process. According to another neurotransmitter theory the therapeutic effect of antidepressants is linked to the

down-regulation of beta-adrenoceptors in the brain (Banerjee and Kung, 1977). Almost all TCA and MAOI have this action (Sulser, 1987). Long term lithium treatment also reduces the functional activity of beta adrenergic transmission by inhibiting the noradrenergic stimulated formation of cAMP at the site of adenyl cyclase (Ebstein *et al*, 1980). It has been reported that the down regulation of the density and agonist affinity of the cortical beta adrenoreceptors depends on 5-HT function (Sulser, 1987). Thus, the addition of lithium to restore deficient 5-HT neurotransmission might indirectly lead to beta adrenoreceptor subsensitivity (Sulser, 1987).

Finally, according to the cholinergic-adrenergic hypothesis of affective disorders (Janowski *et al*, 1972) which proposed that a relative cholinergic hyperactivity is present in depression, lithium might contribute to the normalization of mood by a balancing effect on the two neuro systems. Lithium at therapeutic concentrations has been shown to block cholinergic activation (Worley *et al*, 1988).

It is generally accepted that alterations in a single neurotransmitter cannot account for the therapeutic mechanisms of all antidepressants (Van Praag *et al*, 1987; Lopez-Ibor, 1988). In addition to the 5-HT/NE hypothesis it also has been suggested that antidepressants properties may depend on the effects of the second messengers involving G proteins and phosphoinositides (Heninger and Charney, 1987). Thus, the exact mechanism of lithium's potentiating action has not been established with certainty. However, from the available evidence, lithium augmentation seems to be clearly implicated in altering serotonergic mechanisms (Heninger *et al*, 1983).

### *8.4.3. HOW SOON IS A RESPONSE OBTAINED AFTER THE ADDITION OF LITHIUM?*

Some of the uncontrolled studies confirmed de Montigny's initial claim of a dramatic improvement within two days after the introduction of inositol (Joyce *et al*, 1983; Louie and Meltzer, 1984; Nelson and Byck, 1982), while other uncontrolled studies reported a more gradual response, that is, 1 to 6 weeks (Birkheimer *et al*, 1983; Roy and Pickar, 1985; Schrader and Levin, 1985; Price *et al*, 1986; Thase *et al*, 1989). It is questionable whether a response to lithium augmentation given for only 48 hours can be regarded as fully meaningful. The rationale for the original design of the de Montigny *et al* (1981) trial was based on the hypothesis that chronic administration of tricyclic antidepressants leads to increased sensitivity of forebrain neurons to 5-HT and that the acute administration of lithium releases 5-HT onto these receptors to form the basis of antidepressant efficacy. This acute presynaptic enhancement of transmitter release has been shown to occur at lithium concentrations ≥0.4 mmol/1 (Blier and de Montigny, 1985). Some authors do report a therapeutic effect after 48 hours of lithium augmentation at appropriate concentrations (de Montigny *et al*, 1983; Cournoyer *et al*, 1984; Schopf *et al*, 1989) but others report little or no effect until one week after commencement of lithium (Heninger *et al*, 1983). Schopf *et al* (1989) report an increase in the proportion of responders from about 20% responding at 48 hours, to 40% responding within two weeks. But higher rates of response have also been reported. Ontiveros *et al* (1991) have shown that in 30 melancholic patients resistant to desipramine 57% improved with the addition of lithium.

The rapid effect of lithium augmentation is evidence against an independent "antidepressant effect" of lithium since in most studies several weeks are required before any improvement in depression can be detected (de Montigny *et al*, 1983).

### *8.4.4. WHO RESPONDS TO LITHIUM AUGMENTATION?*

Specificity of lithium augmentation for bipolar depression has been claimed (Nelson and Mazure, 1986). However, good results have been found in some uncontrolled studies which included only bipolar patients (Roy and Pickar, 1985) as well as other uncontrolled studies which included only unipolar patients (Nelson and Byck, 1982; Birkhimer *et al*, 1983; Thase *et al*, 1989).

Schopf *et al* (1989) included bipolar patients who, when depressed, appear to show a response to lithium alone. This could have increased the chance of a spurious positive response to lithium augmentation, but the ratio of responders to non-responders in the unipolar and bipolar groups is similar at one week, so that the response to lithium does not appear to have been biased by the inclusion of bipolar patients. This similarity of response to lithium augmentation in unipolar and bipolar patients has also been reported by Price *et al* (1986).

The clinical pattern of improvement seems to have an 'all or none' feature. In studies done by de Montigny and associates most patients fell either into the 'no change' or 'marked improvement' groups with few showing mild or moderate improvement (de Montigny *et al*, 1988). This finding, however, has been disputed by Price *et al* (1986) who found that the clinical response to

lithium augmentation occurs along a clinical spectrum rather than in a simple all or none fashion.

### *8.4.5. IS LITHIUM POTENTIATION SPECIFIC TO TRICYCLICS?*

One of the most interesting aspects of lithium addition in resistant depression is that it can potentiate not only TCA but a large number of other antidepressants treatments (de Montigny *et al*, 1988). Patients resistant to MAO inhibitors, tetracyclics, serotonin re-uptake blockers, and other antidepressants improved with the addition of lithium (de Montigny *et al*, 1988). The hypothesis that the rapid clinical response after the addition of lithium with tricyclic treatment resistant depression is based on the interaction of lithium induced presynaptic serotonergic enhancement with postsynaptic sensitization (de Montigny *et al*, 1983). Antidepressants that either inhibit monoamine oxidase, e.g. phenelzine, or selectively block serotonin re-uptake, such as indalpine, do not cause postsynaptic sensitization to serotonin. However, since these drugs desensitize inhibitory presynaptic serotonin autoreceptors, the net effect is to enhance serotonin neurotransmission (Price *et al*, 1986). Thus, lithium should enhance the efficacy of these drugs by a different mechanism from that of tricyclics.

### *8.4.6. SHOULD LITHIUM AUGMENTATION ALWAYS BE TRIED IN TREATMENT RESISTANT DEPRESSION?*

Different strategies to deal with treatment resistant depression have been proposed (Extein, 1989; Goodwin, 1990). There is no consensus, however, concerning which strategy should be adopted in treatment resistant depression

or what order these strategies should be presented. A first approach to treatment resistant depression (TRD) may be the optimization of the treatment through a therapeutic trial in which the doses and duration of treatment are adequately monitored. This strategy is more conservative and helps to establish whether a patient who is considered resistant to therapy is in fact not adequately treated. A common step if optimization is not successful is substitution (Extein, 1989). Adding another drug to the therapeutic regimen (combination or augmentation) seems to be a logical step when substitution does not work (Goodwin, 1990). Among the possible alternatives of augmentation, lithium is probably the most common. There is, however, little research done on which strategy is preferable for specific diagnostic groups. Thus, the available data do not permit the categorical recommendation of when lithium should be tried in TRD.

### *8.4.7. METHODOLOGICAL CONSIDERATIONS ABOUT REFRACTORY DEPRESSION*

#### *8.4.7.1. What is an Adequate Definition of Refractory Depression?*

The question poses a major methodological problem in studying refractory depression. This problem was addressed at the World Psychiatric Association symposium on therapy resistant depression in 1974. A distinction was made between absolute and relative treatment resistance. Absolute was defined as failure to respond to 150 mg/day of imipramine or the equivalent after 4 to 6 weeks and relative was defined as the failure to respond to less than 150 mg/day. The implication of this definition was that relative treatment resistance was due to under treatment of depression. The distinction between

absolute and relative treatment resistance appears to be crucial for both methodological and clinical reasons. The evidence from several studies points to under treatment as the crucial variable conferring refractoriness to depressed patients (Schou and Weeke, 1988; Goodwin and Jamison, 1990).

In 1984, Goodman and Charney proposed another definition for refractory depression, being an episode of major depression, not secondary to a medical or drug induced condition, which fails to respond or sustain a response, to an adequate trial of an antidepressant drug of established efficacy for 4 weeks at a dosage considered therapeutic. However, a number of points are to be considered in any definition of TRD: a) how severe must the depression be after an adequate trial of treatment to be considered as resistant? and b) what constitutes adequate treatment for each antidepressant? (Nierenberg, 1990).

The most widely used definition of full antidepressant response in the psychiatric literature is a decrease greater then 50% in the Hamilton Rating Score for Depression (Endicott *et al*, 1981). The problem with this definition is that patients with very high scores will still be depressed even after a decrease of 50% in their HRSD scores. An alternative is to set an upper limit on the Hamilton score , e.g. a maximum score of seven on the 17-item version to be considered improved (Endicott *et al*, 1981). Another approach is to report both the proportion of patients who have a 50% decrease in their Hamilton scores and the proportion of patients whose Hamilton scores are below the upper limit as suggested by Zimmerman *et al* (1985).

Different definitions of adequate treatment have been proposed (Keller *et al*, 1986-a; Goethe *et al*, 1988; Sackheim *et al*, 1990). These criteria integrate antidepressant dose, duration and blood levels. Surveys have demonstrated that antidepressants are often used in sub therapeutic doses (Quitkin, 1985). There is some suggestive evidence that patients should be treated with adequate doses of antidepressants, e.g. 300 mg of imipramine or the equivalent for tricyclic antidepressants, before concluding that the medication is ineffective (Guscott and Grof, 1991). However, there is always the problem of side effects induced by high doses of antidepressants which may prevent the tolerance of these doses in patients.

Inadequate length of treatment emerges as a major factor along with under dosing in the treatment of depression. Some patients show signs of improvement as early as 3 to 10 days after initiation of the treatment (DiMascio *et al*, 1979), but others begin show improvement after two or three weeks of therapy. Taking this fact into consideration, most authors recommend at least 4 weeks of treatment as a minimum therapeutic trial (Keller *et al*, 1986-a; Goethe *et al*, 1988; Sackheim *et al*, 1990).

Tricyclic antidepressant serum monitoring is indicated in patients who fail to respond to treatment despite adequate doses (Hollister, 1979). However, there is no evidence to demonstrate that the use of serum monitoring in routine clinical practice improves outcome (Guscott and Grof, 1991).

There is some evidence that refractory depression is more frequently associated with variables involving the diagnostic (primary vs secondary depression) and treatment (e.g., adequate doses and duration) processes

rather than the patient. Although, there is also ample evidence that some patients are more treatment resistant than others, the degree of the resistance (absolute or relative) is often unclear (Guscott and Grof, 1991).

*8.4.7.2. Was the Diagnosis Correct?*

When confronted by a patient defined as having treatment refractory depression, the possibility of misdiagnosis should be considered. The possibility that there is a primary non affective disorder coexisting with a depressive syndrome should also be considered (Guscott and Grof, 1991). The studies included in this meta-analysis apparently used standard classificatory systems (DSM III and RDC) to diagnose depressed patients .

*8.4.7.3. Were Patients Compliant with Treatment?*

Noncompliance may be an important factor in patients defined as refractory (Guscott and Grof, 1991). It is important to distinguish a non compliant patient from a treatment resistant one (see Section 4.4.2. for a detailed discussion of the clinical implications of compliance). In outpatients, the problem of non compliance is especially highlighted (Nierenberg and White, 1990).

*8.4.7.4. Were Side Effects Important?*

The common occurrence of side effects when high doses of TCA are used is a considerable obstacle to the attainment of adequate therapeutic dosage (Schatzberg *et al*, 1983).

*8.4.7.5. How was Outcome Measured?*

Some studies have made a distinction between improvement of symptoms and psychosocial functioning. It was claimed that antidepressants have more effects on specific symptoms but psychotherapy has more effects on of psychosocial functioning (Klerman *et al*, 1974; Weissman *et al*, 1981). Rating scales have been the standard means of assessing improvement (for a detailed discussion on clinical improvement (see section 5.4.10).

*8.4.7.6. Is There a Coexisting Medical or Psychiatric Disorder?*

Refractoriness to antidepressant treatment was found to to be associated with chronic medical problems and ongoing alcohol abuse (Akiskal, 1982; MacEwan and Remick, 1988). Therefore, it is essential to exclude these variables as possible causes of the refractoriness of depression.

*8.4.8. LIMITATIONS OF THE LITHIUM AUGMENTATION STUDIES*

The interpretation of these trials is confounded by some methodological issues which need to be be taken into consideration regarding the role of lithium in enhancing antidepressant response. Examples of these limitations are:

*8.4.8.1 Small Numbers*

The limitation of small numbers in all the studies is only partly overcome by their combination to give a grand total of 99 patients in all (if Stein's study is included). Since probably up to 30% of patients treated with a tricyclic antidepressant do not respond, this remains a relatively disappointing total. Kantor *et al* (1986) suffered a large number of drop-outs (six patients) and due to the resulting small numbers (4 on lithium, 3 on placebo), this study taken on its own, was entirely inconclusive.

*8.4.8.2. Definition*

Most studies included in this meta-analysis used the de Montigny *et al* (1981) definition of treatment resistant depression (≥150 mg/day of a tricyclic antidepressant given for 2/3 weeks leading to a Hamilton score decrease of less than 40% from the pretreatment value). Many clinicians would favour the World Psychiatric Association definition (1974) which requires that a patient be treated for between four and six weeks with a tricyclic antidepressant at a dose greater or equal to 150 mgs/day, in order to be defined as treatment resistant. Nevertheless, it is doubtful that many clinicians would in practice wait more than 4 weeks before changing to another treatment if no response was seen.

*8.4.8.3. Duration*

Most trials had a duration of prior antidepressant treatment of three weeks. A three week antidepressant trial has been considered to be too short for the antidepressant drug to show its effect fully (see Section 8.4.9.1). The

lithium augmentation period was in some studies, e.g. Kantor *et al* (1986), too short (48 hours). This short period allowed the detection of only those patients who had a fast response to lithium augmentation. As response to lithium augmentation is variable a three week trial has been proposed as an adequate period to assess full benefit (Price *et al*, 1986).

*8.4.8.4. Different Populations*

There is the possibility that different populations of depressed patients might have been studied. A prolonged mean illness duration in some studies (Zusky *et al*, 1988; Schopf *et al*, 1989) may mean that different studies have included different patient populations.

A second aspect for consideration is the inclusion of bipolar and unipolar depressives. It has been reported that lithium augmentation is more effective in bipolar depression than in unipolar depression (Nelson and Mazure, 1986). All trials included only unipolar patients, with the exception of the study by Schopf *et al* (1989) in which one third of the sample was bipolar. Therefore, it is premature to comment on this aspect until further controlled studies are carried out.

A third point refers to the inclusion of patients with double depression (patients who do not have clear cut episodes of depression but are dysthymic continually). If patients had double depression (Keller *et al*, 1982; Klein *et al*, 1988) it was not stated in any of these studies.

*8.4.8.5. Design*

Most of the trials used the same design as de Montigny *et al* (1981), that is adding lithium to an antidepressant trial of only a few weeks' duration. This has been claimed to be methodologically flawed because it leaves open the possibility that improvement shortly after the introduction of lithium may reflect delayed effects of pre-existing antidepressant treatment (Nierenberg and White, 1990). The allocation of patients was non randomized in the studies of Heninger *et al* (1983) and in Stein and Bernadt (1988).

*8.4.8.6. Doses and Serum Levels*

In most of the studies, lithium doses and serum levels were within the accepted therapeutic range with the exceptions of that of Stein and Bernadt (1988) in which serum levels were well below the therapeutic limits (mean level of 0.23 mmol/l), and that of Zusky *et al* (1988) in which low lithium doses and low steady state plasma concentrations (0.10 -0.80 mmol/l) were observed. However, de Montigny *et al* (1981) reported that low plasma levels of lithium (0.4 mmol/l) were sufficient to induce potentiation of TCA drugs. Other studies have reported good results in antidepressant augmentation with plasma lithium concentrations even lower, 0.1 to 0.2 mmol/l (Kushnir, 1986; Madakasira, 1986). The available evidence, however, does not favour a 'low dose strategy'.

*8.4.8.7. Severity of Depression*

While illness severity is said not to influence response to lithium augmentation (de Montigny *et al*, 1983; Schopf *et al*, 1989) the majority of the

patients included in this analysis were moderately depressed (total mean Hamilton score, 24.4). It cannot be assumed that the efficacy of lithium augmentation would be as great in severely depressed patients and thus the range of patients to which the favourable effect of lithium applies remains uncertain.

*8.4.8.8. Use of Other Drugs*

Other problems with the Schopf *et al* (1989) study included the use of small doses of neuroleptics in a number of patients, and less than adequate doses of antidepressants in others (although tricyclic serum levels for these patients were reported to be within the therapeutic range).

*8.4.8.9. Outcome*

A binary outcome scale, required for the Mantel-Haenszel method, may appear too crude to assess an acute treatment such as lithium augmentation. However, it appears to reflect clinical decision-making reasonably well. The other advantage lies in the simplification of the raw data for direct analysis; this minimises methodological bias but allows optimal use of the available data by pooling all study results.

Individual studies contain other minor variations that may limit their comparability. Heninger *et al* (1983) used a nurse rating scale, the SCRS, to assess outcome thus making their results less comparable with those of other studies. They reported, however, unambiguously the favourable clinical outcome of the study.

### *8.4.9. LIMITATIONS OF THIS META ANALYSIS*

A detailed discussion of the limitations of meta-analysis is found in Appendix 5.2. In this section, the drawbacks of quantitative analysis will be related to the lithium augmentation trials. Firstly, meta-analysis is probably the only way to get adequate numbers of patients to estimate an average effect size in lithium augmentation trials. Secondly, the use of simple trials designs should help the interpretation and pooling of data. Thirdly, the need for randomization in future trials must be emphasized. Finally, big numbers of patients can help to stratify patients and therefore provide a more specific interpretation of the data.

# CHAPTER 9

# CONCLUSIONS AND FUTURE RESEARCH

*Study 1 - LITHIUM PROPHYLAXIS AND DISCONTINUATION IN UNIPOLAR DEPRESSION: EFFICACY, WITHDRAWAL SYNDROME AND SEASONAL PATTERN OF READMISSION*

The main practical conclusions of this study are firstly that patients who are doing well on lithium should be encouraged to persevere with it and secondly that the presence of a withdrawal syndrome after lithium discontinuation in unipolar depressed patients is not supported. Additionally, there is no evidence that readmission to a hospital in unipolar depressed patients on and off lithium is increased in autumn-winter or spring-autumn. This study provides further confirmation that lithium is of prophylactic benefit in unipolar depressive illness and it should strengthen the intention to treat recurrent depressive illness with lithium in our everyday clinical practice.

## FUTURE RESEARCH

There are a number of other questions related to the use of lithium in unipolar depression that still need to have an adequate answer. These include:

In 1975, Schou and Thomsen stated that there was no agreement on how long lithium prophylaxis should be continued and no established criteria existed for discontinuing lithium treatment on the basis of their treatment response. Sixteen years later these points have not yet been satisfactorily answered and further research is needed. Similarly, there are no clear guidelines on when lithium prophylaxis should start.

What are the predictors of recurrence and discontinuation? Preventive treatment should continue for those patients who have a high risk of recurrence but up to the moment no specific risk variable, such as biologic markers or personality traits, has been identified that would predict which patients require longer courses of maintenance treatment, nor any variable has been associated with discontinuation of lithium therapy. Similarly, the characterization of patients who fail to comply with lithium needs to be better investigated.

Does one relapse mean that lithium should be stopped? This question is still unanswered.

Is lithium less effective when it is introduced for the second time? The late non-response to lithium treatment may represent an important area of research from both the biological and clinical viewpoint. It also highlights the fact that the response or non-response of lithium may fluctuate instead of being a permanent feature of the illness with some patients showing inconsistent responses to lithium (Carroll, 1979). A similar point is argued by Maj *et al* (1989-b) who has indicated that lithium in bipolar patients may be less effective if it is reintroduced after being discontinued, and poses the question whether this pattern also holds in unipolar depression.

The search for biological features associated with withdrawal syndrome is in the early stages. At the moment, we can only speculate about the possible mechanism of the withdrawal syndrome in bipolar patients discontinuing lithium. This topic is dealt in the hormone discontinuation study in Chapter 6.

The study of seasonality patterns in affective disorders needs to be addressed considering the distinction between unipolar and bipolar affective disorder and the effects of medication. Seasonality data from the southern hemisphere and from regions near the equator are still missing. Both issues should be subjects of future research.

Group therapy and social support in lithium maintenance therapy have been associated with a positive effect on the posthospital course of bipolar patients (Davenport *et al*, 1977; O'Connell *et al*, 1985). The effects of psychotherapy, group therapy and social support on the adherence to lithium therapy and on the outcome after lithium discontinuation in unipolar patients have not yet been fully explored.

Personality disturbances were found in 48% of recurrent unipolar depressed patients and they were able to distinguish with 65% accuracy patients who responded normally and those who responded more slowly (Pilkonis and Frank, 1988). A poor response to antidepressants has been observed in patients with abnormalities of personality (Bielski and Friedel, 1976; Shawcross and Tyrer, 1985). The assessment of the importance of personality variables in the outcome of lithium prophylaxis and discontinuation is another area not yet fully investigated.

Relapse may be defined as a symptomatic exacerbation in a patient who has responded to treatment but not yet fully remitted or an aggravation of symptoms in a patient who has not been well for a sufficient length of time to be declared fully recovered (Thase, 1990) while recurrence is the emergence of a new episode in a patient who has fully recovered from a prior episode (Thase, 1990).

*Study 2 - LITHIUM TREATMENT AND PROPHYLAXIS IN UNIPOLAR DEPRESSION : A META-ANALYSIS*

The magnitude of the effect of lithium in controlled studies of prophylaxis is fully compatible with the observations in uncontrolled studies which in the past have received much criticism, for example, Baastrup and Schou (1967) and Angst *et al* (1970). In all studies, treatment with lithium appears to improve the rate of favourable outcome from 30 to 70%. To summarize, the existing literature strongly supports the value of lithium in prophylaxis of recurrent unipolar depressive illness. This effect size is clinically significant because rates of recurrence in unipolar illness are high. However, no advantage can be claimed for lithium over other antidepressants, particularly the older tricyclic drugs, and the value of lithium alone in acute treatment of depression remains uncertain. The uncertainty remains because remarkably few patients have ever been randomized in trials of acute lithium treatment.

There is a need to put in perspective the evaluation of clinical trials and their comparison with uncontrolled clinical studies and data from audit. The techniques employed here offer considerable advantages and deserve to be much better known. It is difficult, with hindsight, not to reach the conclusion that lithium's value in the prophylaxis of depression was clinically apparent to the workers who first used it. Their quantitative estimates of its value from uncontrolled studies would appear not to have been exaggerated. An argument about the quantities rather than the qualities exhibited by the research might have been more fruitful at the time. There is certainly no reason not to use quantitative methods to address such controversies now and in the future.

Meta-analyses will not necessarily give a different answer to a research review, but it should provide a better quantified answer. By showing the results of the studies and how the analysis was done, meta-analysis allows the reader to draw his or her own conclusions about the validity of the conclusions.

## FUTURE RESEARCH

It is recommended that acute depression should be separated in bipolar and unipolar depression and the use of lithium be analyzed in each disorder. The treatment of acute bipolar depression has been not properly explored . In fact, there has been no placebo-controlled study of any other drug other than lithium in bipolar depression during the past 20 years. A major problem is the practice by the pharmaceutical industry of testing drugs for depression primarily in unipolar patients (Prien and Potter, 1990). The effectiveness of lithium in bipolar depression is less robust than for mania. A review by Fieve and Peselow (1983) found that 65 to 85 patients could be classified as having "partial improvement," but the clinical significance of this term was not clear.

Future studies should assess whether the combination lithium plus antidepressants has unequivocal advantages over lithium alone. Forth coming trials should include not only measures of recurrences rates but also include evaluation on the severity and duration of the episodes.

*Study 3 - TSH, T4 AND CORTISOL AFTER LITHIUM DISCONTINUATION IN BIPOLAR AFFECTIVE DISORDER*

There was no significant difference in thyroid and cortisol status of bipolar patients who relapsed and those who continued well after lithium withdrawal. Thus, the hormonal consequences of lithium discontinuation can not explain clinical relapse.

## FUTURE RESEARCH

The development of techniques for the in vivo measurement of central nervous system thyroid hormone concentrations and effects is essential in order to understand how peripheral hormone metabolism is related to CNS function.

The central effects of pharmacotherapeutic drugs, such as lithium, and the modulation on these effects exerted by the thyroid status should be investigated more extensively.

There is the need to study the thyroid status in unipolar and bipolar patients who had never been on drugs. This population would permit the separation of the effects of the illness on the thyroid function from those of the medication.

The relationship between subtle thyroid hypofunction and affective disorder should be examined in detail in order to assess its importance in the outcome of affective illness.

How peripheral hormone metabolism is associated with CNS metabolism and the importance of the specific enzymes in this process are two topics deserving further investigation.

The short period of observation does not permit comment on the hormonal changes in the medium and long term after lithium discontinuation. However, this is an important question that needs to be addressed

*Study 4 - THE ROLE OF DIETARY INOSITOL ON THE THYROIDAL AND OTHER SIDE-EFFECTS OF LITHIUM*

The main conclusion of this study is that dietary inositol administered for short periods of time in euthymic bipolar patients does not seem to affect thyroid function nor other side effects of lithium therapy. Inositol does not seem to mimic lithium discontinuation. To date, there is no evidence that inositol is useful in the management of the adverse effects of of lithium.

## FUTURE RESEARCH

The evidence available for phosphatidylinositol turnover has ben provided mainly by laboratory and animal experiments. In humans phosphatidylinositol cycle has been studied in red blood cells and platelets (Downes and Mitchell, 1982). Enhanced phosphatidylinositol turnover, however, has not been shown in human tissues or cells. Techniques of *in vivo* $^{31}P$ nuclear magnetic resonance spectroscopy which enable the detection of lithium induced increases inositol 1 phosphate (Renshaw *et al*, 1986) may

allow, in the future, the assessment of differences in the phosphatidylinositol cycle in humans (Agam and Livne, 1989).

The phosphatidylinositol metabolism in human thyroid needs to be clarified and an accurate description of the role of phosphatidylinositol in hormonal secretion must be made. The importance of non-PI mechanisms in thyroid secretion need to be adequately established.

The effects induced by lithium on phosphatidylinositol breakdown in the thyroid gland need to be assessed comprehensively.

*Study 5 - LITHIUM AUGMENTATION IN ANTIDEPRESSANT RESISTANT PATIENTS: A QUANTITATIVE ANALYSIS*

The findings suggest that lithium augmentation is effective. The pooled effect size is large and the results illustrate the difference in emphasis between a statistical analysis based on significance levels and one based on effect size. Thus "negative" studies (Kantor *et al*, 1986; Zusky *et al*, 1988; Stein and Bernadt, 1988), are not statistically discriminating but, equally, are not necessarily "negative" (in terms of effect size) as would be reported in traditional reviews (Schopf, 1989; Schou,1990). The difference is not a trivial one because the analyses lead to opposite conclusions, that lithium is ineffective (because "not significant") or that it may be effective (as shown by a significant effect size) but that the confidence interval is too great to allow certainty. The present review supports the practice of lithium augmentation in treatment resistant patients. The odds of remaining ill are reduced by between 56% and

95% with lithium augmentation. This appears to be a worthwhile benefit. The present data does not offer clues as to who will respond and it is not known how long to continue treatment for. Finally, it is not known what the long-term prognosis of these patients is.

## FUTURE RESEARCH

More research is needed on the importance of diagnostic and treatment variables in the phenomenon of refractory depression (Keller *et al*, 1986-b).

There has been no consensus of which strategy to adopt to treat refractory depression if optimization (increasing the dosage and duration) of the current treatment fails. Three possibilities arise: substitution of a different antidepressant, combination of two different treatments, or augmentation of the initial or primary antidepressant by adding a second drug that enhanced the antidepressant effect of the first drug (Nierenberg *et al*, 1990). If augmentation is to be preferred, two related point need to be fully explored: firstly, to determine which modality of augmentation should be prescribed - lithium, triiodothyronine, L-tryptophan, stimulants or reserpine, and secondly, to assess whether there is any difference in efficacy of different antidepressants after lithium augmentation (Nierenberg *et al*, 1990).

Some studies have investigated the long term outcome of patients with refractory depression, for example Nierenberg *et al* (1990) showed that there was a good outcome in half of their sample within three years after lithium augmentation, additional research on this topic is needed, however, in order to clarify the roles of lithium and primary antidepressants in the maintenance

treatment of acute responders of lithium augmentation and more specifically to determine the duration of treatment with lithium necessary to promote and sustain the treatment response.

# APPENDIX 4.1

## LIFE TABLE

*1) CALCULATION*

The columns in the life able are calculated in the following way:

*Column (A)* presents the number of patients who were still well at the beginning of the indicated three month interval.

*Column (B)* tabulates the number of patients who were last observed well in the particular interval.

*Column (C)* shows the adjusted number of patients studied in the various intervals. If N denotes the number of patients who began the interval well and D the number last seen well during the interval, then only N-D were capable of being observed during the full interval. D is counted as D/2 under the assumption that they were last observed in the middle of the interval, therefore column (C) equals to N - D/2.

*Column (D)* represents the number of patients who were readmitted during the interval. If R denotes the number of patients being readmitted in the interval, the number beginning the next interval well is N - (D+R).

*Column (E)* contains the interval-specific probability (p) of remaining well. It represents the probability of a patient who was well at the start of the interval will be well by the end of the interval..

*Column (F)* indicates the cumulative probability (P) of remaining well at he end of an interval. It is calculation by the successive multiplication of each specific interval probability of remaining well. The value of (P) in any interval is given

by the product of the corresponding value of (p) and of all preceding values of (p).

*Column (G)* displays the 95% confidence interval associated with each cumulative probability of remaining well

*2) CALCULATION OF THE 95 % CONFIDENCE INTERVALS*

The estimation of the 95% confidence limits is given by the cumulative probability of the interval plus minus 1.96 (from the tables of the standard normal distribution) multiplied by the standard error of the interval. Consider, for example the estimation of the the interval 10-12 months of the discontinued group after lithium withdrawal, its cumulative probability is equal to 0.66 and its standard error is calculated as follows:

$$Var(P_{12}) = (0.66)^2 \{(0.18/(39.5 \times 0.82) + (0.13/(31.5 \times 0.87) + (0.08/26.5 \times 0.92)\}$$

$$Var(P_{12}) = 0.076$$

thus the standard error is equal to 0.15 and the 95% CI = $0.66 \pm 1.96 \times 0.15$, or the interval from 0.51 to 0.81, assuming that all dropouts have failed.

*3) COMPARISON OF TWO SURVIVAL CURVES*

To compare two samples at all points simultaneously a chi-square procedure due to Mantel (1966) is used. The result of this chi-square which incorporates a correction for discontinuity is then referred to tables of chi-square with one degree of freedom to test for the significance of the difference between the two series of probabilities. Let $N_1$ and $N_2$ be the two adjusted number of

patients, $p_1$ and $p_2$ the conditional probability of remaining well and $\underline{p}$ their weighted average, i.e., $p^* = (N_1 x p_1 + N_2 x p_2)/(N_1 + N_2)$. The following statistics is used:

$$x^2 = \frac{\{|\Sigma [(N_1 \times N_2)/(N_1 + N_2)] \times (p_1 - p_2)| - 1/2\}^2}{\Sigma \{[p^*(1-p^*)N_1N_2]/(N_1N_2-1)\}}$$

## APPENDIX 4.2.1

Calculation of summary chi-square after time zero between the discontinued x continued groups.

| INTERVAL MONTHS | DISCONTINUED AFTER TIME 0 | | CONTINUED AFTER TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $P_1$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 39.5 | 0.82 | 100.5 | 0.82 | 28.35 | 0 | 0 | 0.82 | 0.14 | 28.55 | 3.99 |
| 4-6 | 31.5 | 0.88 | 74.5 | 0.98 | 22.13 | -0.1 | -2.21 | 0.95 | 0.04 | 22.35 | 0.89 |
| 7-9 | 26.5 | 0.93 | 68 | 0.98 | 19 | -0.05 | -0.95 | 0.96 | 0.03 | 19.27 | 0.57 |
| 10-12 | 23.5 | 0.88 | 62 | 0.99 | 17 | -0.11 | -1.87 | 0.97 | 0.02 | 17.24 | 0.38 |
| 13-15 | 18.5 | 0.84 | 57 | 0.99 | 13.96 | -0.15 | -2.09 | 0.95 | 0.04 | 14.14 | 0.56 |
| 16-18 | 14 | 1 | 51.5 | 0.93 | 11 | 0.07 | 0.77 | 0.94 | 0.05 | 11.17 | 0.55 |
| 19-21 | 13 | 0.85 | 44 | 0.96 | 10 | -0.11 | -1.1 | 0.93 | 0.06 | 10.21 | 0.61 |
| 22-24 | 10 | 1 | 41 | 0.98 | 8 | 0.02 | 0.16 | 0.98 | 0.01 | 8.2 | 0.08 |
| TOTAL | | | | | | | 7.29 | | | | 7.63 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{46.1}{7.63} = 6.0 \quad (p<0.025)$$

## APPENDIX 4.2.2

Calculation of summary chi-square before time zero between discontinued vs continued groups.

| INTERVAL MONTHS | DISCONTINUED BEFORE TIME 0 | | CONTINUED BEFORE TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $P_1$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 39.5 | 1 | 103.5 | 0.83 | 28.58 | 0.17 | 4.86 | 0.87 | 0.12 | 28.79 | 4.89 |
| 4-6 | 37 | 0.98 | 81.5 | 0.93 | 25.44 | 0.05 | 1.27 | 0.94 | 0.05 | 25.66 | 1.28 |
| 7-9 | 30 | 0.94 | 63 | 0.89 | 20.32 | 0.05 | 1.01 | 0.9 | 0.09 | 20.54 | 1.84 |
| 10-12 | 23 | 1 | 44.5 | 0.98 | 15.16 | 0.02 | 0.3 | 0.98 | 0.01 | 15.39 | 0.15 |
| 13-15 | 19.5 | 1 | 37.5 | 0.92 | 12.82 | 0.08 | 1.02 | 0.94 | 0.05 | 13.05 | 0.65 |
| 16-18 | 15.5 | 1 | 28.5 | 0.97 | 10.03 | 0.03 | 0.3 | 0.98 | 0.01 | 10.27 | 0.1 |
| 19-21 | 13.5 | 1 | 23.5 | 0.96 | 8.57 | 0.04 | 0.34 | 0.97 | 0.02 | 8.81 | 0.17 |
| 22-24 | 12.5 | 1 | 22 | 0.96 | 7.97 | 0.04 | 0.31 | 0.97 | 0.02 | 8.2 | 0.16 |
| TOTAL | | | | | | | 9.41 | | | | 9.24 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{79.38}{9.24} = 8.59 \quad (p<0.01)$$

## APPENDIX 4.2.3

Calculation of summary chi-square of the continued group before and after time zero.

| INTERVAL MONTHS | CONTINUED BEFORE TIME 0 | | CONTINUED AFTER TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $P_1$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 103.5 | 0.83 | 100.5 | 0.82 | 50.98 | 0.01 | 0.5 | 0.82 | 0.14 | 51.24 | 7.17 |
| 4-6 | 81.5 | 0.93 | 74.5 | 0.98 | 38.92 | -0.05 | -1.94 | 0.95 | 0.04 | 37.71 | 1.5 |
| 7-9 | 63 | 0.89 | 68 | 0.98 | 32.7 | -0.09 | -2.94 | 0.93 | 0.06 | 32.95 | 1.97 |
| 10-12 | 44.5 | 0.98 | 62 | 0.99 | 25.9 | -0.01 | -0.25 | 0.98 | 0.01 | 26.15 | 0.26 |
| 13-15 | 37.5 | 0.92 | 57 | 0.99 | 22.61 | -0.07 | -1.58 | 0.96 | 0.03 | 22.86 | 0.68 |
| 16-18 | 28.5 | 0.97 | 51.5 | 0.93 | 18.34 | 0.04 | 0.73 | 0.94 | 0.06 | 18.57 | 1.11 |
| 19-21 | 23.5 | 0.96 | 44 | 0.96 | 15.73 | 0 | 0 | 0.96 | 0.03 | 15.54 | 0.46 |
| 22-24 | 22 | 0.96 | 41 | 0.98 | 14.73 | -0.02 | -0.28 | 0.97 | 0.02 | 14.31 | 0.28 |
| TOTAL | | | | | | | -5.76 | | | | 13.43 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{27.66}{13.43} = 2.0 \quad (p>0.10)$$

## APPENDIX 4.2.4

Calculation of summary chi-square of the discontinued group before and after time zero

| INTERVAL MONTHS | DISCONTINUED BEFORE TIME 0 | | DISCONTINUED AFTER TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $P_1$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 39.5 | 1 | 39.5 | 0.83 | 19.75 | 0.17 | 3.35 | 0.91 | 0.08 | 20 | 1.6 |
| 4-6 | 37 | 0.98 | 31.5 | 0.88 | 17.01 | 0.1 | 1.7 | 0.93 | 0.06 | 17.26 | 1.03 |
| 7-9 | 30 | 0.94 | 26.5 | 0.93 | 14.07 | 0.01 | 0.14 | 0.86 | 0.12 | 14.32 | 1.71 |
| 10-12 | 23 | 1 | 23.5 | 0.88 | 11.62 | 0.12 | 1.39 | 0.93 | 0.06 | 11.87 | 0.71 |
| 13-15 | 19.5 | 1 | 18.5 | 0.84 | 9.49 | 0.16 | 1.51 | 0.92 | 0.07 | 9.75 | 0.68 |
| 16-18 | 15.5 | 1 | 14 | 1 | 7.35 | 0 | 0 | 1 | 0 | 7.61 | 0 |
| 19-21 | 13.5 | 1 | 13 | 0.85 | 6.62 | 0.15 | 0.99 | 0.92 | 0.07 | 6.88 | 0.48 |
| 22-24 | 12.5 | 1 | 10 | 1 | 5.55 | 0 | 0 | 1 | 0 | 5.81 | 0 |
| TOTAL | | | | | | | 9.08 | | | | 6.21 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{73.61}{6.21} = 11.85 \quad (p<0.001)$$

## APPENDIX 4.2.5

Calculation of summary chi-square of the continued group before time zero and discontinued group after time zero.

| INTERVAL MONTHS | CONTINUED BEFORE TIME 0 | | DISCONTINUED AFTER TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_2$ | $P_2$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 102.5 | 0.83 | 39.5 | 0.82 | 28.51 | 0.01 | 0.28 | 0.82 | 0.14 | 28.79 | 4.03 |
| 4-6 | 81.5 | 0.93 | 31.5 | 0.88 | 22.71 | 0.05 | 1.13 | 0.91 | 0.08 | 22.92 | 1.83 |
| 7-9 | 63 | 0.89 | 26.5 | 0.93 | 18.65 | -0.04 | -0.74 | 0.90 | 0.09 | 18.86 | 1.69 |
| 10-12 | 44.5 | 0.98 | 23.5 | 0.88 | 15.37 | 0.10 | 1.53 | 0.94 | 0.05 | 15.60 | 0.78 |
| 13-15 | 37.5 | 0.92 | 18.5 | 0.84 | 12.38 | 0.08 | 0.99 | 0.89 | 0.09 | 12.61 | 1.13 |
| 16-18 | 28.5 | 0.97 | 14 | 1 | 9.38 | -0.03 | -0.28 | 0.97 | 0.02 | 9.61 | 0.19 |
| 19-21 | 23.5 | 0.96 | 13 | 0.85 | 8.36 | 0.11 | 0.92 | 0.92 | 0.07 | 8.6 | 0.60 |
| 22-24 | 22 | 0.96 | 10 | 1 | 6.87 | -0.04 | -0.27 | 0.97 | 0.02 | 7.09 | 0.14 |
| TOTAL | | | | | | | 3.56 | | | | 10.39 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{9.36}{10.39} = 0.9 \quad (NS)$$

## APPENDIX 4.2.6

Calculation of summary chi-square of the discontinued group before before time zero and continued group after time zero.

| INTERVAL MONTHS | DISCONTINUED BEFORE TIME 0 | | CONTINUED AFTER TIME 0 | | (A) $\frac{N_1 X N_2}{N_1+N_2}$ | (B) $P_1-P_2$ | (C) (A)X(B) | (D) $P^*=\frac{N_1P_1+N_2P_2}{N_1+N_2}$ | (E) $P^*(1-P^*)$ | (F) $\frac{N_1 X N_2}{N_1+N_2-1}$ | (G) (E)X(F) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_1$ | $P_1$ | $N_2$ | $P_2$ | | | | | | | |
| 0-3 | 39.5 | 1 | 100.5 | 0.82 | 28.35 | 0.18 | 5.1 | 0.87 | 0.11 | 28.55 | 3.14 |
| 4-6 | 37 | 0.98 | 74.5 | 0.98 | 24.72 | 0 | 0 | 0.98 | 0.01 | 24.94 | 0.24 |
| 7-9 | 30 | 0.94 | 68 | 0.98 | 20.81 | -0.04 | -0.83 | 0.96 | 0.03 | 21.03 | 0.63 |
| 10-12 | 23 | 1 | 62 | 0.99 | 16.77 | 0.01 | 0.16 | 0.99 | 0.009 | 16.97 | 0.15 |
| 13-15 | 19.5 | 1 | 57 | 0.99 | 14.52 | 0.01 | 0.14 | 0.99 | 0.009 | 14.72 | 0.13 |
| 16-18 | 15.5 | 1 | 51.5 | 0.93 | 11.91 | 0.07 | 0.83 | 0.94 | 0.05 | 12.09 | 0.60 |
| 19-21 | 13.5 | 1 | 44 | 0.96 | 10.33 | 0.04 | 0.41 | 0.96 | 0.03 | 10.51 | 0.31 |
| 22-24 | 12.5 | 1 | 41 | 0.98 | 9.57 | 0.02 | 0.19 | 0.98 | 0.01 | 9.76 | 0.09 |
| TOTAL | | | | | | | 6 | | | | 5.29 |

$$x^2 = \frac{(|C|) - 0.5)^2}{(G)} = \frac{30.25}{5.29} = 5.71 \quad (p<0.025)$$

# APPENDIX 5.1

## META-ANALYSIS CALCULATIONS

*Calculation of Effect Sizes in Controlled Studies*

Odds ratio are estimated by dividing the observed minus expected (O-E) number of failures in each group and by the variance.

| | failure | success | total |
|---|---|---|---|
| treated | a | b | a+b |
| control | c | d | c+d |
| total | a+c | b+d | N |

The expected number of failures in the treated group ( E ) is given by:

$$E = \frac{(a+c) \times (a+b)}{N}$$

where (a+c) = number of patients failing (or not improving) in the treated and control group.

(a+b) = number of patients in the treated group.

N = total number of patients in the trial.

Then, (E) is contrasted with the observed number of failures in the treated group (O). If treatment was wholly without effect, the quantity (O-E) would differ only randomly from zero with variance (V) and standard error ($\sqrt{V}$) given by:

$$V = \frac{(a+c) \times (b+d) \times (c+d) \times (a+b)}{N^2 \times (N-1)}$$

For 'i' individual studies, the sum $\Sigma(O-E)_i$ would differ randomly from zero (with variance equal to the sum of individual variances , $\Sigma (V_i)$ if treatment were without effect. $\Sigma(O-E)_i$ will be negative if treatment is effective.

The odds of failure of patients treated with lithium relative to the odds of failure of patients receiving another treatment is given by exponential ((O-E)/V) with 95 % confidence intervals ± exp. (1.96 /$\sqrt{V}$) (Yusuf *et al*, 1985). An odds ratio equal to 1.0 means no treatment effect, below the unity favours the treatment and greater than the unity favours the comparing treatment. An odds ratio of 0.9, e.g. suggested a reduction of 10% in the odds of failure with lithium. Each (O-E)/V and the $\Sigma((O_i-E_i)/\sqrt{\Sigma V_i})$ is assumed to be normally distributed.

The calculation of the chi-square of heterogeneity is given by the difference between the total chi-square and the chi-square of association with N-1 degrees of freedom where N is the number of studies, or:

$$\Sigma((O_i-E_i)^2/V_i) - (\Sigma (O_i - E_i))^2/\Sigma V_i \text{ in 'i' studies}$$

*Calculation of Effect Sizes in Uncontrolled Studies*

The procedure to calculate the effect sizes of uncontrolled studies involve the combination of individual Z scores for each study from the one-tailed significance equivalent to that declared in the study. These Z scoreswere combined to derive an overall probability of effect $(\Sigma Z_i)/\sqrt{N}$,where *Z* is the score in standard deviation units corresponding to the level of significance (one tailed) given in any study and N is the number of studies. Effect size in these studies is calculated by transforming published statistics into a common measure such as Pearson's r. From this an estimate of effect size can be made by a transformation of r into Fisher Z (Zr). The mean for N studies, $Z'r = (\Sigma Zr)/N$, is transformed back to r to summarize the overall effect size. The studies were also compared to ensure that the pattern of results appears homogeneous. This was performed for both Z values $(\Sigma(Z - Z')^2)$ and effect size $(\Sigma(N_j-3)\ (Zr_j - Z'r)^2)$, both are distributed as chi-square with N-1 degrees of freedom, where N is the number of studies.

*Calculation of Fail Safe N*

The Z values, previously calculated, can also be used to estimate a so-called "fail safe N", or the number of unpublished statistically non-significant studies that would invalidate the overall trend of the published findings (Cooper, 1979). It was calculated using the formula :

$$n = \frac{k[k(Z')^2 - 2.706]}{2.706}$$

where n = number of studies required to reverse conclusion

k = number of studies

Z' = mean of z

*Calculation of Statistical Power*

Power was calculated according to the formula described by Cohen (1977) for the estimation of effect size and power in contingency tables: $W=\sqrt{\{\sum(\text{Proportion of the observed number of events in each cell - the proportion of the expected number of events in that cell})^2 / \text{the proportion of the expected number of events in that cell}\}}$. W varies from zero (when the paired proportions in all cells are equal and hence there is no effect and the null hypothesis is true) to one (when the difference in proportions is maximum). The result was referred to Cohen (1977) with level of significance equals to 0.05 and one degree of freedom. When the number of the sample was below 25 subjects tables by Detsky *et al* (1985) were used.

## APPENDIX 5.2

*WHAT ARE THE DIFFERENCES BETWEEN A META-ANALYSIS AND A TRADITIONAL REVIEW?*

Traditional reviews use the narrative or qualitative method. The reviewer critically analyzes the selected studies, summarizes their results and assesses the effectiveness of the treatment. The narrative review may be biased in at least five ways: a) selective inclusion of studies, where some studies may be excluded on "methodological" grounds, especially if they views which are opposite to those of the reviewer; b) studies may also be excluded because the theoretical constructs are considered irrelevant; c) crude and misleading interpretation of study findings, frequently only reporting their statistical significance; d) failure to examine possible relationships between the characteristics of the studies and the study results; and e) no or very little report about the methods of reviewing (Glass *et al*, 1981; Wolff, 1986). Inherent to this approach is the process of inference, which is complicated when findings do not agree. Typically, there are private rules for selecting and integrating studies, and no systematic approach for resolving contradictory findings is followed. Studies conflicting with the reviewer's point of view are discarded on the basis of the characteristics of the sample or the research design (Kavale and Glass, 1981). These methods of eliminating conflicting results are usually subjective and *ad hoc*. Another negative aspect of the traditional review is that there is no way of estimating the sampling variance across the studies (Abrami *et al*, 1988). In conclusion, the standards of objectivity, verifiability and replicability are often ignored (Kavale and Glass, 1981).

A second method is the combination of the raw data of the original studies - a secondary data analysis. In this case, the reviewer goes back to the original raw data and combines them to determine the overall effect. The advantage of this method is that it permits research questions to be pursued that have not been previously addressed with a particular data source. There are some problems with this method, however, firstly, raw data are often not available; secondly, the methods used are often not identical; thirdly, it does not account for unbalanced designs which could result in the Simpson's paradox (Simpson, 1951; Glass *et al*, 1981).

The third method of summing studies is the quantitative methods. Ways of integrating findings in a quantitative way have been proposed since the 1930's. Fisher (1932) and Pearson (1938) sought to combine probability values from tests of significance, but it was in the agricultural field that the first quantitative analyses were performed (by Yates and Cochran, 1938). By 1950, social science researchers were trying to establish the combination of probabilities as a useful tool (Mosteller and Bush, 1954). Several quantitative methods for summarizing literature have been developed: combining significance tests (Mosteller and Bush, 1954; Rosenthal, 1978), vote counting (Light and Smith, 1971), cluster analysis (Light and Smith, 1971) and meta-analysis (Glass *et al*, 1981).

Combining significance tests is based on the probabilities associated with the test statistics from each of the original studies. The problem with this method is that sample size and the magnitude of the effect are not taken into account and the results are therefore non interpretable (Hedges and Olkin, 1985).

Vote counting is a very crude way of combining results by counting in terms of statistical significance those studies which favour the control group, those favouring the experimental group and those with non significant outcomes. The category containing the largest number of studies is assumed to represent the direction of the true relationship. This method has a number of shortcomings: firstly, it does not take into account the strength of the relationship nor the magnitude of the effect, i.e. all studies are given the same importance although one may be just significant and the other highly significant; secondly, it ignores sample sizes and since large samples produce more statistically significant results it is biased against studies with small samples, which usually show absence of significance due to inadequate sample size; thirdly, there are no criteria for differentiating studies with good and poor research design (Hedges and Olkin, 1980; Streiner, 1991). If all studies had the same sample size and a unimodal distribution reflecting one population, the reliability of this method would be greater. As these conditions are seldom met, vote counting is not accepted as an accurate method of reviewing. Paradoxically, the power of this procedure decreases as the number of studies reviewed increases (Hedges and Olkin, 1980).

In cluster analysis, studies are clustered based on the question under consideration. The original data used in the analysis must be obtained and if no differences are identified among the clusters, or if there are they can be statistically adjusted, they can be further combined and analysed. The drawbacks in this approach are the difficulty in obtaining the original data and the focus on variation between treatments, rather than on the variation of effect sizes across studies (Pillemer and Light, 1980).

Meta-analysis is the latest development of the quantification approach in integrating studies. In medical reviews, the term overview has also been used (Peto, 1987-a). There are three main objectives that any meta-analysis wishes to satisfy: a) to eliminate bias in study selection; b) to make use of all information; c) to detect statistical interaction (Kavale and Glass, 1981). During the 1970's, meta-analysis flourished in social and educational sciences. In medicine, the earliest meta-analysis was an article by Beecher (1955) on placebo, but it was in the early 1980's that meta-analysis became a popular instrument to review medical literature (Sacks *et al*, 1987). Comprehensive textbooks have been published on the techniques and methodology of meta-analysis (Glass *et al*, 1981; Rosenthal, 1984; Hedges and Olkin, 1985; Wolf, 1986).

Glass (1976) coined the term meta-analysis to refer to statistical analysis of a large collection of analysis results from individual studies with the purpose of integrating their findings. The meta-analysis approach consists of: a) defining the problem and the admissible studies; b) locating the studies; c) classifying and coding the studies' characteristics; d) quantitatively measuring the characteristics of the studies in a common scale; and e) aggregating the study findings and relating those findings to the study characteristics. It is a systematic, reproducible approach to the integration of studies. The main goal of meta-analysis is to establish facts and relationships despite any biases that may be present because of the methodology used in a study (Kavale and Glass, 1981).

There are still some doubt about its usefulness. Some researchers consider meta-analysis to be merely a statistical trick that produces oversimplified generalizations out a complex of disparate results (Thompson and Pocock, 1991). However, meta-analysis is not a fad. It has its roots in central values of the scientific method: replicability, quantification, casual and correlational analysis (Bangert-Drowns, 1986), and because of that it can deliver generalizable answers to basic questions by integrating valuable information that is scattered in individual studies. In addition, there are very little fancy statistics at all in meta-analysis, but as with any scientific method meta-analysis has advantages and disadvantages. The determination of the external validity of a meta-analysis, i.e. how generalizable are its findings, is not that simple. As Smith *et al* (1980) suggested this decision is a responsibility shared by the researcher and the reader. The reader must bear in mind the conditions in which the study took place and compare them with the real situation.

What format for presenting review findings should be preferred is an open and complicated question. In principle, there is no difference between a traditional review and meta-analysis as long as they are conducted without bias. There are situations when a narrative method may be preferable to a meta-analysis, e.g. when effects sizes are diverse and small or the number of methodologically adequate trials is small. If a meta-analysis is performed in these conditions, its conclusions should be considered only as preliminary. Traditional reviews have another advantage: they usually discuss in more depth each study being reviewed, looking for patterns and inconsistencies (Slavin, 1984). In other situations, e.g. when there is a large number of studies, a meta-analysis may be the only possible approach (Cooper, 1979).

Descriptive reviewers are more likely than statistical reviewers to find little or no support for the alternative hypothesis, such as in the study by Cooper and Rosenthal (1980) on sex differences in task performance, where traditional reviewers neglected probabilities or were too conservative in combining them. Statistical procedures can help to identify relationships that may not be large enough to be detected through the traditional method (Light and Pillemer, 1984). If a decision is made in favour of using meta-analysis as a review method, the next decision should concerns which techniques are to be used. The answer to this question will depend on the topic being studied and on the data available from the original studies. The techniques used have been discussed above.

*WHAT ARE THE MAIN ADVANTAGES OF META-ANALYSIS?*

The principal advantages of meta-analysis are: firstly, meta-analysis makes reviews more interpretable due to its procedures being precisely described, objective and repeatable. Vague terms like 'no relationship', 'strong relationship' and 'very significant' are replaced by numerical values. Further, because meta-analytic procedures record the exact p level there is no need to claim a 0.05 result as a significant result and a 0.06 as a non significant one (Rosenthal, 1990).

Secondly, it obtains an estimate of the magnitude of the experimental effects which is scale free, allowing the combination of results using different scales of measurement. In addition, it has the ability to control the contradictions in a group of studies (Pillemer and Light, 1980).

Thirdly, meta-analysis can be used in the design of multi-centre trials because the raw data may not be comparable for the purposes of compiling data at the individual subject level.(Pillemer and Light 1980; Hedges and Olkin, 1985; Abrami *et al*, 1988).

Fourthly, it increases power of the data synthesis due to the integration of findings of small studies in a coherent way. In clinical psychiatry, the sample size or time required to undertake a large randomized trial may be prohibitive, and consequently, clinical decisions must be made based on findings of small trials. If most effects are small to medium and sample sizes are moderate, a predominance of studies with non significant results will be likely (Hedges and Olkin, 1985). Meta-analytic techniques are used to combine the results of similar trials in an effort to integrate their findings. In doing so it increases the power due to an increase in sample size. Even studies with minor flaws can be analyzed and the influence of the flaws can be determined and adjusted for, if necessary (Jackson, 1980; Kraemer and Andrews, 1982).

The importance of meta-analysis was illustrated by Glass (1976) when he pointed out that the results of dozens or even hundreds of studies can no more be grasped in narrative reviews than one can grasp the results of dozens or hundreds of test scores without the aid of techniques for organizing and interpreting the data. Finally, meta-analysis provides ways of integrating studies that can avoid the classic "more research is needed" statement so often found in narrative reviews, meta-analysis provides ways of integrating studies that may make this statement not compulsory (Pillemer and Light, 1980).

*WHAT ARE THE MAIN DISADVANTAGES OF META-ANALYSIS?*

The introduction of meta-analysis is by no means widely spread and accepted. There is strong opposition by some authors, such as Eysenck (1978) who called meta-analysis "mega-silliness". The main objections to meta-analysis are:

*1. Mixing apples and oranges* - Grouping together different types of variables (e.g., outcomes), such as Glass (1976) did when all kinds of psychotherapies were analysed together, is one object of criticism. Combining the results of different studies runs the risk of producing an amalgam that makes no conceptual sense (Gallo, 1978). Glass's argument is that if we combine data from people who are different, why not combine studies that are somewhat different? Furthermore, Glass (1977) and Glass *et al* (1981) observe that such aggregation is useful for the study of the "fruit" and the only studies that need to be compared are different studies. As only one outcome was studied in this meta-analysis, this problem was averted.

*2. Garbage-in garbage-out* - Some meta-analyses collect trials with huge differences in research quality designs and include trials with poor research design which invalidates the conclusions of the meta-analysis (Eysenck, 1978). The critics of meta-analysis do have a point when they say that no meta-analysis is better than the studies that went into it (Slavin, 1984). The defenders of meta-analysis argue that *a priori* decision to exclude studies based on research quality is not acceptable due to possible bias in terms of the reviewer's subjectivity in evaluating research design (Glass *et al*, 1981). To avoid the controversy of mixing good and bad quality trials, this meta-analysis

analyzed controlled and uncontrolled studies separately. This approach had the objective of testing whether differences in quality are related to differences in outcome. Nevertheless, the analyses of the controlled and uncontrolled studies yielded similar results, showing in both cases a positive effect of lithium. Similar results have also been reported by Glass *et al* (1981) who reviewed 12 meta-analyses and found a difference not bigger than 0.1 standard deviation in effect size between high and low internal validity studies, and concluded that no relationship could be postulated between effect size and research validity.

*3. Non-independence* - According to Landman and Dawes (1982) there are five possible sources contributing to results being dependent: a) multiple responses from the same subjects; b) measures taken at various points in time from the same subjects; c) dependence of scores with a single outcome measure (e.g., both a subtest and a global score containing the subtest are treated as outcome measures); d) dependence on studies within a single article (e.g., two different studies using at least some of the same subjects are reported in the article); e) dependent samples across the studies (e.g., two different studies using at least some of the same subjects are reported in different articles). Several methods have been suggested to eliminate these sources of dependency. One is to use only one dependent variable from each study (Cooper, 1979). Another procedure is to use an average effect size from each study (Kulik *et al*, 1979). At the moment, there is no consensus as to how this problem should be handled (Wachter, 1988) mainly because the conceptual and statistical implications of this problem have not yet been worked out (Rosenthal, 1984). The first three problems are particularly common in psychological trials where the same subjects are observed on a series of outcome measures, or repeatedly on the same outcome. But they are non-

existent in this review. The fifth source of dependency was eliminated through the exclusion criteria. Non-independence may also occur, however, when different subjects from different cells of a between group factorial design provides the study outcomes, as is the cause in the fourth source of dependency. In fact, this has ocurred in some of the trials, e.g. in Prien *et al* (1984), where lithium was compared to placebo, antidepressants and the combination of lithium plus antidepressants. An alternative frequent solution to the problem has been to treat each finding as independent (Smith *et al*, 1980; Abrami *et al*, 1988). In this meta-analysis, this latter position was adopted.

*4. Inflated Ns* - The calculation of effect size for every dependent variable inflates the number of effect sizes. This problem did not exist in this meta-analysis due to the fact that only one outcome being studied.

*5. Objectiveness* - A weakness associated with meta-analysis design is that there is no control, except through the selection of papers, over which treatments have been applied or how subjects are assigned to them (Louis *et al*, 1985). The objectiveness of meta-analysis is questioned by Searles (1985) who found opposite conclusions in two meta-analyses of agoraphobia. Searles concluded that the results of meta-analysis are highly dependent upon "how the pie is sliced, and who is doing the slicing". It must be remembered that meta-analysis is not a "cookbook" procedure and the assumptions underlying the meta-analysis must be made explicit, otherwise misleading results may occur (Cook and Leviton, 1980; Kavale and Glass, 1981). To avoid any bias in interpretation of a meta-analysis it has been urged (McConaghy, 1990) that all meta-analysis should include the list of the studies included, and the means and standard deviations of the treated and control

group before and following treatment. To comply with these guidelines, all information concerning the numbers improving and not improving in the lithium and comparison groups was given (see Tables).

*6. Statistical technique vs. human thought and planning* - Strube and Hartmann (1982) have pointed out the danger of the results of the review being limited to the description of statistical techniques. Nevertheless, there should be no contradiction between the meta-analysis and interpretation of the data. As Cooper and Rosenthal (1980) stated, the interpretation of the results of a review using the meta-analysis method is *aided*, not determined, by meta-analytic findings.

*7. Sample bias* - Contrary to the characteristics of good quality research, the sample of studies on which the meta-analysis is based is not *random*, and is consequently biased (Strube and Hartmann, 1982). This bias becomes apparent when it is observed that most meta-analyses is based on published studies (see the file drawer problem, Section 5.4.8). Glass (1977) argues that research design should not be confounded with research integration. Each of the two has a logic of its own, and therefore some concepts appropriate to primary research are not adequate for reviews.

*8. Repeated bias* - if several studies are done by one group of investigators or on one group of participants, this could lead to repeated bias. To avoid this problem, this meta-analysis included only the latest version of any study which used the same group of subjects in more than one publication.

Many of these criticisms extend to traditional reviews. Studies of poor quality may be included, a sampling bias may be observed, and the mixing of studies with different types of patients, where the outcome is measured by different techniques, are all examples of limitations inherent to any review. The only difference is in dealing with these problems. In traditional reviews there is no clear justification, while in meta-analysis reasons must be explicitly stated as to why such a direction was taken as this is a more structure kind of review.

Another criticism of meta-analysis relates to its use in non medical experiemental designs where its use may be trivial. It does not carry the same force for clinical trials where the principles of design are now universally acepted, outcome may deadd or alive and numbers are the main limiting factoirs in small studies.

# APPENDIX 6.1

Effect sizes were calculated using Cohen's d formula (Rosenthal, 1984):

(i) $$d = (M_1 - M_2)/ s \text{ pooled}$$

where $M_1$ and $M_2$ are the means of the two groups to be compared and $\sigma$ pooled is the pooled population standard deviation.

(ii) $$s \text{ pooled} = \sqrt{\{[(n_1-1)s_1^2 + (n_2-1)s_2^2]/[n_1 + n_2]\}}$$

where $n_1$ and $n_2$ are the number of subjects in the two groups and $s_1^2$ and $s_2^2$ are the variances of their failure measures.

Cohen's d is a slightly biased estimate of effect size (Wolf, 1986). Hedges and Olkin (1985) developed a weighted unbiased estimator of mean effect size ($d_w$) which was used:

(iii) $$d_w = \Sigma wd/\Sigma w$$

where w is the reciprocal of the estimated variance of d in each of the studies in the meta-analysis.

(iv) $$w = 2(n_1 + n_2)/ (8 + d^2)$$

The homogneity of effect sizes can be tested to determine whether studies are sufficiently heterogenous to require an analysis of possible moderating variables.

(v) $$X^2 = \Sigma [w (d-d_w)^2]$$

where $d_w$ and w are defined as in (iii) and (iv).

The 95% confidence interval was calculated according to Hedges and Olkin (1985):

$$\text{Effect size } (d_w) \pm 1.96 \sqrt{(1/w)}$$

The number of additional studies necessary to reverse the conclusions of the meta-analysis was calculated according to the formula:

(vi) $$N_{fs} = N(d_{av} - d_c)/d_c$$

where $N_{fs}$ is the fail safe N, $d_{av}$ is the average effect size and $d_c$ is the criterion selected to be assumed by $d_{av}$ when some knowable number of hypothetical studies were added to the meta-analysis. The chosen value of $d_c$ was 0.2, which represents the smallest effect size as proposed by Cohen (1977).

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