# A MULTIDISCIPLINARY LITHIUM CLINIC: THE PHARMACIST'S RÔLE

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Lithium is the treatment of choice in acute mania, and in the prophylaxis of recurrent affective disorder. Lithium has a narrow therapeutic range with potentially serious toxic effects, therefore should be closely monitored to ensure its safe and effective use. The concept of the lithium clinic is well established as a specialist centre which can provide optimum and cost-effective care for lithium patients.

The inclusion of a pharmacist in the lithium team has several potential advantages, including the efficient use of the therapeutic drug monitoring service, an awareness of potential drug and disease interactions, and the provision of patient counselling.

A multidisciplinary lithium clinic was set up in North Staffordshire in February 1990, and this study took place over a period of three years from that date. Patients' knowledge and understanding of their lithium therapy was assessed by interview on entry to the clinic, and a repeat assessment took place at least six months later. Monitoring of serum lithium levels, renal and thyroid function was evaluated, and patient satisfaction was also measured.

The lithium clinic monitored lithium levels more frequently than the out-patient clinic. Renal and thyroid function were regularly monitored by the lithium clinic, with all results being readily accessible. The knowledge and understanding of patients was significantly improved after counselling by the pharmacist, and patients and consultants expressed their satisfaction with the clinic.

In conclusion, the lithium clinic was shown to provide an effective lithium monitoring service which was superior to the out-patient clinic. The addition of a pharmacist to the lithium team provided the added benefits of improved monitoring of drug and disease interactions, better use of the therapeutic drug monitoring service, and most importantly, the promotion of improved patient knowledge and understanding of their lithium therapy by counselling.

**Key words**: patient counselling, drug level monitoring, mania, depression

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# 1. INTRODUCTION

## 1.1.1. CHEMISTRY

Lithium is a simple metallic element which is widespread in nature. It is found in minerals, and in small amounts in plant and animal tissues. In the Periodic Table it is a Group IA alkali metal, with an atomic number of 3. Lithium is characterised by high melting and boiling points, a small ionic radius, and a high ionic charge density. It also displays a similarity to magnesium, a Group IIA metal [1].

The discovery of lithium was made in 1817 by a Swedish chemist, August Arfwedson, while working for Berzelius. He found the new element in a stone, and it was therefore named from the Greek word for stone, *lithos*.

The main world production source of lithium is North Carolina, USA, and the three major bulk lithium chemicals are: lithium sulphate, $Li_2SO_4$; lithium carbonate, $Li_2CO_3$; and lithium hydroxide, LiOH. Less than 1% is used in medicine, the vast majority being used in the production of lubrication greases, synthetic rubber, alloys, batteries and pyroceramics, and many other industrial applications [2]. The British Pharmacopœia 1993 states that lithium carbonate contains not less than 98.5% and not more than 100.5% of $Li_2CO_3$. It is described as a white powder which is slightly soluble in water and practically insoluble in ethanol [3].

## 1.1.2 HISTORICAL USES

Soranus of Ephesus, in the second century AD, advocated the use of alkaline waters in the treatment of mania. It has been suggested that he specifically recommended the waters of Ephesus. Although these waters do contain lithium salts, the quantities are very small, and it is unlikely that he unwittingly used lithium to treat mania.

During the latter half of the nineteenth century, lithium was widely used in the treatment of 'gouty diseases' which included gout, rheumatism and epilepsy. Lithium was thought to be the most effective of the alkaline salts in neutralising the excess uric acid which was believed to be the cause of these diseases. Around 1880, Carl Lange, a Danish neurologist, discovered a new gouty disease which he called "periodic depression", which was also treated prophylactically with the alkaline salts, including lithium. However, no particular significance was attributed to the lithium component, and the theory of 'gouty diathesis' was dismissed early in the 20th century [4].

In the 1940s in the United States of America, solutions of lithium chloride were marketed as salt substitutes for patients with renal and cardiac disease, and several deaths occurred from lithium toxicity [5]. As a result, the United States Food and Drug Administration, established in the early part of the 20th century, was wary of releasing any lithium preparation for general use for about 20 years.

### 1.2.1 PSYCHIATRIC USES

Lithium was introduced into psychiatry in 1949 by the Australian psychiatrist Dr. John Cade who, having observed that lithium had a calming effect on guinea pigs, suggested that it could be used for the treatment of psychotic patients. He administered lithium to ten manic patients who all showed improvement [6]. The dosage that he used was 600mg of lithium carbonate three times a day, which would be considered large at the present time, and one of his first lithium patients died of lithium intoxication within two years of starting lithium treatment.

The progress of lithium therapy was initially slow, for several reasons: lithium was not new, could not be patented, and it was also very cheap. The pharmaceutical industry was much more interested in the advent of chlorpromazine, in 1950, and other neuroleptics.

The main advocates of lithium therapy were John Cade himself, G.P. Hartigan and others in Great Britain, Mogens Schou and P.C. Baastrup in Denmark, and Ronald R. Fieve in the USA, and it is unlikely that lithium would have attained its present status in psychiatry without their perseverence.

### 1.2.2 USE IN ACUTE MANIA

Since its introduction, lithium has become established as the treatment of choice in acute mania, supported by the findings of several controlled trials. In a trial where thirty eight manic patients were treated, fourteen were classified as experiencing a positive effect under lithium treatment, eighteen had a possible effect and the remaining six showed a negative effect [5].

Lithium was shown to be significantly superior to placebo in a trial in which eighteen manic patients were randomly assigned to receive two week periods of treatment with either lithium or placebo [7].

In a summary of findings over a ten year period, it was shown that lithium was effective in controlling acute manic states in 44 to 80 percent of patients [8]. Good results were obtained in 44% of 25 chlorpromazine-resistant manic patients, 78% of 33 manic and hypomanic patients in an open study, and 80% of 35 manic and hypomanic patients in a double-blind study. Equivocal results were obtained in 36% of the chlorpromazine-resistant manic patients, 6% of the patients in the open study and 6% in the double-blind study, and the failure rates were 20%, 16% and 14% respectively.

In a comparison of lithium carbonate and chlorpromazine in 23 patients, it was found that lithium was superior to chlorpromazine in acute mania, but the difference was not statistically significant [9].

A double blind crossover trial demonstrated a significant advantage of lithium over placebo in decreasing the severity of mania during acute attacks [10]. Four consecutive treatment periods of 7-10 days were used in 38 patients, and 75% of patients improved during the lithium treatment periods compared to 41% who improved during the placebo treatment.

### 1.2.3 USE IN ACUTE DEPRESSION

The use of lithium in the acute treatment of depression has been somewhat more controversial. Initially this may have been because mania and depression were viewed as opposite states, and it may have been difficult to visualise the use of a single treatment for both conditions. In addition, whereas the treatment of acute mania was often difficult before the introduction of lithium, several antidepressants have been available for the effective treatment of acute depression for many years [11] .

A study carried out in 1971 failed to show any significant benefit from treating acute depression in 18 patients, but the effects of lithium treatment were only observed for 10 days [10]. Despite this shortcoming, the results of this study were widely accepted at the time.

However, other studies carried out since have shown that lithium does have an acute antidepressant effect. A study of 52 mixed group patients, taking lithium or placebo on an alternating basis, showed 15 complete and 21 partial remissions [12]. In another study, thirteen of 21 patients with primary affective disorder showed unequivocal improvement with lithium treatment, and seven of these relapsed with placebo substitution [13]. In both of these trials the effect was most marked in bipolar patients.

### 1.2.4 PROPHYLACTIC USE

The main use of lithium is in the prophylaxis of recurrent affective disorder. Its effectiveness in preventing future episodes in both bipolar and unipolar depressive illnesses, and in reducing the frequency, severity and duration of such episodes when they do occur, is well documented [14,15].

The prophylactic effect of lithium on sixty nine patients with recurrent affective disorders was studied [16]. Admissions to hospital for episodes of mania and/or depression, and the length of stay in hospital, decreased during lithium treatment, and only two patients had higher admission rates and longer time in hospital than the period before lithium treatment.

In a discontinuation trial, patients who had been receiving lithium for up to seven years were randomly allocated to receive lithium or placebo for a period of five months [17]. Twenty one of thirty nine patients relapsed on placebo whereas none of the lithium patients relapsed.

A double-blind placebo-controlled trial of lithium was carried out in sixty five patients [18]. It was shown that patients receiving lithium had significantly less affective illness than patients on placebo, and lithium seemed to be equally effective in both bipolar and unipolar disorders.

Another placebo-controlled trial was carried out, where the incidence of manic and depressive relapses was significantly lower in patients on lithium than those on placebo [19].

A study comparing lithium carbonate and imipramine, found that both lithium and imipramine were effective in preventing unipolar relapses, but that lithium was

significantly more effective than imipramine or placebo in preventing relapses in bipolar patients [20].

A Medical Research Council trial comparing lithium, amitriptyline and placebo in the prophylaxis of unipolar depressive illness showed that lithium was as effective as amitriptyline, and that both drugs were significantly better than placebo [21].

### 1.2.5 OTHER PSYCHIATRIC USES

Lithium has been used in other psychiatric conditions, including schizophrenia and schizo-affective disorders, alcoholism, pathological impulsive aggressiveness, drug addiction, pathological hypersexuality and premenstrual tension [22,23]. However, the use of lithium in these conditions has not been fully established and must therefore be considered experimental.

### 1.2.6 NON-PSYCHIATRIC USES

Lithium has several suggested uses outside psychiatry, for example in the management of hyperthyroidism, leucopenia, Ménière's disease, tardive dyskinesia, Huntington's chorea and Gilles de la Tourette's syndrome [24,25]. It has also been used for its antiperiodic actions in disorders including epilepsy, migraine, and cluster headache, but the evidence for its use in these conditions is contradictory and anecdotal, and requires further investigation.

Interest has been expressed in the antiviral effect of oral or topical lithium, and a topical preparation of lithium succinate (Efalith®) is now licensed in the UK for the treatment of seborrhoeic dermatitis [26].

## 1.3 MODE OF ACTION

The precise mechanism of action of lithium has not been fully elucidated. However, several theories have been postulated.

### 1. Reduction of inhibitory effect of vanadate

Lithium is the smallest alkali ion, and shares many properties with other members in group I of the periodic table as well as with some group II metals. It competes with sodium, potassium, magnesium and calcium cations in biological tissue [27]. Cations are distributed across membranes in excitable and non-excitable tissues. There have been reports that erythrocyte $Na^+/K^+$ ATPase activity (involved in cation transport across membranes) is abnormal in affective disorders, and that lithium increases the activity of this enzyme. It has been suggested that lithium may work by reducing the inhibitory effect of vanadate on erythrocyte $Na^+/K^+$ ATPase [28]. A low vanadium diet, or ascorbic acid which is a treatment of vanadium poisoning, is effective in the treatment of mania and depression. Methylene blue acts as an electron carrier, reducing vanadate to vanadyl ions which are less inhibitory of $Na^+/K^+$ ATPase, therefore methylene blue may be an effective alternative treatment in manic depressive psychosis.

### 2. Reduction of catecholamine activity

Lithium seems to decrease catecholamine activity by three mechanisms [29]. It enhances the uptake of noradrenaline and 5-hydroxytryptamine (5HT) into synaptosomes, reducing the action of these neurotransmitters at the synapse. The release of noradrenaline from synaptic vessels is thought to be reduced by lithium due to its interference with calcium. Lithium is also believed to inhibit the formation of cyclic adenosine monophosphate (cAMP) by adenylate cyclase, suggesting that the postsynaptic action of noradrenaline is also reduced.

3. **Inhibition of prostaglandin $E_1$ synthesis**

It has been found that lithium selectively inhibits the synthesis of prostaglandin (PG) $E_1$ at concentrations that are used in psychiatry, and that this is likely to be clinically relevant [30]. At much higher anti-inflammatory concentrations, lithium reduces the levels of free fatty acids, and of both 1 and 2 series of prostaglandins. In humans, $PGE_1$ infusions are associated with mild euphoria. Platelets from patients with mania produce more $PGE_1$ than normal, whereas platelets from depressed patients produce less. Alcohol will selectively increase the production of $PGE_1$. $PGE_1$ may therefore be important in regulating mood, and may produce euphoria during mania and alcoholic intoxication. The effects of lithium in treating mania and reducing the behavioural effects of alcohol could be mediated through its action on $PGE_1$ concentration.

At high lithium concentrations, the release of all fatty acids is reduced, and there is also strong inhibition of formation of all prostaglandins. This is similar to the effect of glucocorticoids, and may account for the anti-inflammatory actions of topical lithium.

4. **Inhibition of phosphoinositide turnover**

Another possible mode of action is the inhibition of phosphoinositide turnover by lithium. The phosphoinositide system is important in mediating the response to cholinergic agonists. Stimulation of this system results in the formation of two secondary messengers: inositol triphosphate ($IP_3$) and diacylglycerol (DG). $IP_3$ regulates the mobilisation of intracellularly bound calcium, and DG modulates the activity of adenylate cyclase and controls calcium channels. Lithium administration has been reported to cause a large decrease in inositol and an increase in inositol monophosphate. Since neurons need inositol to regenerate the phosphoinositides, neuronal activity may be compromised due to the lowered levels of $IP_3$ and DG [31].

Other theories involve the alteration of the rate of transport of small precursor molecules, such as choline and glycine, into cells.

### 1.4.1 PHARMACOKINETICS

Lithium is absorbed readily from the gastrointestinal tract when administered in liquid form. It is absorbed mainly in the jejunum and ileum, with absorption decreasing as it continues through the intestines. It distributes unevenly around the body within eight hours. Lithium concentration in erythrocytes, spinal fluid and liver is less than half the serum concentration, whereas concentrations in the bone, brain and thyroid gland are 50% more than the serum lithium concentration. It follows a two compartment model, has first order kinetics and its volume of distribution is slightly more than total body water [32].

Lithium is not bound to plasma and tissue proteins, and is not metabolised. It is mainly excreted unchanged by the kidneys, with very small amounts excreted in sweat, saliva and faeces, and the rate of excretion is slowest at night. The elimination half-life varies between 14 and 33 hours, and increases as renal function deteriorates. Eighty percent of the filtered load of lithium is reabsorbed with sodium and water in the proximal convoluted tubules of the kidney, with the remaining 20% being excreted in the urine [33]. Thus lithium clearance is approximately one-fifth of the glomerular filtration rate. No reabsorption nor secretion occurs in the distal tubules, except possibly some reabsorption may occur with extremely low sodium intake.

### 1.4.2 FORMULATION

Lithium is usually given orally as the carbonate salt, in tablet form. Formulations may be standard or slow release, although release characteristics can vary widely

between different brands of lithium. In general, standard release preparations result in a high peak serum concentration which is reached quickly, whereas slow release preparations result in a blunted peak serum concentration which is reached more slowly, and sustained for longer. Slow release preparations are thought to reduce the transient side-effects associated with the high peak lithium levels from standard release products. The British Pharmacopœia 1993 lists a standard for Lithium Carbonate Tablets, which should contain 95.0 to 105.0% of $Li_2CO_3$ [3].

Studies have shown that Priadel® and Camcolit 400®, both slow release tablets, possess similar absorption rates under controlled conditions [34]. However, diurnal variation in lithium clearance, the effect of food on the rate of absorption, and other factors, may affect the pharmacokinetic profiles of the various lithium tablets. Unless there is published evidence to show that products are interchangeable, as is the case with Priadel® (400mg) and Priadel 200®, then it is recommended that a change from one preparation to another should be accompanied by monitoring of lithium levels and clinical assessment [35].

### 1.4.3 THERAPEUTIC RANGE

Lithium has a narrow therapeutic range with potentially serious toxic effects. The twelve hour standard serum lithium (12h-stSLi) has become established as a measurement of serum lithium concentration which is reproducible in the same patient and comparable between different patients [36]. As well as overcoming the problem of diurnal variation in lithium clearance, it was also chosen because of convenience : the 12h-stSLi comprises of a blood sample being drawn approximately 12 hours after the evening dose of lithium, (i.e. during the morning) with the concentration expressed as millimoles of lithium ion $Li^+$ per litre of serum.

However, there are inherent difficulties in the 12h-stSLi measurement. The value can be affected by whether the lithium preparation used has standard or slow release properties, and also by the dose regimen (once, twice or three times a day). The lithium half-life also varies between patients, and it has been suggested that those with short half-lives should be kept on a comparatively low 12h-stSLi.

In the effective therapeutic monitoring of lithium, it is essential that the correct sampling procedures are observed in order to obtain meaningful results. If the time elapsing between the evening dose of lithium and the sampling of blood is less than eight hours, the distribution phase will not be complete and erroneously high levels will be obtained. When estimating serum lithium after initiating therapy or altering the dose, a period equivalent to five half-lives, or approximately one week, must have elapsed to ensure that steady state level has been reached, or results will be lower than anticipated.

There is close correlation between serum lithium concentration and clinical response. At levels below the therapeutic range lithium may not be effective, and at levels above the range there is an increased frequency of dose-related side-effects and a greater risk of lithium toxicity.

The therapeutic range for acute anti-manic treatment is 0.8 to 1.4 mmol/l. The optimum range for the prophylaxis of recurrent affective disorder is widely quoted as being between 0.6 and 1.2 mmol/l [37]. This arose from a slight reduction of the anti-manic range rather than from any direct supporting evidence. However, there is recent evidence that lower levels in the region of 0.5 to 0.8 mmol/l are equally effective and are associated with a lower incidence of adverse effects, particularly in the elderly [38]. Furthermore, one study could not determine a minimum level of lithium below which prophylaxis of depression was ineffective [39].

Sensitivity to lithium varies greatly between different patients, and it is necessary to adjust the dose individually; consequently the same therapeutic range may not be appropriate in all patients. Elderly patients may require levels of only 0.3 to 0.5 mmol/l, whereas young patients may need levels in excess of 1 mmol/l.

The use of levels of lithium in saliva and tears has been investigated as a less invasive method of monitoring lithium. However, at present these methods are not thought to give results which are consistent enough to replace serum lithium levels [40].

### 1.5.1 ADVERSE EFFECTS

The side-effect profile of lithium is extensive since the lithium ion has an effect on most of the physiological systems of the body. They include gastrointestinal, central nervous, mental, endocrine, haematological, teratogenic, neuromuscular, cardiovascular, genitourinary and dermatological adverse effects. These side-effects can be divided into those occurring:

I within the first few days of lithium therapy

II between 5 days and 6 weeks after initiating therapy

III on maintenance therapy.

They occur within the normal therapeutic range, and as such are distinct from the toxic effects of lithium, which occur at much higher serum levels, and will be discussed later.

Within the first 5 days after commencing lithium therapy the patient may experience symptoms such as nausea, loose stools, fine tremor, thirst, abdominal pain, increased frequency of micturition and increased urine volume. It was found that tremor and nausea coincided with the steepness of the rise in serum lithium, but that abdominal pain and loose stools were not related to the dose of lithium, serum level, or

steepness of the rise [41]. Persistent diarrhoea may be helped by changing from a slow release to a standard release preparation, since if lithium is released lower down in the large intestine, it can act as an osmotic cathartic [42]. Conversely, other gastrointestinal effects such as nausea may be reduced by using a slow release tablet.

Side-effects which may occur later on include polyuria and polydipsia, hand tremor, lethargy and muscle weakness. Polyuria and polydipsia were reported to occur in 60% of patients in one study, although in other studies the incidence was reported to be as low as 4% [43,44]. In the vast majority of patients, polyuria and polydipsia are thought to occur as a result of nephrogenic diabetes insipidus, in which the renal distal tubular cells exhibit reduced sensitivity to antidiuretic hormone, that is, an inability to concentrate urine.

Polyuria, polydipsia and hand tremor may persist during long term maintenance therapy. Hand tremor may disappear if the lithium level is reduced slightly, or it may be necessary to prescribe a β-adrenergic blocking agent such as propranolol, either regularly, or on a when required basis if the tremor is exacerbated by situations of anxiety [45].

Other adverse effects which may become apparent during maintenance therapy include hypothyroidism and goitre, weight gain, oedema, leucocytosis, and memory impairment [46].

In a survey of 237 patients on long-term lithium treatment, 20% reported weight gains exceeding 10kg during the treatment period [47]. Reasons for this may be that patients quench their increased thirst with calorie-rich drinks, or that they are eating more because they are no longer depressed, or that lithium itself may have a direct effect by decreasing glucose tolerance, or a combination of some or all of these.

Lithium has several effects on the endocrine system including hyperparathyroidism, hypothyroidism and goitre [48-50]. Thyroid function should be regularly monitored, and hypothyroidism can be corrected by the co-administration of thyroxine, or by stopping lithium if this is a viable alternative.

In the 1970s, the observation that lithium caused morphological changes in the kidney gave rise to several extensive studies. It was found that lithium lowered the renal concentrating ability by reducing the response of the distal tubules to antidiuretic hormone [51]. However it was also shown that prolonged lithium treatment did not lead to progressive reduction of the glomerular filtration rate [52]. The main danger to the kidneys during lithium treatment occurs when toxicity develops rather than chronic use at therapeutic levels of lithium.

Lithium may cause ECG changes: the following abnormalities have been reported [53]. Abnormalities of conduction through the sinoatrial node have been noted, such as sinus node arrhythmias and block, and there have been cases of first degree atrioventricular block. The most common effect is flattening of the T wave, although this change is not accompanied by any clinical changes. It is important to note that many of the patients in which these changes were described had other medical conditions, or were taking other medications more likely to cause cardiac problems, most notably the tricyclic antidepressants. In general, lithium does not cause severe cardiac problems [54].

### 1.5.2 TOXICITY

Lithium intoxication can occur after suicide attempts, inadvertent overdosage by patients, or starting lithium at higher doses than necessary, but more commonly it is as a result of long term treatment where a decrease in renal lithium clearance has occurred. Renal lithium clearance is dependent on sodium and water balance. During

sodium depletion, the proximal tubule reabsorbs more sodium to compensate for the negative sodium balance. However, lithium is also reabsorbed leading to an increase in serum lithium concentration which may be of sufficient magnitude to precipitate lithium toxicity [55]. Any condition causing dehydration may result in sodium depletion, such as feverish illness, diarrhoea, increased sweating in hot weather, vomiting, or perioperative fluid deprivation [56]. Certain drugs, including diuretics, may also precipitate lithium toxicity by causing sodium depletion.

Chronic lithium toxicity presents as nausea, vomiting, diarrhoea and tremor. Acute overdose is characterised by neurological features of tremor, rigidity, nystagmus and convulsions [57]. The patient becomes stuporous and coma may ensue. Acute renal failure may occur, and permanent neurological damage and even death have been reported [58]. There have been case reports of lithium toxicity presenting as mania, with important consequences as the tendency would be to increase the dose of lithium to control the mania [59].

The management of lithium toxicity is essentially supportive. Gastric lavage should be carried out within six hours of acute overdosage to remove any lithium remaining in the stomach. The serum lithium level should be measured to determine the extent of toxicity. Forced or saline diuresis may be used in mild to moderate toxicity (1.5 - 2 mmol/l), where 1 to 2 litres of isotonic saline are infused over 6 hours. This method is most useful in patients with volume depletion, because the glomerular filtration rate will increase, and thus the lithium clearance will also be increased. Peritoneal dialysis, which involves instilling dialysate into the peritoneal cavity, may be used, but is not very efficient, clearing lithium at a rate of 15ml/min. Haemodialysis is the treatment of choice for severe intoxication (3 - 4 mmol/l and above). This is an effective method of removing lithium, with a lithium clearance of 50ml/min. Repeated dialyses may be necessary as lithium redistributes from the tissues into the bloodstream [60,61].

## 1.6 DRUG INTERACTIONS

There are several clinically important interactions involving lithium. These are of two main types:

I those which interfere with sodium and water balance (pharmacokinetic interactions), and

II those which may enhance the neurotoxic effects of lithium (pharmacodynamic interactions).

The most important interaction is between lithium and thiazide diuretics [62,63]. They produce sodium depletion by inhibiting the reabsorption of sodium in the distal tubules. The compensatory increase in proximal tubule reabsorption and the associated increase in lithium reabsorption results in increased serum lithium levels.

Frusemide and other loop diuretics do not appear to affect lithium to such an extent. It was found that there were no significant changes in serum lithium levels during a 2 week period of concomitant administration of lithium and frusemide in patients previously stabilised on lithium [64]. This was probably because frusemide inhibits lithium reabsorption in the loop of Henle thus compensating for the increase in proximal tubule reabsorption.

Amiloride and other potassium-sparing diuretics do not appear to affect lithium excretion because their effect on sodium excretion is not large enough to stimulate proximal sodium (and thus lithium) reabsorption [65]. Amiloride is the initial treatment of choice for lithium-induced polyuria, because it blunts the inhibitory effect of lithium on water transport in the collecting tubule of the kidney. Thus it reduces the urinary output without significantly reducing lithium clearance. In contrast, spironolactone, an aldosterone antagonist, increases sodium excretion and reduces potassium secretion, and has been associated with increased serum lithium levels [66].

The second group of drugs which interact with lithium are the non-steroidal anti-inflammatory drugs (NSAIDs). They include indomethacin, mefenamic acid, diclofenac, piroxicam and ibuprofen [67-71]. It is thought that they decrease renal lithium excretion by inhibiting renal prostaglandins , thus increasing serum lithium levels. Sulindac has been reported not to interact with lithium, and it may have some renal-sparing properties [72]. It has been shown that aspirin does not interfere with renal lithium clearance [73].

Angiotensin converting enzyme (ACE) inhibitors such as enalapril can also cause an increase in serum lithium concentration, due to increased sodium excretion associated with decreased aldosterone secretion [74].

Drugs which can reduce the serum lithium level by increasing renal lithium clearance include theophylline and acetazolamide, and it may be necessary to increase the dose of lithium during concurrent administration of these drugs.

Sodium salts increase lithium excretion by reducing sodium and lithium reabsorption. Some antacids have a high sodium content, and low sodium alternatives are preferable in lithium therapy. Care should also be taken when giving fluid loads of sodium chloride, for example with the antineoplastic agent cisplatin [75]. Oral rehydration therapy in diarrhoea is used to correct electrolyte imbalance, and is not usually problematic. In severe diarrhoea, lithium should be stopped to reduce the risk of high serum lithium concentrations.

Lithium and neuroleptic drugs are commonly used together to control the acute phase of mania in agitated patients. However, concurrent therapy with lithium and neuroleptics has very rarely given rise to neurotoxic reactions and increased extrapyramidal side-effects at therapeutic levels of lithium. Drugs which can exacerbate neurotoxicity are haloperidol, and thioridazine and other phenothiazines [76].

These reactions occur mainly at high doses, and their occurrence could be minimised by using lower doses. However if a neurotoxic reaction does occur, both lithium and the neuroleptic should be discontinued to avoid permanent neurological damage.

Other drugs which have been reported to produce neurotoxic reactions in combination with lithium include metoclopramide, methyldopa, phenytoin, carbamazepine, diltiazem and verapamil [77].

Alcohol has a minimal effect on lithium kinetics, although excessive consumption could lead to increased serum lithium concentration attributable to the diuretic effect of alcohol [78]. Lithium has been used to antagonise the acute effects of alcohol such as intoxication and decreased mental acuity, in addition to its mood-stabilising effects.

## 1.7 PREGNANCY AND LACTATION

It has been reported that lithium has a teratogenic effect during the first months of pregnancy. The cardiovascular system is most affected, in particular malformations of the tricuspid valve (Ebstein's anomaly). Most studies place the risk of malformation at around 3%. In 1970 a "Register of Lithium Babies" was assembled to monitor all pregnancies exposed to lithium during at least the first trimester, and between then and 1980, 25 of 225 cases were found to be congenitally malformed. However, of those who were not malformed, follow-up at around 5 years of age did not show a statistically significant difference in developmental abnormalities between lithium-exposed and non-exposed children [79].

A study of 148 women taking lithium during the first trimester of pregnancy found that the rate of congenital malformations did not differ significantly between the lithium-exposed group (2.8%) and control group (2.4%) [80]. The authors concluded that lithium is not an important human teratogen, but this has been disputed because

of the small sample size involved [81].

Lithium clearance doubles in pregnancy, and it may be necessary to increase the dose of lithium. Care should be taken at delivery as the sudden fall to normal clearance may precipitate toxicity in the mother.

A 'floppy baby' syndrome has been described with toxic and non-toxic maternal lithium levels. The baby exhibits hypotonia, lethargy and cyanosis. Other symptoms may be bradycardia or tachycardia, shallow respiration, heart murmur, hypotension, hypothermia and neurological depression. Normally these signs disappear without sequelae within about 10 days [82].

Lithium freely enters breast milk, with serum concentrations in the neonate approaching therapeutic values. It is therefore important to ensure that the baby is not deficient in water or sodium, as toxicity may occur [83].

### 1.8.1 PATIENT COUNSELLING

Studies have shown that patient counselling is necessarily an important part of lithium therapy [84]. The patient should be made conversant with all aspects of his or her therapy, including the main drugs to be avoided and the dangers of dehydration. To this end, written information has been produced to supplement careful patient counselling. The Royal Pharmaceutical Society of Great Britain produced a lithium card in 1989 (see Appendix Ⅲ), based on the work of a pharmacist at Hollymoor hospital [85], and the manufacturers of Priadel® and Camcolit® have designed information booklets. Dr. Mogens Schou, a world authority on lithium, has written a concise yet comprehensive book specifically for patients and their relatives, which is available in several languages [86].

A recent study evaluated a patient education programme at a lithium clinic [87]. It was shown that the programme, consisting of a videotape, a written handout and a follow-up home visit, produced a substantial and sustained improvement in the knowledge of patients about their lithium treatment. It was noted that the follow-up visit was likely to have stimulated patients to revise their knowledge and understanding from their information leaflets.

**In summary, the important points to consider for the safe and effective use of lithium are:**

I Correct sampling times must be observed in order to obtain meaningful results

II The dose of lithium should be titrated according to serum concentration but with due regard to individual variation

III The clinician should be aware of the effects of concurrent drug administration and disease states on serum lithium levels, and adjust doses where necessary

IV The patient should be counselled on all aspects of his or her therapy in order to gain maximum benefit.

### 1.8.2 THE LITHIUM CLINIC

The concept of the lithium clinic is well established, it has evolved from psychiatric out-patient clinics [88,89]. This specialist centre enables staff to become familiar with the drug and its potential problems, providing a high level of expertise which can only be of benefit to the patient. The personnel required consists of medical and nursing staff, with a laboratory technician in the better equipped clinics to measure serum lithium levels on site. There is scope for the involvement of other health care professionals including social workers, clinical psychologists, occupational therapists, dietitians, and pharmacists.

A detailed study was undertaken at the Foundation for Depression-Manic Depression in New York, USA, to evaluate the cost effectiveness of a lithium clinic [90]. It was found that the patients studied had fewer affective episodes and hospitalisations in three years on lithium therapy than in the three years before starting lithium therapy. Of a total of 113 patients, 81 had fewer affective episodes on lithium, 21 had the same number before and after lithium, and 11 had more episodes on lithium. The overall cost of treating the patients for affective episodes (hospitalisations and out-patient visits) before lithium therapy was $522,000 compared with $145,200 on lithium therapy. Visits while the patients were euthymic on lithium therapy cost a further $188,800, which left a total cost saving over the three years on lithium of $188,000 or 36%. In addition to the costs of hospitalisation, there are also costs to society due to loss of productivity, when patients are unable to work due to illness.

A comparison of the supervision of lithium treatment in patients treated in a lithium clinic, as hospital out-patients and by general practitioners, found that the lithium clinic carried out more frequent checking of lithium levels, had fewer elevated levels and lower maintenance levels [91].

The authors of a similar study expressed concern that one third of the general practitioners investigated had not responded to raised lithium levels within six weeks of the report [92]. They called for guidelines to reduce the differences in standards of monitoring between different practitioners.

## 1.9 THE ROLE OF THE PHARMACIST

At the beginning of this study there had been no published reports of pharmacist involvement in lithium clinics. The results of the initial questionnaire, used to assess patients' understanding of lithium therapy at entry to the lithium clinic, were presented as a communication at the Pharmacy Practice Research session at the British Pharmaceutical Conference in Liverpool [93]. Since then, a similar study has been reported [94]. Another pharmacy-managed lithium clinic has been reported, although no data have been published so far [95].

The pharmacist has specialist knowledge of pharmacokinetics and therapeutic drug monitoring, is conversant with potential drug interactions, and is in an ideal position to counsel patients on their lithium therapy.

The purpose of this study was to investigate the extent to which a pharmacist could contribute to the care of patients in a lithium clinic, particularly in relation to the specialist skills of a pharmacist.

# 2. METHOD

## 2.1 BACKGROUND

Lithium clinics have been in existence since the 1960s. Psychiatrists in North Staffordshire had wanted to start a lithium clinic for many years, but needed someone to provide the initiative. As a result of an application to study for an MPhil research project by a pharmacist, it was decided to set up a lithium clinic, to be run jointly by a pharmacist and a psychiatrist. After conducting a literature search to establish current practices in lithium therapy, several discussions took place between pharmacists, psychiatrists and nurses.

This project consists of setting up and running a multidisciplinary lithium clinic, as detailed in the clinic protocol, and evaluating its effect on patient care. In February 1990, the first lithium clinic was piloted. The results discussed in this thesis were collected over a period of three years from this date, up to February 1993.

## 2.2 AIMS AND OBJECTIVES

The aims and objectives of this study are:

I To study the course of existing lithium therapy by reviewing patients' hospital medical records at a district general hospital in North Staffordshire

II To ascertain the extent of patients' understanding of their lithium therapy by interview

III To provide structured patient counselling supplemented by relevant written information

Ⅳ To monitor concurrent drug therapy and be aware of potential drug interactions

Ⅴ To make efficient use of the therapeutic drug monitoring service

Ⅵ To evaluate any improvement in the service provided by a lithium clinic over the existing management of lithium therapy in a psychiatric out-patient clinic.

## 2.3 LITHIUM CLINIC PROTOCOL

The lithium clinic is held every Tuesday morning from 9.00 a.m. to 12.30 p.m., in the ECT suite in the Psychiatric Unit, City General Hospital, Stoke-on-Trent. The suite consists of a waiting room with toilet, a clinic room for taking blood samples and general discussion, and a separate room where patients can be interviewed or counselled. The clinic staff consists of a pharmacist, a staff nurse and a clinical assistant in psychiatry. Patients are seen by all three clinic staff together in an informal setting, although there are facilities for private discussion if necessary.

### REFERRAL

Patients are referred directly to the clinic by the psychiatrist responsible for their care. Referral forms (Appendix I) are completed for all patients attending the lithium clinic. Appointments will be sent out to patients as soon as possible, with priority given to urgent cases. The same forms may be used for patients whose details are to be kept on the computer database, but who will not be attending the clinic.

### BLOOD SAMPLES

Blood samples are taken routinely at each visit for the determination of serum lithium

levels, unless there are reasons where this would not be appropriate e.g. when a patient has taken a morning dose of lithium.

Urea and electrolytes, creatinine and free $T_4$ are measured at entry into the clinic, then every 6 or 12 months at the consultant's discretion. Where renal impairment or hypothyroidism have occurred, or where the results are borderline, these tests may be performed at each visit. Patients return to the clinic every 8 or 12 weeks (depending on the consultant) unless any particular problems have arisen.

Samples are taken as follows:

| | |
|---|---|
| Lithium | 10ml plain white tube |
| Thyroid function tests | 10ml plain white tube |
| U&E, creatinine | 5ml orange (Li heparin) tube |

Any other blood tests e.g. full blood count, can be performed as necessary by the clinic doctor.

At the end of each clinic blood samples are transported to Ward 90 in the Psychiatric Unit from where they are taken to the Central Pathology Laboratory for analysis. Results are returned to Ward 90 and collected the following Tuesday. Any high lithium levels (above 1.5 mmol/l) are immediately brought to the attention of the clinic doctor by telephone. The clinic doctor checks and signs all results before they are filed in the patients' records.

## THERAPEUTIC RANGE

The therapeutic range used by the clinic is usually 0.5 to 0.8 mmol/l, although the range may vary according to the consultant's preference and the patient's response. In general, levels above 1.0 mmol/l are investigated further.

## LITHIUM DOSE OR PREPARATION ADJUSTMENT

In some cases it may be necessary to change the dose or preparation of lithium. As lithium follows first order pharmacokinetics, increasing or decreasing the dose of lithium leads to a proportional change in the serum level, e.g. if a dose of 400mg gives a level of 0.3 mmol/l, then increasing the dose to 800mg would give a level of 0.6 mmol/l. When the dose is altered, a period of one week should elapse before the serum level is measured, so that steady state has been reached.

The dose of lithium is only changed after discussion with the patient's consultant. The consultant and general practitioner are kept informed of any change in dose or preparation.

In general, the use of controlled release preparations of lithium (e.g. Priadel®, Camcolit 400®) leads to fewer side-effects than standard release preparations (e.g. Camcolit 250®). However, it has been reported that sustained release products are more likely to cause diarrhoea than conventional preparations, since the release of lithium low down in the large intestine can act as an osmotic cathartic. Where side-effects are problematic, a reduction in dose or change of preparation may be beneficial.

## OTHER MEDICATION

All patients are questioned about other drugs they may be taking (prescribed or over-the-counter) at entry into the clinic and on subsequent visits. Potentially interacting drugs, in particular thiazide diuretics and NSAIDs, are changed whenever possible to preparations less likely to cause problems.

## INITIATION OF LITHIUM TREATMENT

Patients due to start lithium treatment are referred to the clinic in the same way as patients already taking lithium. On their first visit, kidney and thyroid function tests are performed, and where appropriate a test dose is given for prediction of the maintenance dose using a pharmacokinetic method (Appendix Ⅱ). In some instances, where it is necessary to start lithium quickly, an empirical dose is given which is then altered if necessary.

The lithium dose is checked weekly at first, then at increasing intervals until the patient is stabilised, when the patient then visits every eight or twelve weeks in the same way as other patients.

## PATIENT INFORMATION

Each patient is interviewed by the pharmacist, usually on their first visit to the clinic. The interview takes place as an informal discussion of the important points concerning lithium therapy, and acts as a basis for counselling patients on areas where their knowledge may be inadequate. Modified RPSGB lithium information cards (Appendix Ⅲ) are given to every patient. These provide basic information on lithium, but patients are encouraged to ask questions, and to telephone the clinic in between visits if they have any problems. Patients about to visit hot countries are counselled on the importance of maintaining fluid intake, and other points are reinforced where necessary, such as the action to take during feverish illness, and advice about other medication and diet.

## APPOINTMENTS

Initial appointments are sent out by post, and subsequent appointments are arranged

at each visit. If an appointment has been missed, the patient is followed up by letter or telephone. Where two consecutive appointments have been missed, patients are referred back to the consultant for follow-up.

## DISPENSING

It is not practical to dispense all medication from the lithium clinic, therefore dispensing is carried out by the pharmacist under the following circumstances:

I Patients starting lithium treatment, until they are stabilised

II Where the dose or preparation of lithium has been changed

III When non-compliance is suspected

IV Where patients have run out of tablets

Medication other than lithium can be obtained from the hospital pharmacy where necessary (usually one week's supply).

## PATIENT RECORDS

A set of records is kept for each patient attending the clinic. These records include the referral form, a folder for laboratory results, weight chart and continuation sheet. The doctor records a brief summary at each visit, and the nurse or pharmacist may add appropriate comments e.g. telephone calls to the clinic.

## AIMS AND OBJECTIVES OF THE LITHIUM CLINIC

I To maintain serum lithium concentrations within the desired therapeutic range

II To monitor any adverse effects of lithium treatment, including deterioration in renal and thyroid function

Ⅲ To monitor concurrent drug therapy, and be aware of potential drug or disease interactions

Ⅳ To use the therapeutic drug monitoring service effectively and efficiently

Ⅴ To provide structured patient counselling supplemented by relevant written information

Ⅵ To provide a support service for patients and their relatives

Ⅶ To maintain computerised records of all lithium patients in North Staffordshire

## 2.4 PATIENT SELECTION

Approximately one person in 2000 in Britain is prescribed lithium carbonate [94]. In North Staffordshire, which has a catchment population of around 500,000, it is expected that approximately 250 people will be undergoing lithium therapy. A survey of five of the consultant psychiatrists in North Staffordshire revealed that an estimated 90 to 120 of their patients were taking lithium. This was considered to be a feasible number to start running a clinic.

It was decided initially to take on the patients under the care of consultant psychiatrists based at the City General Hospital in Stoke-on-Trent, then to progress to the patients of the psychiatrists at St. Edward's Psychiatric Hospital in Cheddleton, Staffordshire. It is eventually hoped to include all patients undergoing lithium treatment in North Staffordshire.

## 2.5 OUTCOME PARAMETERS

A range of outcome parameters were measured during the study, which were patient knowledge and satisfaction, lithium monitoring, and renal and thyroid function monitoring.

Patients' medical records were retrospectively reviewed following the format in Appendix Ⅳ. The main information required was the previous monitoring of lithium levels, renal and thyroid function tests, to compare with monitoring in the lithium clinic. Patients who were already taking lithium before attending the lithium clinic could therefore act as their own controls.

Patients who were referred to the lithium clinic for initiation of lithium treatment were started on lithium using a pharmacokinetic dose-prediction method (Appendix Ⅱ). The time it took for their lithium levels to stabilise was compared with that in control patients (matched for age and sex), who had been started on lithium before attending the clinic.

### 2.5.1 PATIENT KNOWLEDGE AND SATISFACTION

An initial interview questionnaire (Appendix Ⅴ) was designed, drawing from information on the lithium information card produced by the Royal Pharmaceutical Society of Great Britain (RPSGB). This was used to assess the extent of patients' knowledge of their lithium treatment at entry into the lithium clinic, i.e. on their first visit. The questions were intended to reflect the information most likely to be useful to the patient. Each patient was interviewed by the pharmacist, using the questionnaire, and the interview was also a format for counselling patients on areas where their knowledge may have been inadequate. The interview was standardised, that is the same interviewer, surroundings and wording of questions were used

throughout, to limit bias, and to facilitate collation and analysis of data [97]. Patients started on lithium by the clinic were counselled using the questionnaire as a guide.

Lithium information cards produced by the RPSGB were given to all the patients at their first visit to the clinic. The cards were slightly modified so that they could also be used as appointment cards, ensuring that the patients carry them at all times (Appendix Ⅲ).

A second interview questionnaire (Appendix Ⅵ) was developed in consultation with a clinical psychologist. This was used after patients had been attending the lithium clinic for at least six months. The first part was a repeat of the most important questions from the first questionnaire, so that any change in patient knowledge could be measured. The remainder of the second questionnaire was concerned with the patients' satisfaction with the clinic. This was thought to be an important aspect of the project, although more difficult to quantify. The questions used ranged from general questions about physical surroundings, to more personal questions such as their opinion of the attitude of clinic staff. There are several drawbacks to the use of satisfaction questionnaires, including a tendency to report a high level of satisfaction with the service [98]. However, these drawbacks have been taken into account, and will be discussed later.

### 2.5.2 LITHIUM MONITORING

Lithium levels were measured at each visit to the clinic, every 8 to 12 weeks. Samples were analysed at the Central Pathology Laboratory, North Staffordshire Hospital Centre. The apparatus used was a high specification Pye Unicam SP900 atomic absorption spectrophotometer, using the flame emission spectrometer mode. This works as follows: a sample solution is sprayed into a flame, and the sample then dissociates into free atoms. Some of these free atoms absorb additional energy from

the flame and become excited. They then return to the ground state, emitting light as they do so. The intensity of the light is proportional to the concentration of lithium in the sample [99].

The lithium levels collected were reviewed to identify whether or not they conformed with the standards set out in the lithium clinic protocol, i.e. that lithium levels should be measured every 8 to 12 weeks, and should fall within a range of 0.5 to 0.8 mmol/l.

### 2.5.3 RENAL AND THYROID FUNCTION TESTS

Renal function was monitored by measuring urea, electrolytes and creatinine, and thyroid function was indicated by free $T_4$ (thyroxine). If the $T_4$ was low, TSH (thyroid-stimulating hormone) was also estimated by the laboratory. A raised TSH level indicates lithium-induced hypothyroidism.

The renal and thyroid function tests were also studied for compliance with the lithium clinic protocol, that they should be measured every 6 months.

### 2.5.4 OTHER PARAMETERS

Other information was also collected, including details of individual cases, and the prescribing of potentially interacting drugs.

# 3. RESULTS

The lithium clinic was piloted on 27th February 1990, and the following results were obtained over a period of three years since that date. Each result will be discussed briefly, with a more detailed discussion in the next section.

## 3.1 PATIENT CHARACTERISTICS

One hundred and twenty two patients were on the lithium clinic register by February 1993, that is, a referral form for each of these patients was kept at the clinic. Four patients (3%) never attended the clinic, and a further twenty eight patients (23%) had attended the clinic at some point but were no longer attending by February 1993. The remaining ninety patients (74%) regularly attended the clinic. The twenty eight (23%) patients who had stopped attending the clinic gave the following reasons:

I The time of the clinic was not convenient, e.g. one patient worked night shifts and could not attend a morning clinic

II The location of the clinic was not convenient, e.g. some patients preferred to be monitored by their GPs because of the distances involved in travelling to the clinic

III The patient had moved away from the area

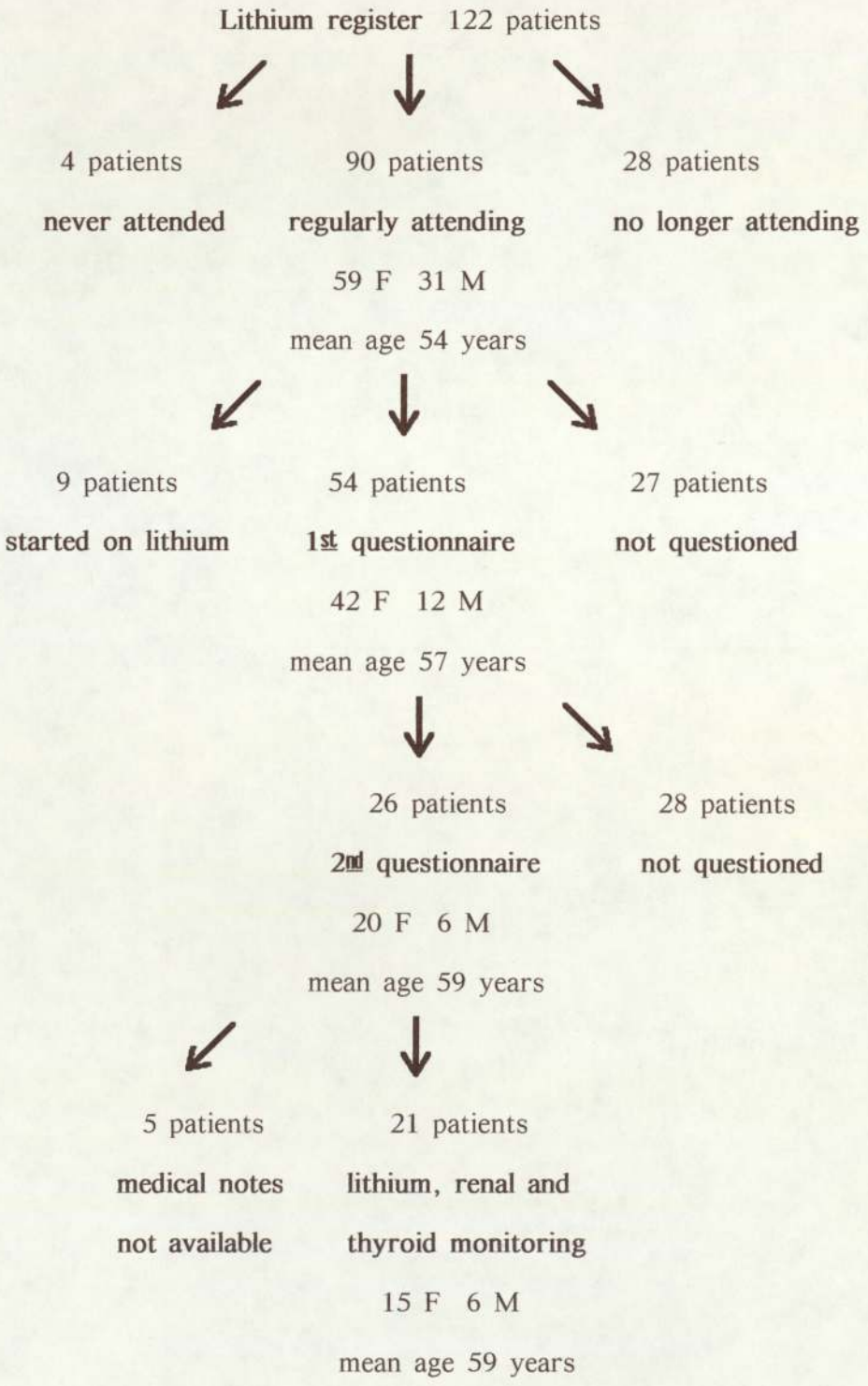
IV The patient was no longer taking lithium

Of the 90 patients attending the clinic, there were 31 males (34%) and 59 females (66%). The mean age was 54 years (range 24 to 93 years). This is consistent with the observation that unipolar depression is about twice as common in women as in men, and bipolar disorder is also more likely to occur in females than in males although the difference is not as great [98]. The age range at onset has been reported to be as wide as 8-74 years, and there is some evidence to suggest one peak of incidence before the age of 30 and another from the mid to late 40s. Bipolar disorder

usually manifests itself earlier than unipolar disorder.

### 3.1.1 PATIENT PROGRESS

The following is a flow chart showing the progress of patients through the various questionnaires and investigations.



## 3.2 INITIAL KNOWLEDGE

Fifty four patients were interviewed on their first visit to the clinic, using the questionnaire in Appendix V. Forty two (78%) were female, and twelve (22%) were male, with a mean age of 57 years. There was a higher proportion of females, with an older mean age than the lithium clinic population as a whole. The results obtained are illustrated in Figures 3.2.1 to 3.2.7.

1. **Time on lithium** (Figure 3.2.1)

The mean length of continuous lithium treatment was 5.5 years (range 5 weeks to 20 years). Twenty one patients (39%) had been taking lithium for between one and three years. Several patients had been taking lithium at some time in the past, then had stopped and restarted. The length of time recorded was the period in which the patients had been taking lithium without interruptions.

The largest number of patients (21) had been taking lithium for between 1 and 3 years, and the number of patients decreased until 13 to 15 years, with a further small increase in patients who had been taking lithium for more than 15 years (5 patients or 9%).

2. **Reason for lithium** (Figure 3.2.2)

Three more patients said that they had been prescribed lithium for manic depression (19 patients or 35%) than for depression (16 patients or 30%). Eleven patients (20%) gave other reasons such as "nervous breakdown" or "lithium deficiency". Eight patients (15%) did not know why they were taking lithium.

The patients who did not know why they were taking lithium did not appear to be particularly interested in the answer. It was sufficient for them that their psychiatrist had prescribed the best treatment for their illness, and that was all they needed or

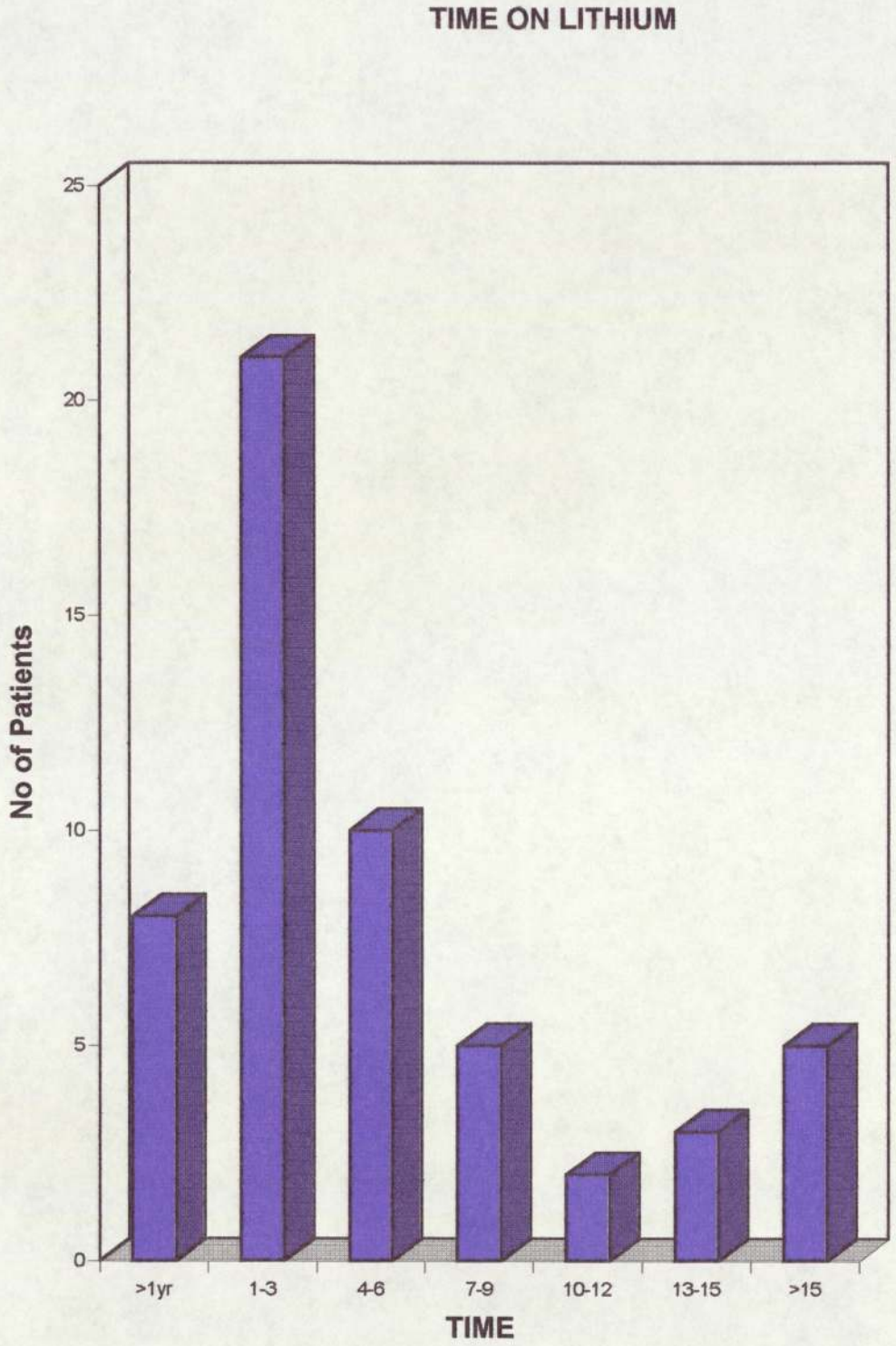



**Figure 3.2.1** A graph showing the length of time in years for which 54 patients had continuously been taking lithium.

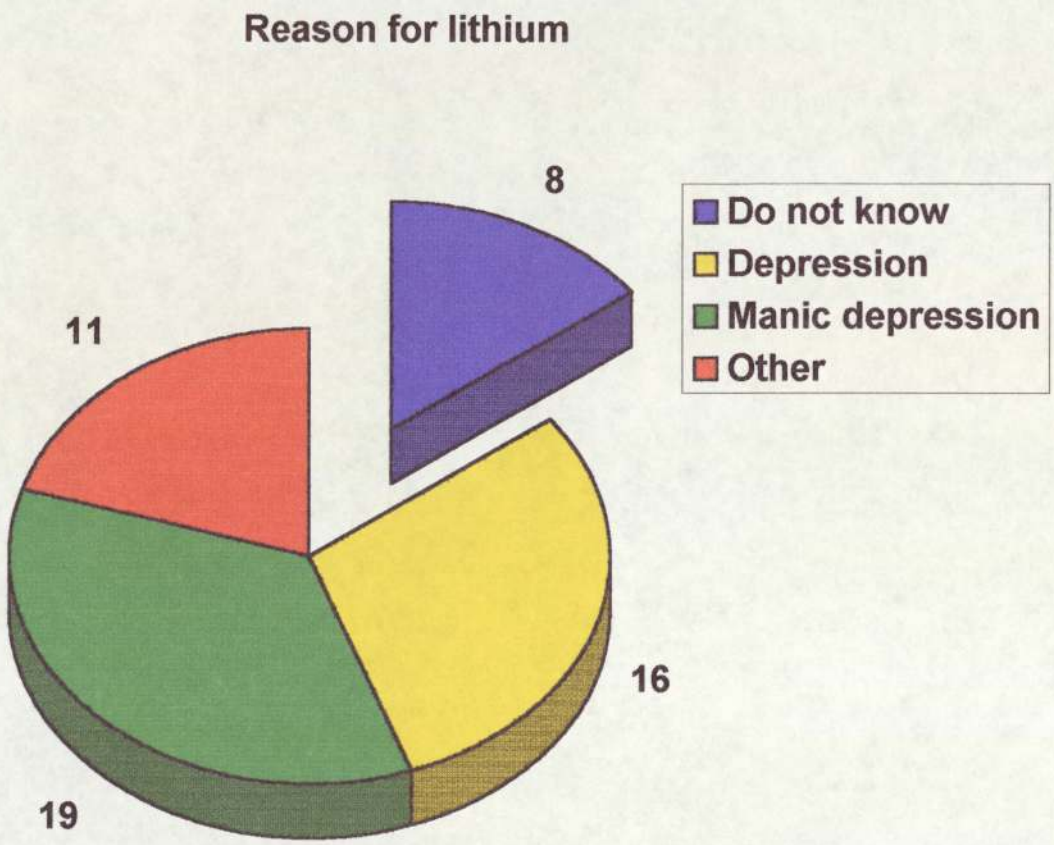



**Figure 3.2.2** A chart showing the different reasons for which 54 patients thought they were taking lithium.

wanted to know.

3. **Preparation of lithium** (Figure 3.2.3)

More patients took Priadel® than Camcolit® brand of lithium tablet, although seven patients (13%) were unable to name the preparation of lithium. There was a preference for Priadel® locally, although the reasoning for this is unclear. The psychiatric wards at the City General Hospital stocked Priadel®, whereas the wards at St. Edward's Psychiatric Hospital kept Camcolit®. Therefore the decision on which preparation to prescribe usually depended on where the patients had been treated. Although other preparations of lithium are available, they were not used locally.

4. **Dose and frequency**

Forty patients (74%) knew the strength in milligrams of the lithium tablets they were taking. Twelve patients (22%) knew how many tablets to take (but not the strength) and had also been able to name the preparation of lithium in Question 3. Only two patients (4%) knew neither the strength nor the preparation of their lithium tablets. This is encouraging as it means that it is possible to find out from most of the patients their dose of lithium. Priadel 200® is the most distinctive tablet as it is oval-shaped, but as the vast majority of patients take the stronger round tablets, this is not an aid to identification. There is a space on the front of the RPSGB lithium information card (Appendix Ⅲ) to record the brand of lithium taken.

5. **Verbal and written information** (Figure 3.2.4)

Less than half the patients (24 patients or 44%) had received any verbal information about lithium. Most of these had received information from a doctor (G.P. or hospital doctor), with one patient having talked to another patient on the ward who was already taking lithium. The amount of verbal information received was very variable; some patients recalled being told only that lithium was a "mood stabiliser", and that it would "keep blood flow level to the brain". Other patients also said that

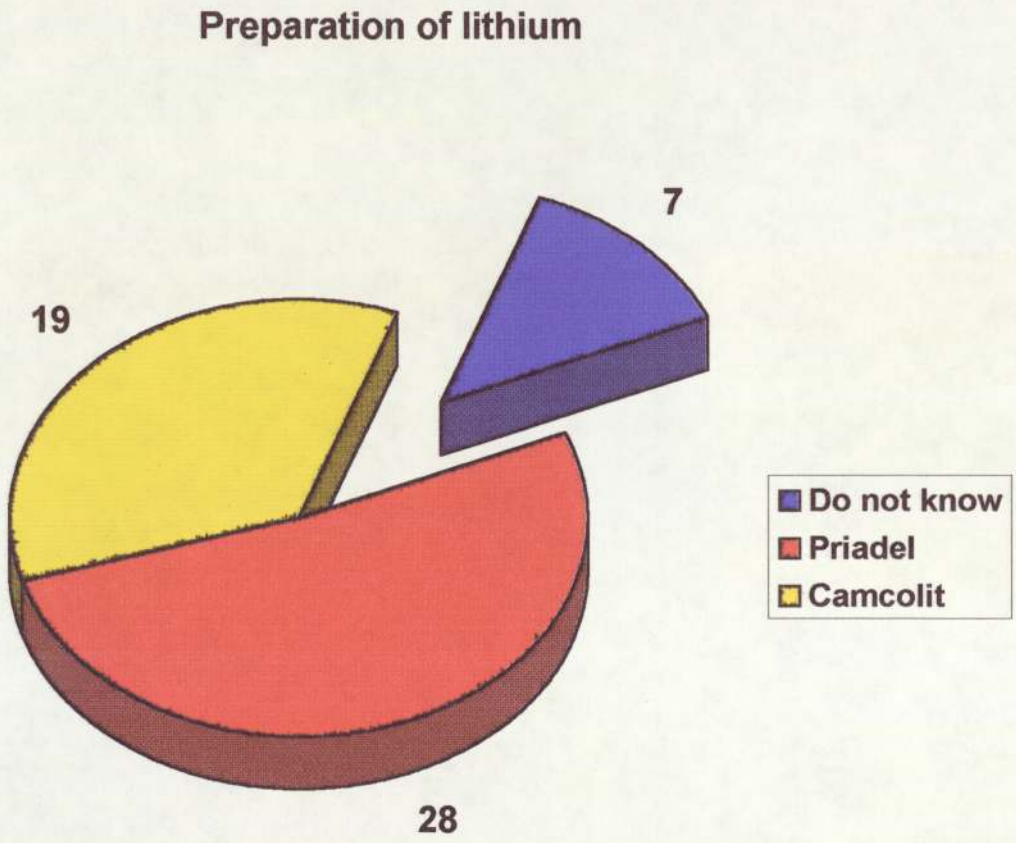



**Figure 3.2.3** A chart showing the different preparations of lithium taken by 54 patients.

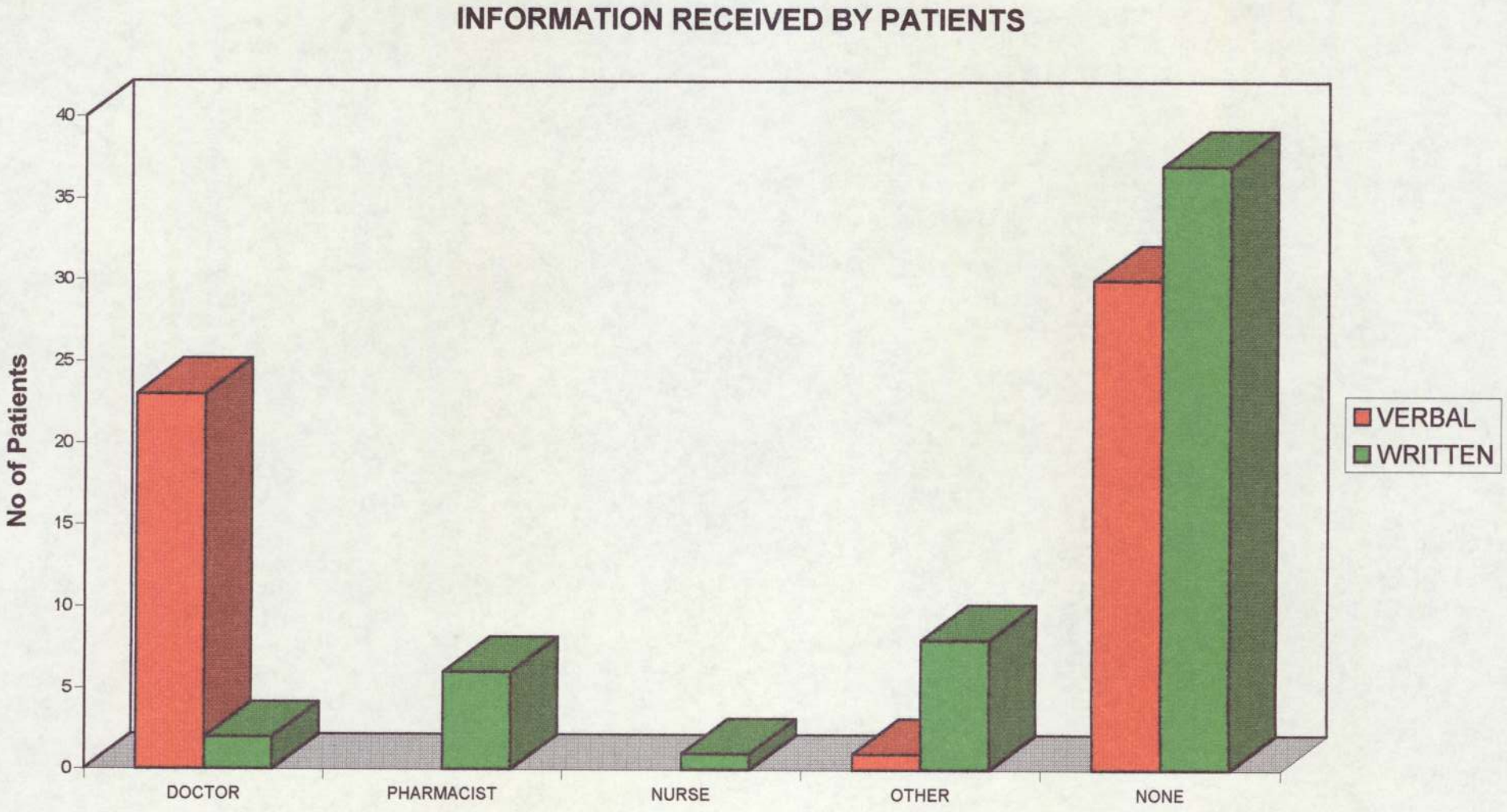



**Figure 3.2.4** A graph showing the number of patients, out of a total of 54, who received verbal and written information from a variety of sources.

they had been told very little. The standard of information given did not seem to be consistent between different doctors, although it would be difficult to evaluate this because of the subjectiveness of the patients. One patient said that she had questioned the doctor to obtain the information she wanted.

Thirty seven patients (69%) had received no written information at all on lithium. Almost as many patients had read books and magazine articles, or had sent away for information, as had received information from the more usual sources (doctors, pharmacists and nurses). The information received from pharmacists was in the form of package inserts, and one patient had received a RPSGB lithium information card from a community pharmacist. The patients who were well informed appeared to be so because of persistence on their part, by questioning the doctor, obtaining information by post or from a library, and by talking to other patients who were taking lithium.

6. **Side effects** (Figure 3.2.5)

Patients were questioned about any side-effects that they had actually experienced, rather than ones which they had heard about, as it was felt that this would give a more representative view. The range of side-effects experienced by these patients was wide, the most common complaints being thirst, tremor and weight gain, followed by diarrhoea, nausea and increased frequency of urination. One patient (who has since stopped taking lithium) complained of four side-effects, but fourteen patients (26%) said that they had not experienced any adverse effects attributable to lithium therapy. In most cases, the side-effects were not particularly problematic to the patient, and were accepted as minor drawbacks of an otherwise beneficial treatment.

7. **Taking lithium tablets**

Fourteen patients (26%) said that lithium tablets should be swallowed whole, forty (74%) said that they should be taken with water, and twenty (37%) that they should be

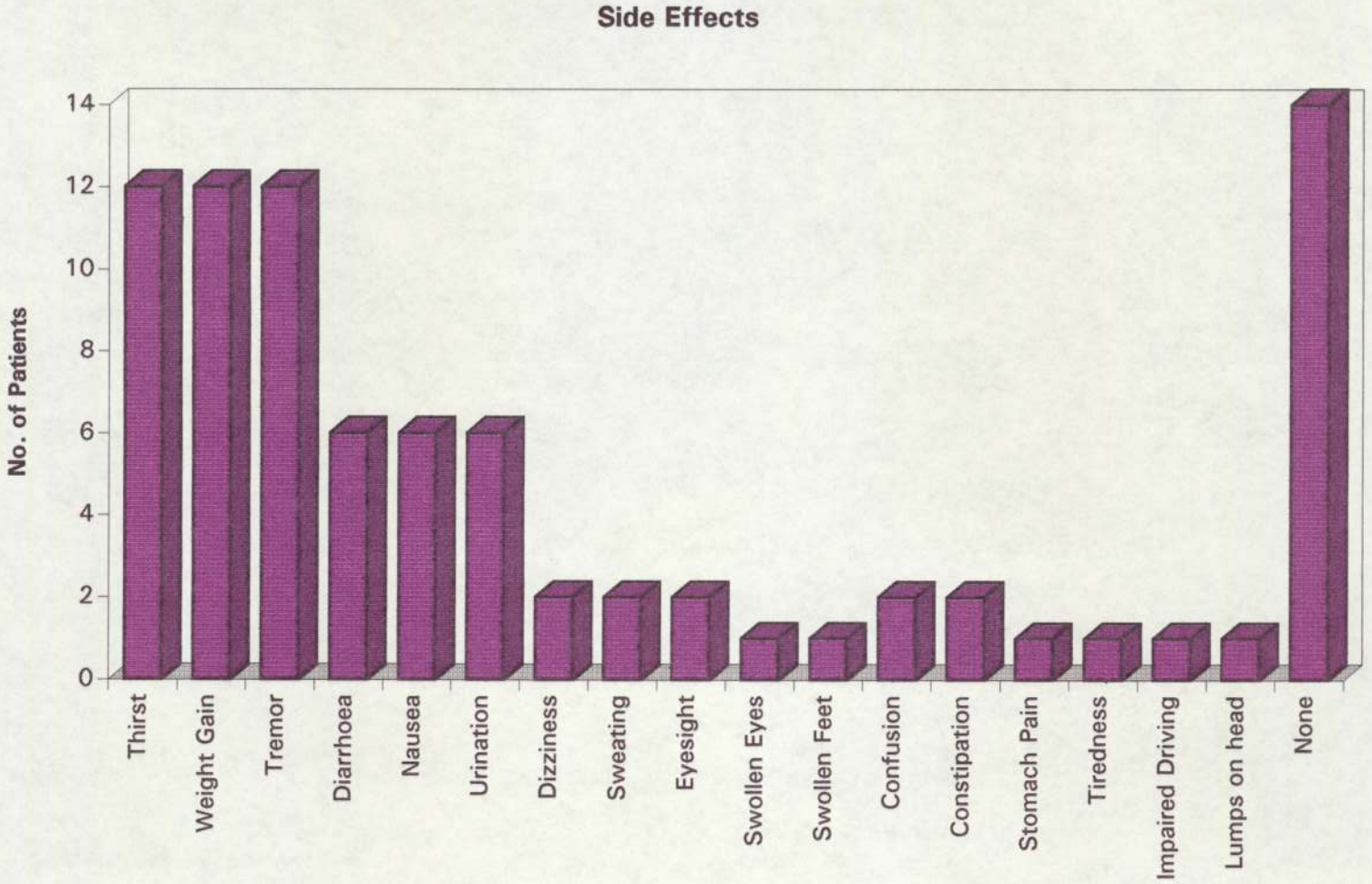



**Figure 3.2.5** A graph showing the range of side-effects experienced by 54 patients while taking lithium.

taken at the same time each day. Nine patients (17%) could not think of any particular points on how to take the tablets. This was a rather difficult question to ask without providing the answer. One patient had not realised that the tablets should be swallowed whole, and had been breaking them into small pieces before swallowing them. This problem was overcome by changing to the small Priadel 200® tablets, which can be broken in half and are easier to swallow.

8. **Missed doses**

Eleven patients (20%) knew that they should not take double the dose to compensate for missing a dose of lithium, and fifteen (28%) said that the next dose should be taken at the usual time. Thirty six (67%) patients did not know what to do in the event of missing a dose of lithium, and several of these said the question was not applicable to them as they had never missed a dose. This is unlikely to be the case as some of the patients had been taking lithium for several years, but it reflects the fact that respondents to a questionnaire will try to present themselves in a favourable light, and deny anything they think the interviewer would find unacceptable [96].

9. **Reason for blood test**

Forty two patients (78%) knew that a blood test was necessary to check the level of lithium in the blood, and twelve patients (22%) did not know why they had blood tests. Having blood samples taken and analysed is a routine part of lithium treatment, so it is surprising that as many as twelve patients did not question the reason for blood tests.

10. **Factors affecting lithium level**

Two patients (4%) said that drugs affected the lithium level, three (6%) mentioned alcohol and four (7%) said water and salt balance. The vast majority of patients (forty seven or 87%) did not know of anything which could alter the lithium level. Two of the patients (4%) said that both drugs and water balance could affect the blood level of

lithium. Therefore most of the patients were unaware that the lithium level could be affected by anything other than the dose of lithium taken. This has very important consequences, for example a patient might start a low salt diet, which could lead to lithium toxicity.

11. **Drugs to avoid**

Again, most patients (43 patients or 80%) could not think of any drug which they should avoid taking with lithium. Three patients (6%) named diuretics, three (6%) said NSAIDs, and six (11%) patients named other drugs, which were co-proxamol, chlorpromazine, antibiotics (2 patients), and cough medicines (2 patients). One patient named two drugs which she thought should be avoided.

It is interesting to note that the drugs mentioned (other than diuretics and NSAIDs) were thought to interact with lithium when in fact they had provoked a reaction in the patient which was unlikely to be related to the lithium. For example, one patient had reacted badly to chlorpromazine in the past, and knew she should not take any. It was not appropriate to tell her that this was probably not a lithium-chlorpromazine interaction as it might have confused her.

As with the previous question, it is a matter for concern that so few patients knew which drugs they should avoid with lithium, or even that they should avoid any drugs at all (without necessarily knowing which ones). It is important that patients are aware that other drugs can affect the lithium level, even "safe" OTC medicines.

12. **Alcohol with lithium**

It was thought by many patients (thirty three patients or 61%) that it was safe to drink a small amount of alcohol with lithium. Nineteen patients (35%) thought that alcohol should be avoided altogether, although one of these patients said that if he wanted to drink he would miss a couple of doses of lithium. The remaining two

patients (4%) said that it was safe to drink any amount of alcohol with lithium. The definitions of a "small amount" varied between patients, from "half a shandy" to "a couple of pints", but most patients seemed to have learned by experience what was a safe level for them.

13. **Signs of toxicity** (Figure 3.2.6)

Only thirteen patients (24%) knew any of the signs of impending lithium toxicity. One patient named three signs of toxicity. Forty one (76%) patients did not know what to look out for if the lithium level went too high. This is a potentially dangerous situation, because lithium toxicity can develop rapidly as a result of dehydration, for example in an elderly patient confined to bed because of feverish illness, and who is unable to maintain an adequate fluid intake. If the patient is not aware of the warning signs of impending toxicity, then serious problems may occur before medical help is sought.

14. **Dietary precautions**

No dietary precautions were thought to be necessary by the majority of patients (forty eight patients or 89%), although five patients (9%) said that it was important to keep salt and water constant. One patient said a low sugar and fat diet because she had hypercholesterolaemia and was also taking lipid-lowering drugs. The response to this question was not as important as the previous questions, but patients were advised to try to keep their salt and water intake consistent, and not to ignore feelings of thirst.

15. **Concurrent drugs** (Figure 3.2.7)

A vast range of other drugs was prescribed with lithium: a total of eighty additional prescriptions in 39 patients (fifteen patients or 28% took only lithium). The most commonly prescribed drugs were the antidepressants, as would be expected in this type of patient, followed by the hypnotics. Three patients (6%) had been prescribed

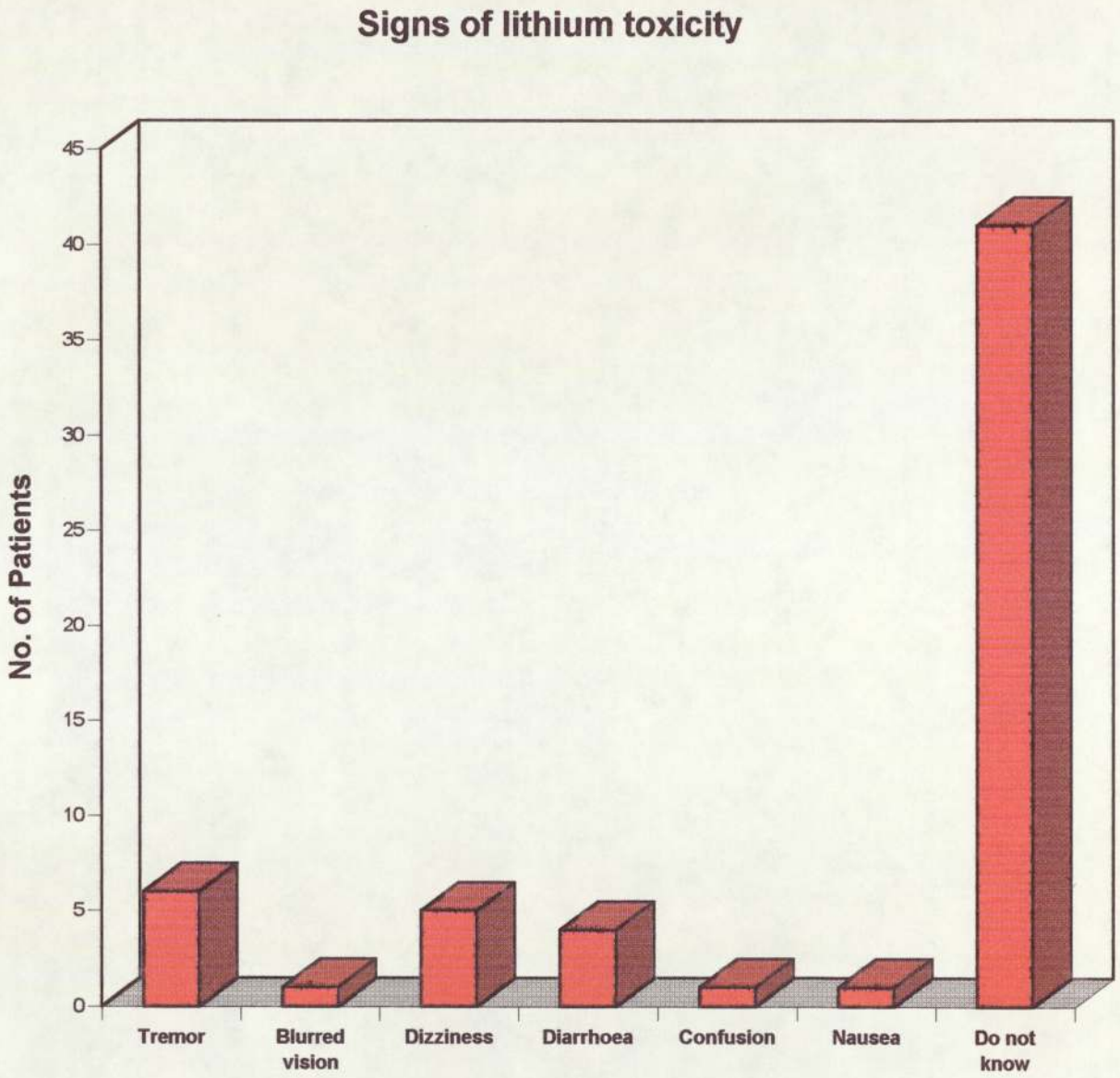



**Figure 3.2.6** A graph showing the signs of lithium toxicity known by 54 patients.

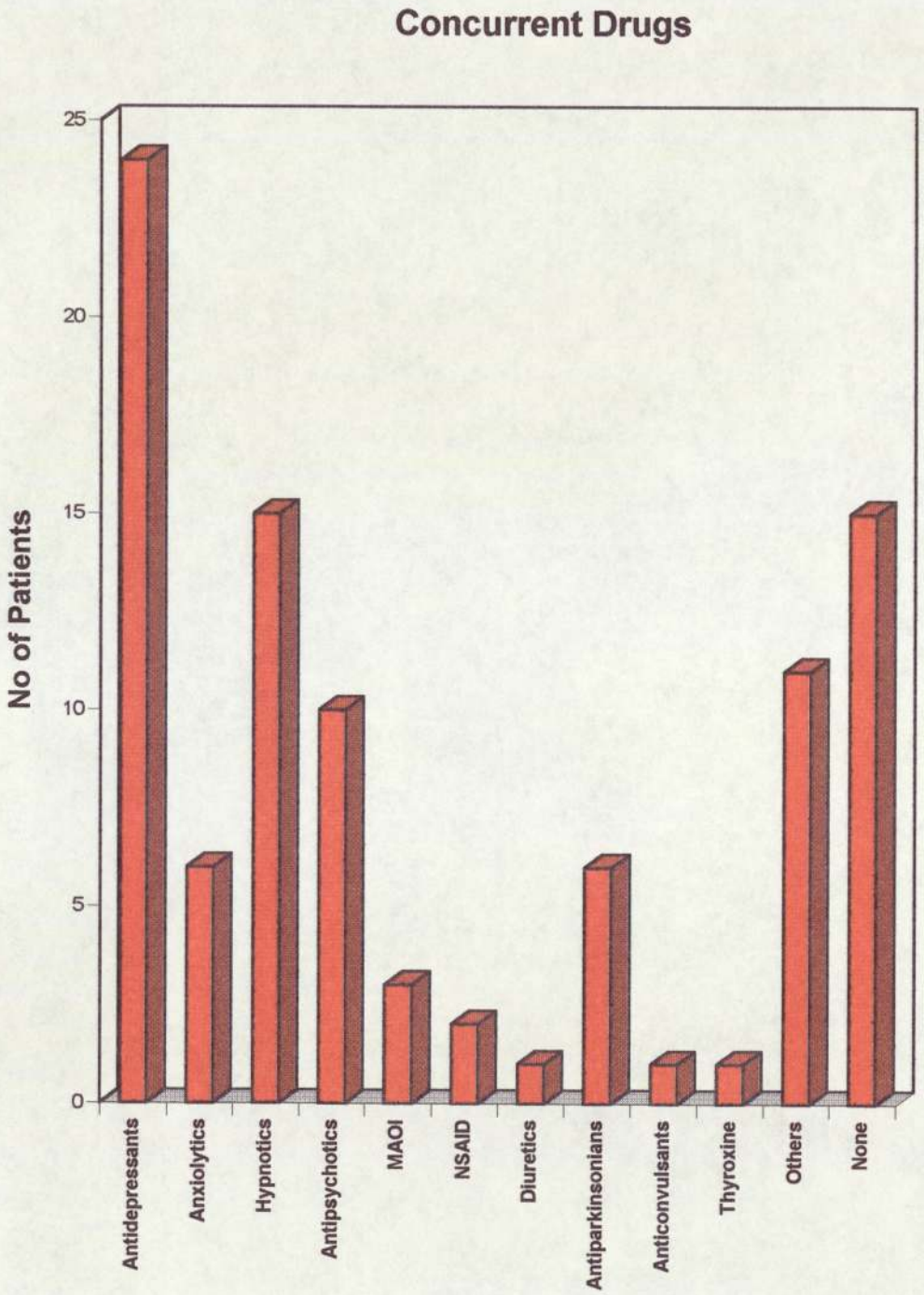



**Figure 3.2.7** A graph showing the range of drugs prescribed with lithium in 54 patients.

potentially interacting drugs: two were taking ibuprofen for rheumatic complaints, and one was taking bendrofluazide. The ibuprofen was successfully changed to sulindac (which is not thought to interact with lithium) by the clinic, with far superior symptom control experienced by one patient as a result. The bendrofluazide was changed to amiloride. One patient was prescribed thyroxine for lithium-induced hypothyroidism: she had been taking lithium for 18 years, and developed hypothyroidism in 1987 which was corrected by 100 micrograms of thyroxine daily.

### 3.3 CHANGE IN KNOWLEDGE

The change in knowledge of twenty six patients between the time they first attended the clinic, and a date at least six months after their first visit, was assessed by comparing the difference in score between the first and second questionnaires. One point was given for each correct answer given to the three key questions listed below. The maximum possible score was fourteen points.

There were 20 females (77%) and 6 males (23%) in this group, with a mean age of 59 years, that is, the group is older with proportionately more females than the clinic population. However it is a representative sample of the group used for the first questionnaire, in terms of age and sex distribution, and also the scores obtained in the first questionnaire. The results obtained are illustrated in Table 3.3.1 and Figure 3.3.1.

It is important to note that the patients were not warned that they would take part in a repeat interview before the event. This was to ensure that the answers given were what they remembered all the time, rather than what they would have revised before the interview.

| | | Before clinic→ | | | | | |
|---|---|---|---|---|---|---|---|
| | Score | 0 | 1 | 3 | 4 | 6 | Total |
| After clinic ↓ | 0 | 8 | 1 | 0 | 0 | 0 | 9 |
| | 1 | 3 | 1 | 0 | 0 | 0 | 4 |
| | 2 | 2 | 1 | 0 | 0 | 0 | 3 |
| | 3 | 2 | 0 | 0 | 0 | 0 | 2 |
| | 4 | 2 | 0 | 1 | 1 | 0 | 4 |
| | 5 | 1 | 0 | 0 | 1 | 0 | 2 |
| | 7 | 0 | 0 | 1 | 0 | 0 | 1 |
| | 10 | 0 | 0 | 0 | 0 | 1 | 1 |
| | Total | 18 | 3 | 2 | 2 | 1 | 26 |

**Table 3.3.1.** Cross tabulation of the change in knowledge of patients between their first visit to the clinic and at least six months later.

Example: To find out how many patients scored 3 on the first questionnaire, read across the top line to reach 3, then look to the bottom of that column: the total is two patients. By locating the numbers in the same column then looking across to the far left hand column, it can be seen that one of these patients increased their score to 4, and the other patient increased it to 7.

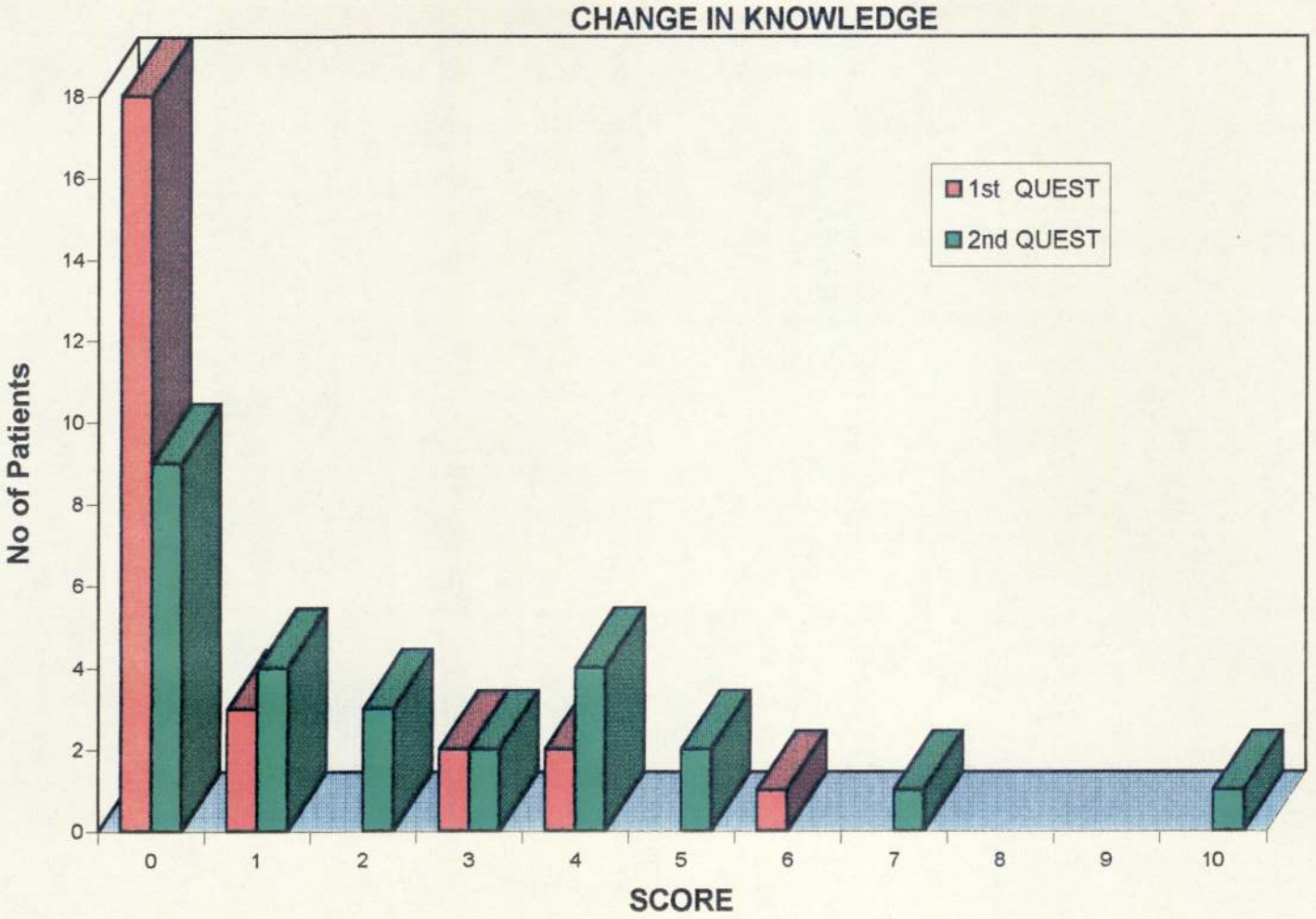



**Figure 3.3.1** A graph comparing the scores obtained by 26 patients in two questionnaires.

The key questions on which patients were assessed were:

I What can change the amount of lithium in the blood?

II Are there any medicines you should avoid when taking lithium?

III What are the signs when the lithium level gets too high?

The number of patients scoring zero decreased from eighteen (69%) on the initial questionnaire to nine (35%) on the second questionnaire. The highest score increased from 6 to 10 out of a possible score of 14 (both these scores were from the same patient). The largest increase in score by a patient was from 0 to 5. One patient's score decreased from 1 to 0.

The increase in knowledge exhibited by patients between the two questionnaires was shown to be very highly significant ($p<0.001$) using the Wilcoxon signed ranks matched pairs test [99]. This is a non-parametric test, used for studies where each patient has acted as his own control, so that most variables are unchanged between the two different sets of results. This means that any difference in results is likely to be due to the treatment, that is, patient counselling.

These results are extremely encouraging. The significance is very high, so is unlikely to be due to incidental factors such as being more at ease in the clinic by the second questionnaire. Lithium information cards (Appendix III) were given to each patient, but it has been suggested that written information on its own is of no measurable benefit to the chronically ill [85]. It seems probable therefore that the improvement in the knowledge and understanding of patients of their lithium therapy is due to patient counselling by the pharmacist.

Although one patient increased her score from 6 to 10 which was impressive, it is more encouraging that ten patients (38%) managed to increase their score from 0 in the first questionnaire to scores ranging from 1 to 5 in the second questionnaire. From knowing none of the important points about lithium, they at least became aware that there were some facts that they should know.

Five patients (19%) scored 0 on the question of medicines to be avoided in the second questionnaire, because they could not name the drugs. Of these patients, one said that she asked her chemist which medicines she could take, another said that they were "the ones on the card", and the third patient said she should only take paracetamol. The other two patients said that they should only take prescription medicines. These patients showed an increased awareness of the potential problems of lithium therapy, even though this was not reflected in their scores.

### 3.4 PATIENT SATISFACTION

The remainder of the second questionnaire (Appendix Ⅵ) was completed by the same twenty six patients. This was intended to assess the patients' satisfaction with the clinic. There are some inherent difficulties with this type of questionnaire, as mentioned earlier. These include a high level of reported satisfaction, lack of meaningful comparison bases, lack of a standard satisfaction scale, difficulty in avoiding sample bias, and high cost and low relevance [96].

In this study, the patients who were questioned are, in a sense, a captive audience, because if they were very dissatisfied or found the time or location of the clinic very inconvenient, they would have left the clinic and made other arrangements. There is no indication that the patients who stopped coming to the clinic did so because they were dissatisfied, but this reason cannot be dismissed. Therefore the patients interviewed in this second questionnaire were likely to be satisfied with the service.

A period of at least six months after the first visit needed to elapse before the second questionnaire was used, so that patients would have experience of at least three clinic visits. This may have been biased against patients who dropped out early, but any results obtained earlier than six months would not have been meaningful. The following results are interpreted taking these limitations into account.

1. **Location of clinic**

All patients said that the location of the clinic was convenient, although seven patients (27%) would have preferred to go somewhere closer to their homes, such as their GP's surgery. Six patients (23%) had experienced problems with buses or a shortage of car parking space. Three patients (12%) did not like having to walk through the psychiatric wards, where they had previously been in-patients, to reach the clinic, whereas others liked to go on to the wards to see friends and have a cup of tea.

The lithium clinic was situated in the ECT suite, a Portakabin in between the two blocks of psychiatric wards, and the only access was through one of the wards. Ideally the clinic would be better situated away from the wards, and this may be possible in future.

2. **Time of clinic**

All patients when questioned thought that the time of the clinic was convenient. Although they were not specifically asked, most of the patients commented that they appreciated the flexibility of being able to turn up when it suited them, except for one patient who would have preferred to have fixed appointment times.

The clinic had to be run in the morning, because of the need to measure lithium levels 12 hours after the evening dose (12h-stSLi). Tuesday was the most appropriate day because the Central Pathology Laboratory in Stoke-on-Trent measured lithium levels on this day, so there would be no delay in notification of high lithium levels. Most

patients arrived at the time which best suited them during the morning, for example patients who worked often arrived before 9 a.m., so that they could be seen first. The patient who wanted fixed appointments had once arrived when the clinic was particularly busy, and this probably influenced his judgement.

With the advent of the Patients' Charter, appointment times had to be given to all patients, but it was emphasised that patients could still attend at their preferred time, as this was seen by them as an advantage of the lithium clinic.

3. **Surroundings**

Comments on the actual building ranged from "alright" to "pleasant" and even to "marvellous". One patient (an amateur artist) appreciated the pictures on the walls! There was not much that could be done about the building, but it was adequate for the clinic.

4. **ECT equipment**

Five patients (19%) found the electroconvulsive therapy (ECT) equipment in the clinic room upsetting, as it reminded them of previous unpleasant experiences. One of these patients (a 79 year old lady) had particularly unpleasant memories as she had been given ECT many years previously, before anaesthetics were used. However, another patient commented that he did not find the ECT equipment disturbing, precisely because he had received ECT in the past and had found it to be very helpful. This question was included as some patients had previously commented on the equipment, but after the initial visit it did not seem to present a problem to the patients, as they had become used to the surroundings.

5. **Waiting time**

All of the patients when questioned thought that the length of time they had to wait before being seen was reasonable, although some observed that it depended on what

time they arrived as the clinic could get very busy. The waiting time was said to be far shorter than at the out-patients clinic - one patient said that she had to wait for 2½ hours to be seen there on one occasion. Two said that, as patients, they expected to have to wait to be seen.

Apart from a few occasions, particularly in the early days of the clinic (when registrars from the psychiatric wards were the clinic doctors), when there had been delays in seeing patients, most patients were seen promptly. The number of patients seen at each clinic was usually about twelve, allowing time to sort out particular problems as well as attending to the routine monitoring of patients.

6. **Telephoning the clinic**

Fifteen patients (58%) said that they had telephoned the clinic. All of these patients had telephoned either to check the date of their next appointment or to change their appointment. This was a useful facility, as occasionally patients would change their appointments because they were ill. This provided an opportunity for clinic staff to advise the patients on what to do, for example in the event of feverish illness.

7. **Information card**

When questioned, twenty (77%) of the twenty six patients said that they had used the information on the Royal Pharmaceutical Society lithium information card which they had been given. Three (12%) of these patients said that they had read the information on the card but could not remember what it said. Several of the patients said that they carried the card with them. The sections which patients found most useful were varied; they included the sections on drug interactions, signs of lithium toxicity, taking lithium twelve hours before the blood test, what to do when a dose was missed, possible side-effects especially weight gain, and not crushing the lithium tablets. One patient said that there was nothing on the card which she did not know already, but that she found it useful to show other people.

The lithium information cards were also used as appointment cards so that patients would be encouraged to look at them rather than just read them once then discard them. This approach seemed to work well, with patients knowing that they could refer to the card even if they were unable to memorise the contents.

### 8. Further information

Most patients (22 patients or 85%) thought that the information on the card was adequate for their needs, but four patients (15%) would have preferred more information on what lithium is used for, how it works, its long term effects, and when to come off lithium.

It is difficult to balance the need for more information with what can be written concisely on a small card. This is a project which could be done at a future date, to design an information booklet specific to the lithium clinic, combining an appointment card and more information.

### 9. Learning about lithium

Fifteen patients (58%) felt that they had learned something about lithium since they had been attending the lithium clinic. One had learned not to take ibuprofen with lithium, and another of its side-effects, but the remainder were more philosophical: "to treat lithium with respect", "I should have had it long ago", "lithium is the most suitable treatment for me" and "I have learned to accept lithium" were a few of the comments received.

It is encouraging that patients feel they have an increased understanding of lithium from attending the clinic, as well as the increase in knowledge shown by the questionnaires.

10. **Attitude of staff**

All patients commented favourably on the attitude of the staff. Various comments were "very nice", "helpful", "pleasant", "friendly", "splendid" and "couldn't be better".

It is unlikely that patients would have made unpleasant comments about the staff when they were being questioned by one of the staff, so the comments should be taken in this context, but even so it is pleasing to receive them.

11. **Atmosphere of clinic**

Ten of the patients thought that the general atmosphere of the clinic was "alright". Others said that it was very friendly, happy and chatty. One patient thought the clinic was "a bit of an insight", but others felt it was "like any other waiting room" with "normal people". One of the patients said it was "an exclusive club" where they could "meet old friends from the ward".

The emphasis of the clinic was to treat the patients in a friendly, relaxed environment, and meeting other patients could contribute greatly to this atmosphere. Patients had often felt isolated before, and did not like being treated like "psychiatric patients" when they had their blood samples taken at the pathology laboratory. By attending the lithium clinic patients could meet other people with similar problems, and waiting room discussions could be very interesting to patients and staff. Efforts were made to give patients who got on well together the same appointment dates so that they would derive the most benefit from attending the clinic.

12. **Clinic staff**

**Doctor** The patients said that the doctor "takes blood", "checks the lithium level is OK", "asks questions about diet, sleep and general welfare", "sorts out any problems", and "has the ultimate decision and responsibility".

**Nurse** The nurse was said to be "the PR of the unit", "receptionist" and "liaison officer", and her function was to "reassure and comfort", "see things are running smoothly", "deal with certain problems" and "see to us".

**Pharmacist** Some comments made about the pharmacist's perceived rôle were "administration", "manageress", "can ask (her) anything", "asks us questions", "knows about tablets and chemistry", "guides us on what to take" and "knows what's in the tablets".

These comments were mainly what would be expected. Some of the patients did not know the professions of the nurse and pharmacist, but their functions were seen to be interlinked. Some patients realised that research formed part of the pharmacist's rôle, although others thought that there were just a lot of questions to answer.

13. **Improvements**

One patient thought that the waiting room should be bigger, two would have preferred the clinic to be situated away from the psychiatric wards, and three felt that fixed appointment times would be better. There were no other complaints.

Some of the other comments received were:

"Superbly managed. I don't want to be made to feel ill."

"I look forward to coming."

"I like being able to ask questions and get the right answers."

"Very well organised throughout."

"An improvement on the ward."

"It's better not to wait with other patients at the path lab."

"An ideal situation - we need places like this."

"Anyone who complains must have something wrong with them!"

"I like seeing the same staff and being treated personally."

## 3.5 LITHIUM MONITORING

Two parameters were looked at to evaluate the effectiveness of lithium level monitoring by the lithium clinic, compared to the psychiatric out-patient clinic where patients were previously monitored. These were the frequency of monitoring and the values of the serum lithium levels obtained. The medical notes of twenty one patients were reviewed following the format in Appendix Ⅳ. These 21 patients were the same patients that underwent the second questionnaire; the other 5 patients' medical records could not be traced. Fifteen (71%) were female and six (29%) were male, with a mean age of 59 years.

### 3.5.1 Frequency of monitoring

The number of serum lithium estimations before attending the clinic, and while attending the clinic, were estimated. The rate of measurement was calculated by dividing the number of levels measured by the number of weeks over which the measurements were obtained. This gave a rate per week, therefore this figure was multiplied by 12 to obtain the number of lithium levels per 12 weeks. Twelve weeks was adopted as the "standard" rate of measurement, following the guidelines in the British National Formulary [100]. The time limit before and after the first visit to the clinic was 150 weeks. Two values were obtained for each patient, a "before" and an "after" result, which are shown in Figure 3.5.1.

Rates of measurement of lithium levels by the clinic were consistently better than the standard apart from patient 5 where the rate was slightly less. The rates of measurement before attending the clinic only equalled or exceeded the standard in four out of 21 patients. A misleadingly high result was obtained for patient 16, as he had been started on lithium only twenty four weeks before attending the clinic, and his lithium level had been measured six times during this period. Patient 13 also had a

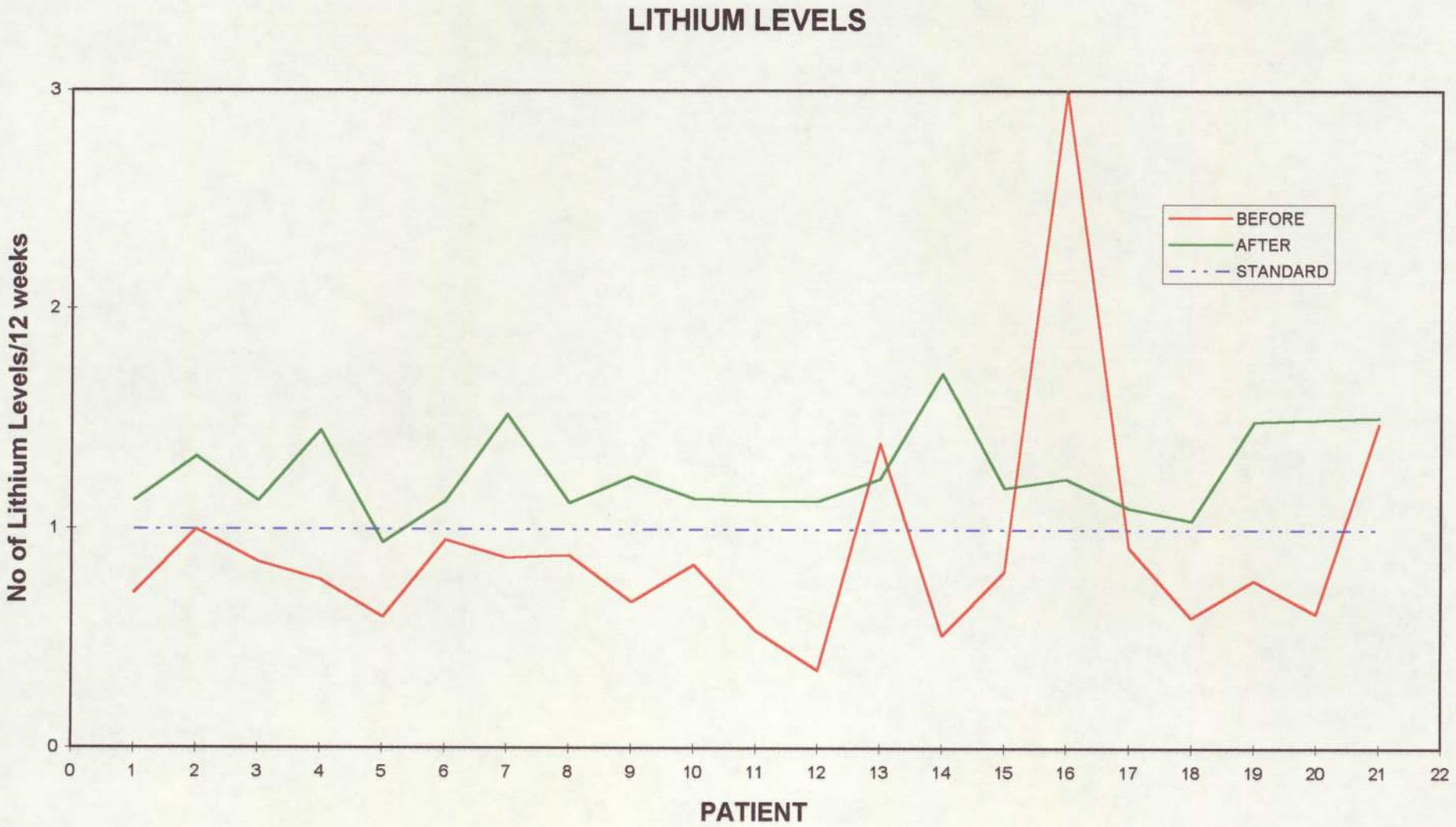





**Figure 3.5.1** A graph showing the rate of measurement of serum lithium levels, as a number per 12 weeks, in each of 21 patients before and after attending the lithium clinic.

high rate of measurement before the clinic: this was because of fortnightly monitoring while she had been an in-patient for 12 weeks, which probably was not necessary.

Some of the patients had rates of measurement of around 1.5 levels/ 12 weeks after attending the clinic. This is because one of the consultant psychiatrists who used the clinic requested that her patients be seen every 8 weeks instead of every 12 weeks. Rates of measurement that are much greater than the standard could be viewed as unnecessary and wasteful of resources, and indeed at a later date, the consultant agreed that her patients could be seen every 10 weeks. Patient 14 has a high rate of measurement because her GP prescribed bendrofluazide, which led to high lithium levels (see Case 1 in section 3.8).

These results show that, in general, the rate of serum lithium estimations was greater in the lithium clinic than in the psychiatric out-patient clinic. The greatest interval between subsequent lithium levels was 66 weeks in the out-patient clinic, and 16 weeks in the lithium clinic. The shortest interval was 1 week in both cases.

There is a possibility that more lithium estimations had been performed than were recorded in the medical notes at the out-patients clinic, but without a record in the notes, any lithium levels measured could not have been acted upon.

### 3.5.2 Range of lithium levels

The second parameter to be evaluated was the actual values of the lithium levels measured. The results are shown in Figure 3.5.2. Percentages are used because of the larger number of lithium levels measured by the clinic (266 compared with 182 in the out-patient clinic). 56.9% of the lithium levels measured by the clinic were within the therapeutic range of 0.5 to 0.8 mmol/l, compared with 52.9% in the out-patient clinic. If the range is extended to 0.4 to 1.0 mmol/l, then the percentages rise to

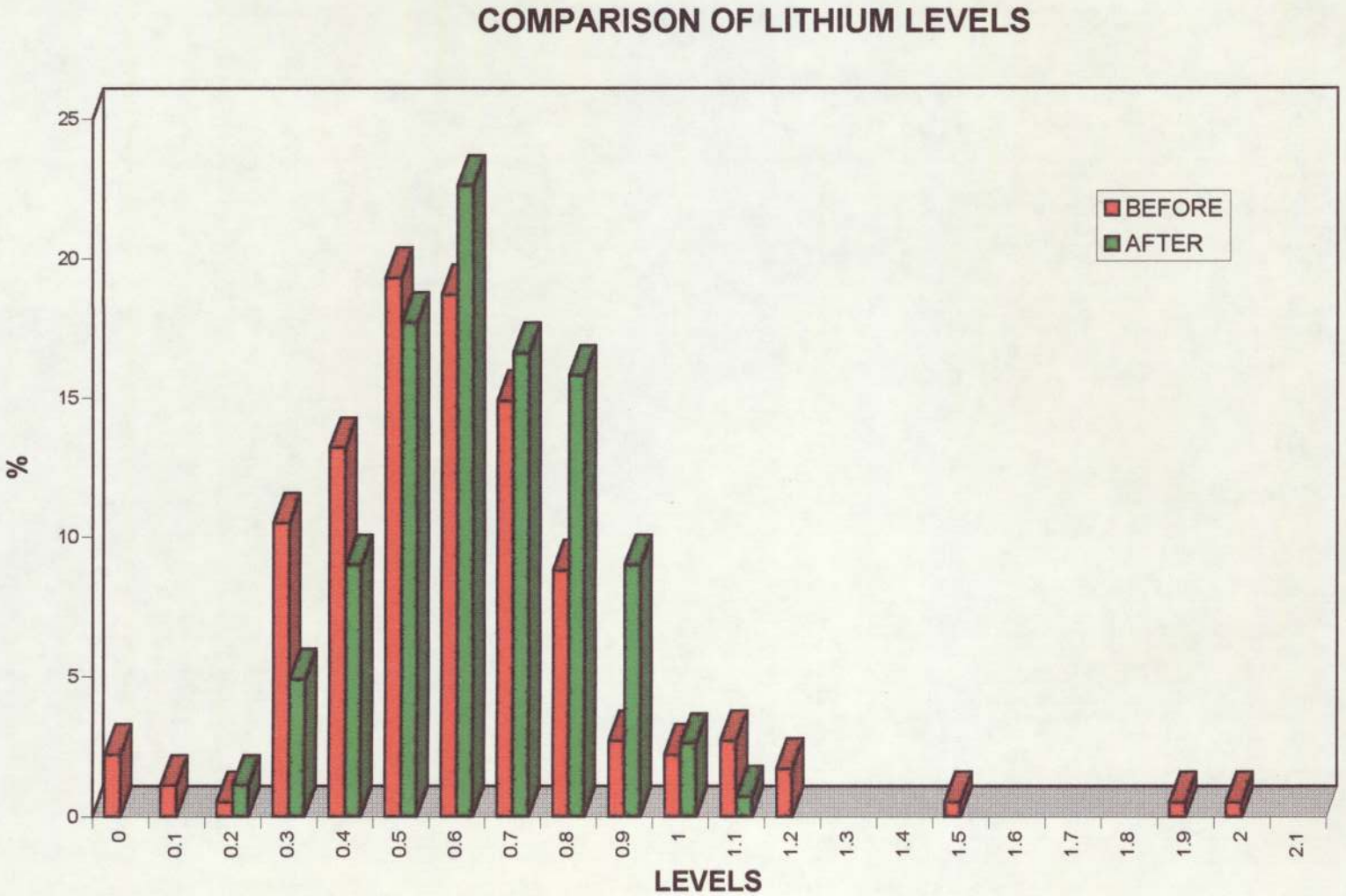



**Figure 3.5.2** A graph comparing the range of lithium levels (in mmol/l) measured in 21 patients in a 150 week period before and after attending the lithium clinic. The bar at e.g. 0.3 indicates levels of 0.30–0.39 mmol/l.

90.7% for the lithium clinic, and 77.6% for the out-patient clinic. There is therefore a tendency for the results obtained by the lithium clinic to adhere more closely to the therapeutic range. The extent of patient compliance is likely to affect the values of the serum lithium levels, but this is difficult to assess effectively.

In the lithium clinic, the median of the serum lithium concentrations measured (that is, the value above and below which half the results are found) was 0.66 mmol/l, the first quartile was 0.55 mmol/l and the third quartile was 0.84 mmol/l. In the out-patient clinic, the median was 0.63 mmol/l, the 1st quartile was 0.46 mmol/l and the 3rd quartile was 0.76 mmol/l. This shows that the lithium levels in the lithium clinic tended to be higher than those in the out-patient clinic, although it also shows that 50% of results were within a band of 0.29 mmol/l for the lithium clinic, and a band of 0.30 mmol/l for the out-patient clinic. The 5th percentiles were 0.39 mmol/l in the lithium clinic and 0.30 mmol/l in the out-patient clinic, and the 95th percentiles were 0.97 mmol/l and 1.14 mmol/l respectively, showing that the results in the out-patient clinic were distributed over a wider range.

Overall, the lithium clinic measured lithium levels more frequently, and maintained them within the therapeutic range to a greater extent than the out-patient clinic. This is in accordance with the findings of a study which compared the supervision of lithium treatment by a lithium clinic, a hospital out-patient clinic and general practitioners [89].

There may be several reasons for this:

I Some results may not be recorded in the medical notes of out-patients

II Improved compliance as a result of attending the lithium clinic may become apparent because of the increased number of levels within the therapeutic range

III Patients may be more aware of the signs of impending toxicity because of

attending the lithium clinic, and may present themselves earlier for treatment

Ⅳ Lithium levels are monitored more regularly by the lithium clinic, because of a standardised clinic protocol, and more vigilance in contacting patients who default

## 3.6 RENAL AND THYROID FUNCTION TESTS

The rate of measurement of renal and thyroid function tests was calculated in a similar way to the lithium levels, but with the rate expressed as the number of tests performed every 6 months. Unlike lithium level monitoring, there are no standard accepted guidelines for the frequency of monitoring of renal and thyroid function. Some reference sources advocate six-monthly monitoring, whereas others recommend yearly tests. At the beginning of the clinic, consultants were asked whether they wished renal and thyroid function tests to be carried out every six or twelve months (see the referral form in Appendix I). After the clinic had been running for about a year, the clinic staff decided that all patients should be tested every six months, and this was the consensus "standard" rate adopted by the clinic. Results were obtained for the same twenty one patients as were used in the lithium levels, by reviewing their lithium clinic notes and their medical out-patient notes.

### 3.6.1 Renal function tests

The results of the renal function tests are illustrated in Figure 3.6.1. Rates of measurement by the lithium clinic were better than the standard in all but three (14%) of the patients. As explained above, the rate of monitoring was changed during the study period. The three patients with rates of measurement less than the standard were initially monitored yearly, then the rate of measurement was changed to every six months for all patients.

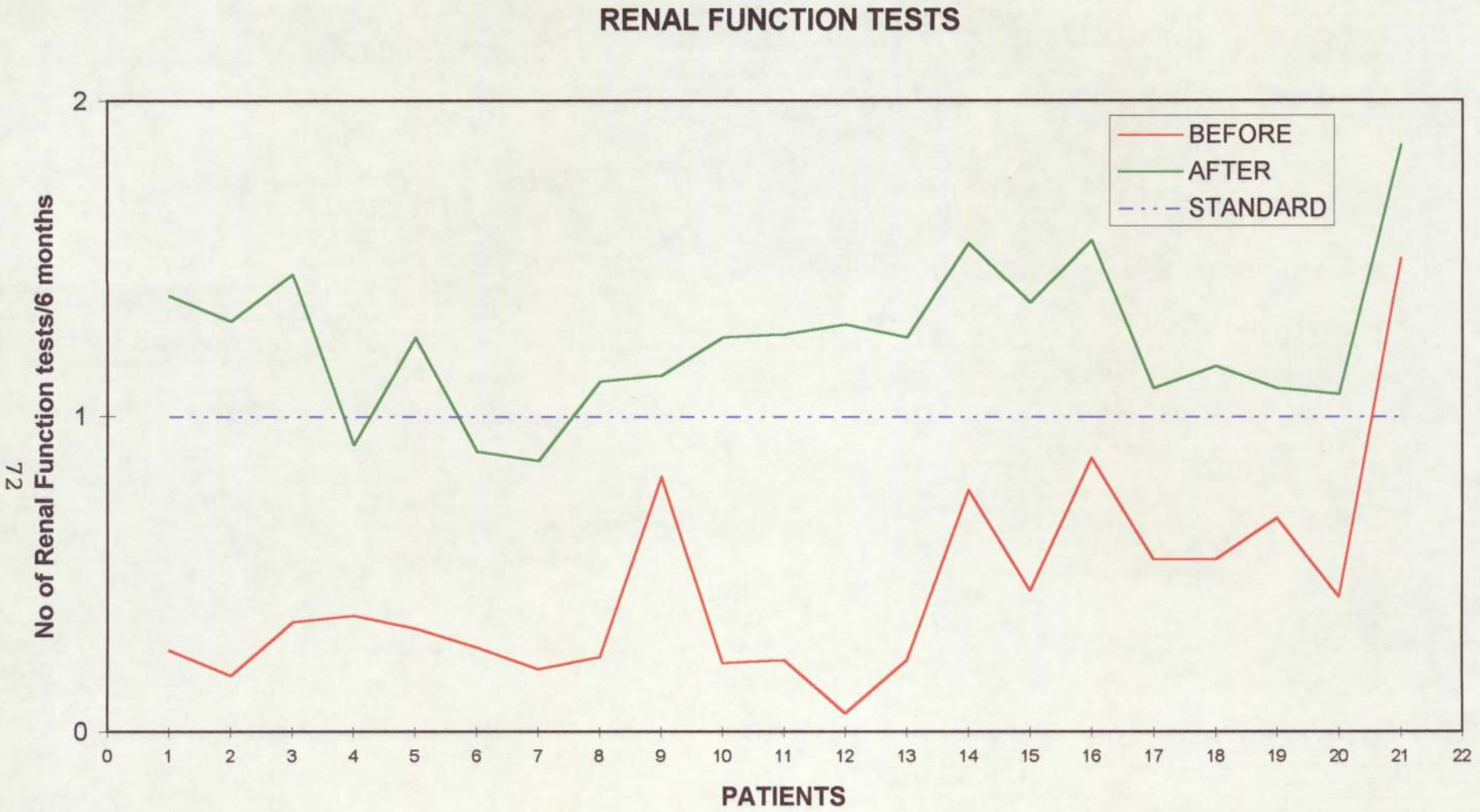



**Figure 3.6.1** A graph showing the rate of measurement of renal function tests, as a number per 6 months, in each of 21 patients in a 150 week period before and after attending the lithium clinic.

In the out-patient clinic, the rate of monitoring exceeded the standard in only one patient. Patient 21 had renal impairment, so the renal function was measured with every serum lithium estimation. In all the other patients, the rate was below the standard. In patient 12, the renal function tests had been performed only once in 5½ years. There were 11 abnormal renal function tests in the lithium clinic out of a total of 114 (9.6%).

### 3.6.2 Thyroid function tests

The rates of measurement of thyroid function are shown in Figure 3.6.2. Again, the rate for two of the patients in the lithium clinic was slightly less than the standard rate used by the clinic, because of the change in monitoring frequency mentioned in section 3.6.1. The rates of measurement in the out-patient clinic were consistently below the standard. The most striking difference in monitoring rates is in patient 12: before the clinic her thyroid function was measured only once, almost 8 years before first attending the clinic, while in the lithium clinic she was found to have borderline hypothyroidism, so the thyroid function tests were repeated at almost every visit. There were 10 abnormal thyroid function tests in the lithium clinic out of a total of 106 (9.4%).

In summary, both the renal and thyroid function tests were measured more frequently by the lithium clinic than by the out-patient clinic, particularly if renal impairment or hypothyroidism had occurred.

## 3.7 NEW LITHIUM PATIENTS

Nine patients were started on lithium therapy at the lithium clinic, using the pharmacokinetic dose-prediction method described in Appendix II. Of these, six were matched with suitable control patients (on the basis of age and sex) who had started

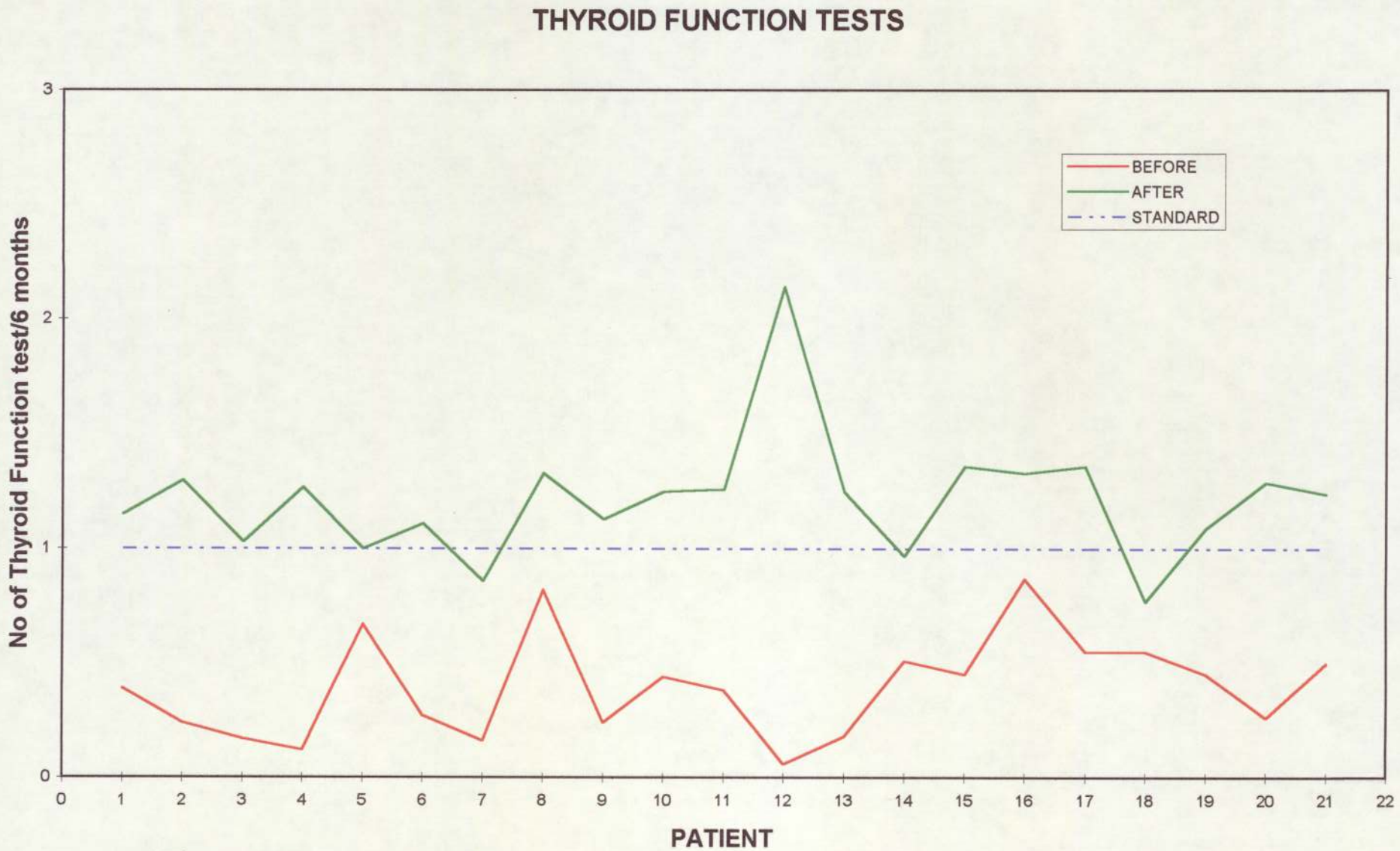



**Figure 3.6.2** A graph showing the rate of measurement of thyroid function tests, as a number per 6 months, in each of 21 patients in a 150 week period before and after attending the lithium clinic.

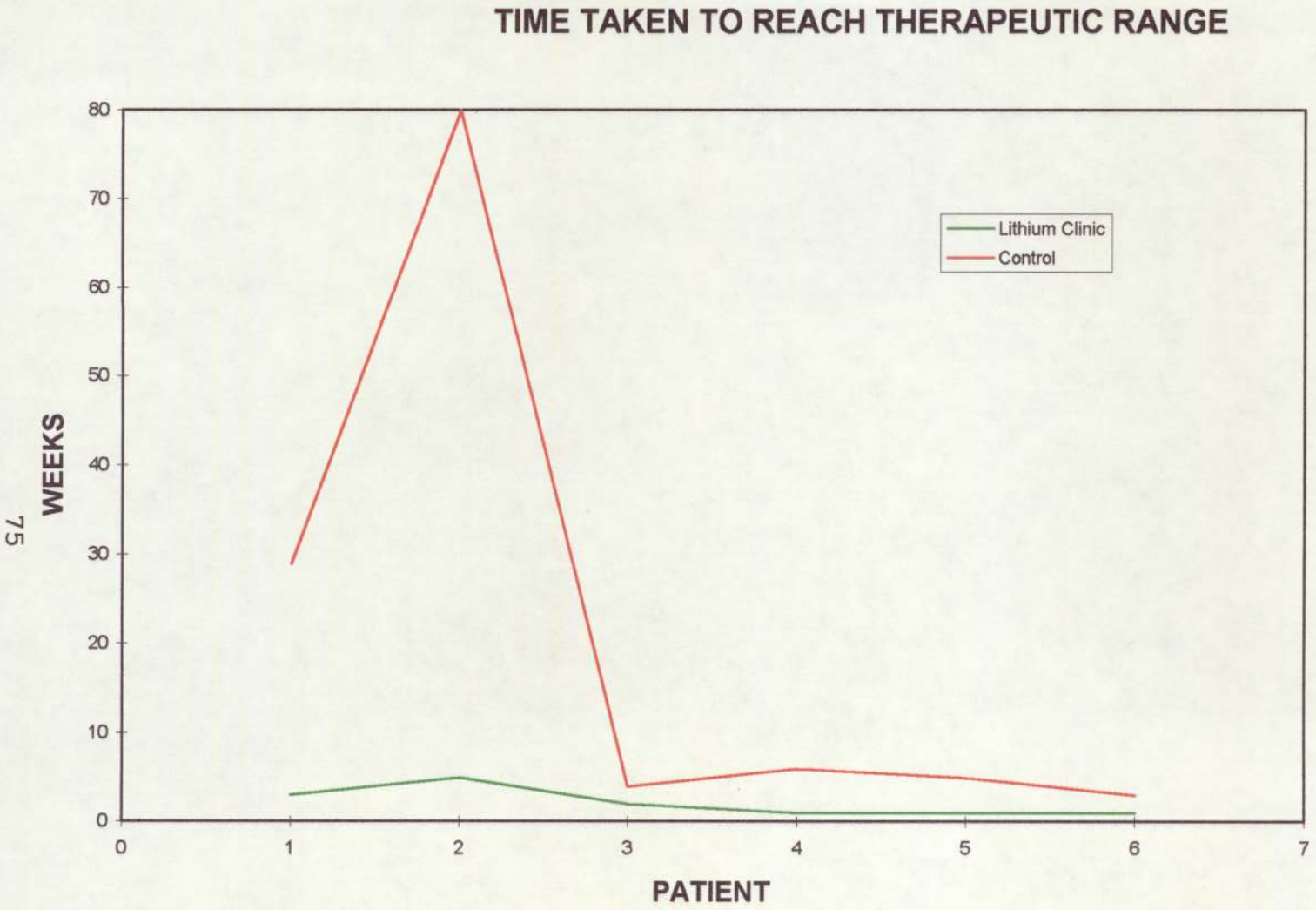



**Figure 3.7.1** A graph comparing the time, in weeks, taken from starting lithium to reaching the therapeutic range in six patients started by the lithium clinic, and six control patients.

lithium before attending the lithium clinic. The time taken from starting lithium to reaching the therapeutic range was compared in both sets of patients, and the results are illustrated in Figure 3.7.1. One control patient took 80 weeks to reach the therapeutic range, or at least this was the only conclusion that could be drawn from the information in the medical notes. Another control patient took 29 weeks to reach the therapeutic range. The other four took less than 6 weeks. In the patients started on lithium by the lithium clinic, all six reached the therapeutic range within 5 weeks, with patients 4, 5 and 6 reaching the therapeutic range in one week, that is, they were started on the correct dose without need for subsequent adjustment.

In the six control patients there were eleven dose changes before the therapeutic range was reached, whereas in the lithium clinic patients there were only two dose changes. Although this is a very small sample, it is sufficient to show the differences between the two groups. The patients started on lithium by the lithium clinic reached the therapeutic range more quickly and needed fewer dose changes than the control group.

All new patients started on lithium were counselled fully by the pharmacist and other staff in the lithium clinic. The extent to which the information was retained was not formally tested, as this was not thought to be appropriate in patients who had recently started lithium. The important points to remember about lithium were constantly reiterated at each clinic visit, as with all the other patients.

In all other respects, the patients started on lithium at the lithium clinic were treated in exactly the same way as the other patients, and it was not thought to be useful to investigate the rate of lithium level and renal and thyroid function monitoring.

## 3.8 INDIVIDUAL CASES

The following are case reports of three patients which were used as part of a workshop on pharmacist involvement in lithium clinics, at the Psychiatric Pharmacy Group Conference at York University in October 1992. All three are patients attending the lithium clinic, and the cases reflect some of the main problems which may be encountered with lithium therapy.

Case 1 Drug interaction with lithium

Case 2 Non-compliance with lithium treatment

Case 3 Lithium toxicity

The sequence of events described in the three cases is what actually happened in the clinic, and the way the problems were dealt with is also identical.

The other main problem encountered in the lithium clinic was with side-effects. One patient complained of diarrhoea with Priadel®, a slow release preparation. This was changed to standard release Camcolit 250®, and the problem was resolved (see also section 1.5.1). Another patient complained of fine hand tremor, which improved on reducing the dose of lithium from 800mg to 600mg nocte.

Some patients were prescribed potentially interacting drugs. Thiazide diuretics were changed to either a loop or potassium-sparing diuretic, and non-steroidal anti-inflammatory drugs were changed to sulindac.

## CASE 1

Mrs A is a 67 year old female who has a long-standing obsessional neurosis with features of major affective disorder. Her symptoms have been well controlled since starting lithium and an antidepressant in 1977. Lithium level have been maintained between 0.81 and 0.97 mmol/l over the past two years, on a dose of 600mg nocte of lithium carbonate.

March 1992 Mood stable, ankles and legs slightly swollen. U&Es, creatinine, TFTs all normal.

April 1992 Mood stable but feels cold and slowed down, both legs puffy. Gained 2 stone in weight over part 6 months. Repeat TFTs - normal.

May 1992 Ankles still swollen. Had been to see GP - prescribed bendrofluazide.

**********

1. What possible problems could be caused by the combination of lithium and bendrofluazide?
2. What alternative diuretic drugs could be used?
3. What other measures could be used to reduce the risks?

## CASE 1 - ANSWERS

1. Diuretics can interact with lithium, causing an increase in serum lithium concentration, which may lead to lithium toxicity. Approximately 95% of a dose of lithium is excreted via the kidneys, therefore any drug which influences renal function is likely to affect lithium clearance.

Thiazide diuretics, such as bendrofluazide, cause sodium depletion by inhibiting the reabsorption of sodium in the distal tubule. In an effort to compensate for this negative sodium balance, more sodium is reabsorbed in the proximal tubule. Lithium is also reabsorbed, resulting in increased serum lithium levels. Mrs A's lithium level rose to 1.03 mmol/l after the introduction of bendrofluazide, and the urea was raised to 9.5 mmol/l (range 3.5 - 8.5 mmol/l).

2. Frusemide and other loop diuretics may cause an increase in serum lithium levels is some patients, although studies have failed to show significant changes. This is probably because frusemide inhibits lithium reabsorption in the loop of Henle, which compensates for the increase in proximal tubule reabsorption.

Amiloride and other potassium-sparing diuretics may produce a slight increase in the excretion of sodium, therefore theoretically they could also cause a slight decrease in lithium excretion. However, studies have not demonstrated a significant effect on lithium excretion. Mrs A's prescription was changed to frusemide with potassium supplementation, and the next lithium level was 0.84 mmol/l.

3. Although frusemide is less likely to interact with lithium than bendrofluazide, there is still a possibility that the serum lithium level could rise.

Like many patients who have been taking lithium for several years, Mrs A's lithium levels have been maintained at the upper end of the therapeutic range. A slight rise in the lithium level induced by frusemide might precipitate lithium toxicity. This is an unacceptable risk, particularly in an elderly patient who could be prone to dehydration and deteriorating renal function. Mrs A's dose of lithium was reduced to 400mg nocte in June 1992. She returned two weeks later feeling much better. The ankle oedema had improved, urea was 6.4 mmol/l, and the lithium level was 0.73 mmol/l.

## CASE 2

Mrs B is a 65 year old female who was referred to the lithium clinic in July 1990 for initiation of lithium treatment. Since her husband's death in 1988 she has experienced recurrent episodes of depression, with a recent episode of hypomania. She is a smoker, with a history of obstructive airways disease.

She was commenced on a dose of 600mg nocte of lithium carbonate, which gave levels of 0.60 to 0.73 mmol/l.

March - November 1991 Serum lithium levels became consistently low 0.26-0.39 mmol/l.

**********

1. What methods are available to choose an initial dose of lithium?
2. What could have caused the reduction in lithium levels?
3. What factors are likely to affect patient compliance with lithium treatment?

## CASE 2 - ANSWERS

1. There are two main methods of deciding on an initial dose of lithium:

a) Empirical dosing. The patient is given a small dose of lithium (e.g. 400mg lithium carbonate nocte) for one week, and the lithium level measured. The dose is then increased to give a lithium level within the therapeutic range. As lithium has first order kinetics, doubling the dose will double the serum level. This is the simplest method but is also the least accurate.

b) Pharmacokinetic methods. Several different methods have been described, varying in complexity and thus accuracy. The method used in this case was described by RW Fitzpatrick and RB Bye, *Pharm J* 1986; **237**: 726. It involves giving a test dose of

16mg/kg body weight of lithium carbonate, measuring the level after 24 hours, then calculating a maintenance dose of lithium. Although there is slight delay in starting treatment, the dose will be within the therapeutic range and should only require minor adjustment.

2. Some drugs can lower lithium levels, for example acetazolamide and theophylline. Acetazolamide inhibits carbonic anhydrase, and as a result sodium (and thus lithium) excretion is increased. Theophylline also increases lithium excretion, thus reducing serum lithium levels. There is a possibility that Mrs B could have been prescribed theophylline for the obstructive airways disease, but this was not the case.

The most likely cause of the low levels is patient non-compliance. Mrs B admitted to not liking taking the tablets, but maintained that she did take them regularly.

3. There are many reasons why a patient fails to comply with lithium treatment:

a) The most common side-effects mentioned as a reason for non-compliance are weight gain, memory impairment, tremor, thirst and lethargy.

b) Manic patients may miss the advantages of mild "highs".

c) The patient may feel well, and see no reason to continue taking lithium.

d) Some patients may feel that lithium changes their personality.

e) Other patients are opposed to the idea that their mental state is controlled by a drug.

Mrs B was worried about gaining weight while on lithium. She was advised to follow a well-balanced diet, to take gentle exercise, and to quench her thirst with low-calorie drinks. On subsequent visits her lithium levels had risen to within the therapeutic range, and are now maintained at around 0.6 mmol/l.

## CASE 3

Mrs C is a 71 year old female who was referred to the lithium clinic in November 1991, four weeks after starting lithium as a hospital in-patient. Her diagnosis is of a major depressive illness unresponsive to lofepramine and fluoxetine.

Medical history:

Hiatus hernia

Ca colon 1985, removed by hemicolectomy

Chronic tongue pain after oral surgery

Hypothyroidism, treated with thyroxine 100 micrograms daily

November 1991 1st visit to the clinic. Lithium level 0.72 mmol/l on 400mg nocte

Two weeks later Complaining of nausea and vomiting since the previous visit, and also of shaking, but also says she felt like this when she was first admitted to hospital. She looks unwell, and is complaining of epigastric pain. Has been in bed for the past week. Lithium level on 400mg nocte is 0.97 mmol/l.

**********

1. What is likely to be happening in this patient?
2. What should be done to prevent this?
3. How should lithium toxicity be managed?

## CASE 3 - ANSWERS

1. Nausea, vomiting and tremor are some of the symptoms of lithium toxicity. Other symptoms include diarrhoea, drowsiness, unsteady gait, muscle weakness, slurred speech and dizziness. The second level of 0.97 mmol/l, although perhaps not "toxic", was markedly higher than the previous level of 0.72 mmol/l, and

could be a sign of impending toxicity. Mrs C is also vomiting, and is likely to become dehydrated, which will exacerbate the risk of lithium toxicity.

2. The main priority is to stop lithium treatment until further investigations are done to determine the possible cause. Mrs C's physical problems are likely to at least contribute to the nausea and vomiting, and the lithium was stopped while this was investigated. She was also advised to take plenty of fluids.

3. Lithium toxicity may be severe and life-threatening. Acute renal failure or permanent neurological damage can occur, and may lead to death. Although lithium toxicity can occur as a result of an acute overdose, more commonly it develops insidiously. Precipitating factors such as febrile illness or drug interactions should be identified and corrected.

In an acute overdose, gastric lavage or emesis should be used to remove any lithium remaining in the stomach. In all cases of toxicity, the lithium level should be measured to determine the extent of poisoning (lithium levels are usually greater then 1.5-2 mmol/l), and lithium should be stopped.

Treatment of insidious lithium toxicity is essentially supportive, the aim being to maintain fluids and electrolytes while reducing the serum lithium level. In mild to moderate toxicity (1.5-2 mmol/l), forced or saline diuresis may be used, where 1 to 2 litres of isotonic saline are infused over 6 hours. This is most beneficial in patients with volume depletion.

Severe intoxication (3-4 mmol/l and above) is treated with dialysis. Peritoneal dialysis may be used but is not very efficient. Haemodialysis is the treatment of choice, as it is very effective in removing lithium from the blood. However, repeated dialyses may be necessary as lithium redistributes from the tissues into the blood.

CASE 4

One of the patients started on lithium at the lithium clinic (a 35 year old male) kept a record of his mood swings for several months. The change in mood when lithium was started is shown in Figure 3.8.1. He found the depressive episodes easy to quantify as he knew he was "at the bottom", but was unable to assess the manic episodes accurately as he lost all perspective during these periods.

Often while treating a patient it is easy to concentrate on the serum lithium level, but it is more important to the patients to see an improvement in their mental state. It was also very interesting for the clinic staff to see such a graphic illustration of the mood swings of manic-depression being controlled by lithium.

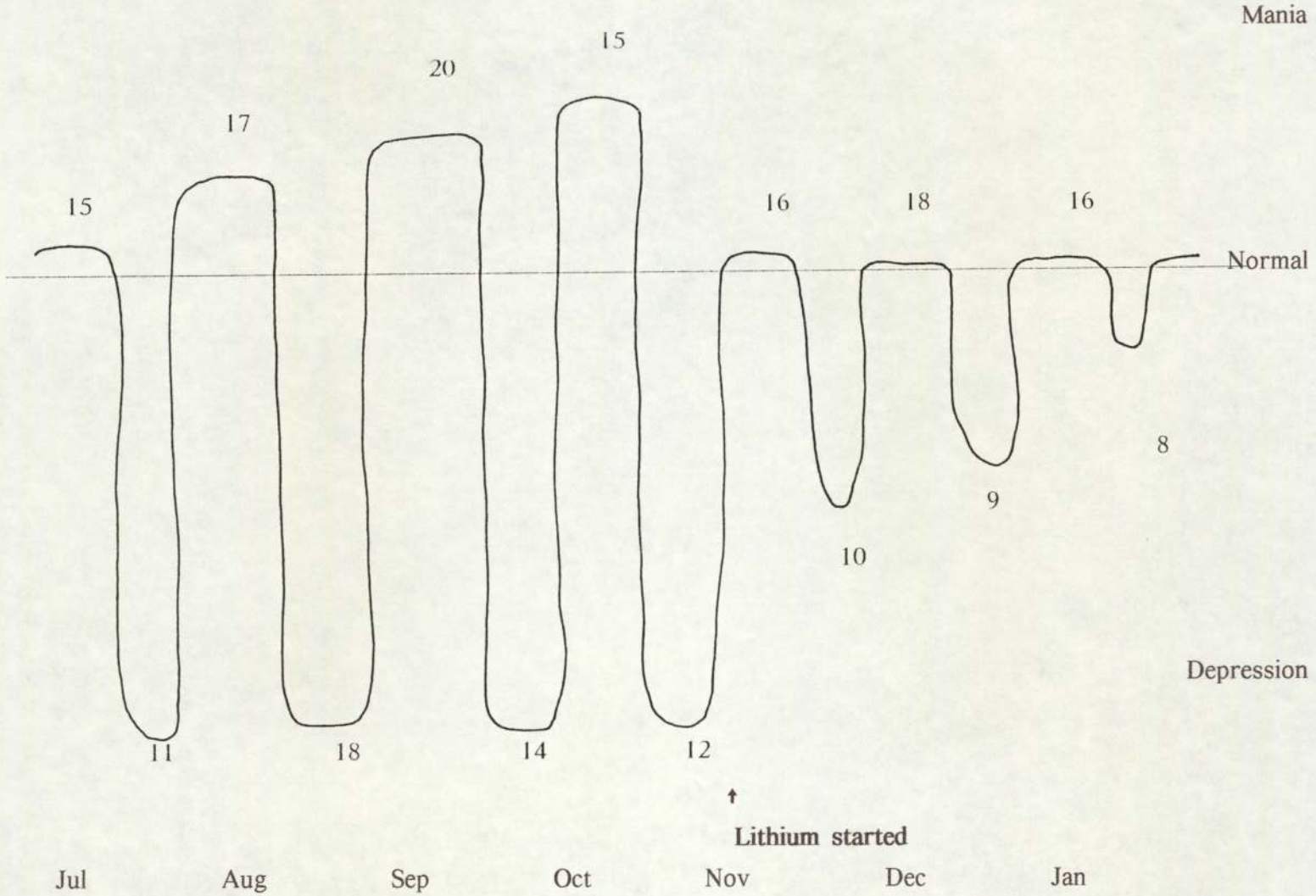



**Figure 3.8.1** A graph charting the moods of a lithium clinic patient over several months, showing the improvement in mood when lithium was introduced. The scale of mood swings is the patient's own assessment.

# 4. DISCUSSION

## 4.1 INITIAL KNOWLEDGE

The results of the first questionnaire clearly show that most of the patients were very poorly informed about their lithium therapy. Of particular concern was the lack of awareness of the signs of lithium toxicity, the importance of maintaining sodium and water balance, and the potential for drug interactions. The handful of patients who were knowledgeable about lithium appeared to be so because they had taken the trouble to find out the information for themselves, rather than relying on passively accepting any information given to them.

There are several possible reasons why patients' knowledge is so poor:

I The information was given to them when they were too ill to recall it. Patients may have been told about lithium during the acute stages of their illness, when they would not have been receptive to the information, and it may not have been repeated when they were better.

II The information may have been aimed at too high a level, with less intelligent patients not being able to understand, and thus retain, the information. Any information given should be matched to the educational level of the patient as closely as possible.

III The information may not have been given in any great detail.

It is difficult to assess how far these possibilities may be true, because the answers to the questionnaire rely totally on the subjective view of the patients. It is likely that a combination of all three reasons is responsible.

What is apparent, however, is that the previous system failed to inform patients about their lithium therapy. Patient counselling by the pharmacist in the lithium clinic was aimed at improving this situation. By using the questionnaire format as a guide, each patient was counselled on the important aspects of lithium treatment. The effectiveness of this counselling was assessed in the second questionnaire.

### 4.2 CHANGE IN KNOWLEDGE

The results of the second questionnaire show conclusively that the patients had improved their knowledge and understanding of lithium therapy during the intervening period. This was not because the patients had been taking lithium for a longer period by the time the second questionnaire was used, as most of the patients had already been taking lithium for a number of years before attending the clinic. The major influence on this improvement was patient counselling by the pharmacist. Many of the patients questioned commented on how useful it was to go through the questionnaire and discuss some points which they had not previously considered. Attending the lithium clinic itself was probably also a major factor in the increased awareness of precautions with lithium, as patients were constantly reminded of the important facts during the informal discussions at each visit.

### 4.3 PATIENT SATISFACTION

The answers given to the remainder of the second questionnaire shows that most of the patients were satisfied with the quality of care that they received from the lithium clinic. Some problems were highlighted, such as the location of the clinic, problems with buses and car-parking, the effect of seeing the ECT equipment on some patients, not having fixed appointment times (although this was seen as an advantage by most patients), and the size of the waiting room. Most of these problems were beyond the control of the clinic. The waiting room could get very full on occasions, particularly

when patients brought their husbands or wives with them, as was often the case. It may be possible in the future to address some of these problems, as a new ECT suite and psychiatric department were being planned at the City General Hospital.

The main advantages of the clinic as perceived by the patients were its friendly atmosphere, not being treated as "psychiatric patients", meeting other patients, and being able to have their questions about lithium answered. These comments were particularly pleasing as they were made when the pharmacist asked whether any improvements could be made to the clinic, so they were largely unsolicited remarks.

### 4.4 LITHIUM MONITORING

The rate of measurement of lithium levels was much greater in the lithium clinic than in the out-patient clinic, and was greater than the accepted rate of once every twelve weeks. As previously mentioned, some rates were higher because the consultant responsible for those patients requested that they should be monitored every eight weeks. This did present some problems to the running of the clinic, because of inconsistencies between different consultants, but later on the monitoring interval was increased to ten weeks which alleviated the problem to some extent.

More of the lithium results were in the therapeutic range in the lithium clinic than in the out-patient clinic. There were far fewer results which were either very high or very low in the lithium clinic, possibly due to increased compliance because of increased counselling, and a greater awareness of the signs of lithium toxicity. There was still a substantial proportion of the results which were outside the range of 0.5 to 0.8 mmol/l, which emphasises the difficulty of a "therapeutic range". Some of the patients had been on lithium for several years, with levels maintained around 0.9 to 1.0 mmol/l, but were unwilling to have their dose of lithium reduced because of the fear of relapse. These patients were reminded of the signs of lithium toxicity, and

kept on their usual doses. One was so adamant that she did not want her dose reduced that, having had her dose reduced from 1400mg daily to 1200mg daily after a lithium level of 1.13 mmol/l, she promptly increased the dose herself back up to 1400mg daily.

The lithium clinic measured lithium levels more frequently and maintained the levels within the therapeutic range to a greater extent than the out-patient clinic. This is mainly due to the lithium clinic being primarily concerned with lithium monitoring, rather than the different priorities of an out-patient clinic, where the consultant will see many different types of patients with different diagnoses during one clinic session. Because patients are seen regularly by the same staff in the lithium clinic, it is much easier to realise when patients have not attended for some time, and then to contact them and encourage their attendance.

### 4.5 RENAL AND THYROID FUNCTION TESTS

As with lithium levels, the lithium clinic measured renal and thyroid function tests more regularly than the out-patient clinic. By having all the results filed in chronological order in the lithium clinic notes (which was not a common occurrence in the medical notes which were reviewed), it was easy for the clinic doctor to check the previous results and to observe any trends in the results (e.g. progressively worsening renal function).

There was some inconsistency when the clinic was started, as some consultants requested yearly tests whereas others asked for six-monthly tests. After about a year it was decided that all patients should be monitored every six months. This highlights the need to agree on standards for running a lithium clinic, when there are no widely accepted guidelines. Experience of running the clinic enabled the staff to set their own standards for the monitoring of renal and thyroid function.

## 4.6 NEW LITHIUM PATIENTS

The therapeutic range was reached very quickly in patients started on lithium at the lithium clinic, with very few dose changes required. This was in contrast to some of the patients started on lithium as hospital in-patients or in the out-patient clinic. Although this was a small sample, however it is apparent that the method used by the lithium clinic to predict maintenance doses was successful. One patient required a slight decrease in dose and another required a slight increase, but the other seven remained on their initial dose.

## 4.7 CONSULTANTS' OPINIONS

The results obtained during this study show that the lithium clinic monitored lithium therapy effectively, and that patients appreciated the service. Another important consideration is the opinions of the other major customers of the lithium clinic: the consultant psychiatrists responsible for the patients who were referred to the lithium clinic. No formal questionnaire was used to find out the consultants' opinions, but valuable responses were obtained from them as the lithium clinic progressed.

At the beginning of the clinic, the patients of four consultant psychiatrists were accepted. It took about 18 months for all these patients to be seen at the clinic, including new referrals and patients to be started on lithium by the clinic. As the clinic became ready to receive the patients of other consultants, the "zoning" scheme was introduced in North Staffordshire. Previously, patients were referred to a particular consultant depending on the special interests of the psychiatrists, but under the "zoning" scheme, each consultant was responsible for the patients living in a particular postal area of North Staffordshire. As a result of this, many of the patients attending the lithium clinic had their consultant psychiatrist changed.

Unless the new consultant requested otherwise, all these patients still attended the lithium clinic, in order that some continuity of care was provided. Several of the patients had been under the care of the same consultant psychiatrist for many years, and they found it upsetting to have to change consultants. The lithium clinic alleviated this to a certain extent, and also accepted patients who had been transferred to the care of the original four consultants. Because of this, the number of patients attending the clinic had increased to such a level that it was difficult to accept new patients without compromising the time and attention that could be given to individual patients.

In February 1993 discussions were taking place about increasing the number of clinic sessions to twice a week, and one of the consultants had expressed an interest in a satellite lithium clinic, held at local health centres for patients who found the travelling to Stoke-on-Trent difficult.

The consultant psychiatrists were very supportive of the lithium clinic. They still saw their patients, but now every six months instead of every three months, which eased their workload. Also because the lithium clinic took care of the routine of lithium monitoring, they found that they were able to concentrate more on other aspects, such as the mental state of the patient.

The consultants knew that they would be contacted if there were any problems with their patients, and that they would be consulted about any changes to the treatment, and the patient's GP would also be notified. The amount of information which the consultants wanted from the clinic varied greatly: one consultant wanted copies of all the lithium, thyroid and renal function results, while another only wanted to be notified if the lithium level went too high.

All the consultants appreciated the simplicity of the records kept at the clinic. The test results were filed in chronological order, with brief notes written at each visit. Any results which had not been returned to the clinic would be checked by telephoning the pathology laboratory. The lithium clinic notes were a complete but concise record of each patient's progress, and were kept at the clinic so were easily accessible to consultants during the clinic session.

One of the most important factors to the consultants was the standard of care which their patients received: all four consultants had heard good reports about the lithium clinic from their patients, and were very complimentary about the service.

Recently, funding has been made available by the Mental Health directorate for the lithium clinic to continue running permanently, underlining the commitment of the psychiatric service to the clinic.

# 5. CONCLUSION

## 5.1 THE LITHIUM CLINIC NOW

This study shows that the lithium clinic set up in North Staffordshire has been successful in improving the monitoring of lithium therapy of its ninety patients. Serum lithium levels are measured more frequently by the lithium clinic, but because of the efficient use of the therapeutic drug monitoring service, all the results obtained are meaningful and can be acted upon if necessary.

Renal and thyroid function tests, which are necessary to monitor the effects of long-term lithium therapy, are monitored regularly. All the results are kept together and are easily accessible, so that any trends in these results are noticed.

The extent of patients' knowledge and understanding of lithium therapy has greatly improved as a result of attending the lithium clinic, leading to increased awareness of the benefits and drawbacks of lithium. All patients have been counselled on lithium so that they can derive the most benefit from their treatment. The patients have also expressed their satisfaction with the lithium clinic in general.

Concurrent drug therapy is monitored, to minimise the dangers of potential drug interactions. Patients are encouraged to telephone the clinic between visits if they have any problems, and advice is given if patients are ill. Relatives are also actively involved as one of the aims of the clinic is to provide a support service for both patients and relatives.

Consultant psychiatrists are informed of the progress of their patients, and training is provided for junior doctors, student nurses and any other health care professionals visiting the clinic.

The number of patients attending the lithium clinic, including constant new referrals, has exceeded all expectations. The clinic is a victim of its own success, in that the demand may soon exceed the capacity of the clinic to accept new patients.

## 5.2 THE PHARMACIST IN THE LITHIUM CLINIC

The initial aim of this study was to assess the benefits of including a pharmacist in the lithium clinic team. It has been shown that pharmacists have a rôle in other out-patient clinics such as the anticoagulant clinic, jointly managed by pharmacists and physicians, which has been running very successfully in North Staffordshire since 1979 [104]. Here patients are counselled, the dosage of warfarin is adjusted, and warfarin tablets are supplied by the pharmacist.

It is difficult to prove conclusively that the pharmacist has a beneficial effect on patient care in addition to the advantages of the lithium clinic itself, as the pharmacist in this study was an integral part of the lithium clinic even before it started. To prove the hypothesis, it would be necessary to have a lithium clinic without pharmacist involvement running alongside to act as a control clinic. However, some important conclusions can be drawn from this study. The dramatic improvement in patients' knowledge can be attributed mainly to patient counselling by the pharmacist. Added to this was the knowledge that all patients attending the lithium clinic had been counselled to the same standard, and that even if patients could not recall the advice given, they could refer to their information cards or telephone the lithium clinic for more advice. The pharmacist also contributed to the lithium clinic the knowledge of drug and disease interactions, exhibited by changing potentially interacting drugs for safer ones, and advising patients on the course of action to take during concurrent illness. The pharmacist exhibited pharmacokinetic expertise in advising on changes in dose or preparations of lithium, and especially when starting new patients on lithium.

All three members of the lithium clinic staff (doctor, nurse and pharmacist) worked very well together, with each member appreciating and respecting the others' capabilities. It would be very difficult to assess each person's contribution to the lithium clinic, as it is very much a team effort.

**In conclusion, the lithium clinic provides a lithium monitoring service which is superior to the out-patient clinic, both quantitatively and qualitatively. The inclusion of a pharmacist in the lithium team provides additional benefits in the monitoring of drug and disease interactions, the use of the therapeutic drug monitoring service, and most importantly, in patient counselling.**

## 5.3 THE LITHIUM CLINIC IN THE FUTURE

The multidisciplinary lithium clinic in North Staffordshire has been running since February 1990, and has become an established part of the psychiatric services in the area. There are several potential areas for development:

I To improve on the standard of patient counselling already provided, a booklet could be designed specifically for the lithium clinic, providing a concise written information source to supplement the verbal advice given in the clinic.

II The telephone "helpline" could be improved by extending the time for which it is available

III Information collected in the computer database could be analysed at a future date to provide demographic data on patients taking lithium in North Staffordshire.

Ⅳ Training could be increased to include all staff likely to visit and use the clinic, including doctors, nurses and pharmacists, and open days could be organised for general practitioners, community psychiatric nurses, community pharmacists and other health care professionals.

Ⅴ More research could be carried out, e.g. to assess the knowledge and understanding of patients started on lithium at the lithium clinic.

Ⅵ Meetings could be organised for patients and their relatives, e.g. videos on lithium, talks by dietitians and organisations such as MIND.

Ⅶ More clinic sessions could be organised, including satellite lithium clinics at outlying health centres, to cope with the increased demands from patients and psychiatrists.

Ⅷ Communication with community pharmacists could be implemented, encompassing the concept of 'seamless care', and providing a means by which community pharmacists could update the medication records of their patients who were taking lithium.

**Finally, the overriding conclusion which can be drawn from this study is that the multidisciplinary lithium clinic shows that pharmacists can work in an out-patient setting on an equal standing with doctors and nurses, with each professional contributing their own skills to the clinic.**

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# APPENDIX I

## LITHIUM CLINIC PATIENT REFERRAL FORM

| Surname | Christian name | Unit no | DOB | Sex | Consultant |
|---|---|---|---|---|---|
| Address<br>Postcode | | | | | |
| GP | | | | | |
| Referral for | Initiation of treatment □ | | Monitoring □ | | tick box |
| Present medication<br>Drug | Dose | Frequency | Period | | |
| Diagnostic code ICD9 | | | | | |
| Clinical summary | | | | | |
| Medical history | | | | | |
| Consultant directions on lithium therapy<br>Lithium range 0.5 to 0.8 mmol/l or to (please specify)<br>Thyroid/renal review period 6/12 12/12 | | | | | |
| Date referred | Consultant signature | | | | |

# APPENDIX II

## PHARMACOKINETIC METHOD OF PREDICTING MAINTENANCE LITHIUM DOSE

(Modified from R.W. Fitzpatrick and R.B. Bye [103])

A single dose of lithium carbonate 16mg/kg body weight is administered, then the resulting serum lithium level is measured 24 hours later. This result is substituted into the following equation :

$$\text{Maintenance dose} = \frac{C_{p\ des} \times K_e \times T \times D \times e^{-K_e t}}{C_{p\ stat}}$$

where $C_{p\ des}$ = desired maintenance concentration

$K_e$ = elimination rate constant (population estimate)

T = maintenance dose interval

D = single initial dose

t = time single dose level drawn

$C_{p\ stat}$ = concentration after single dose

As the half-life of lithium varies greatly between patients, four average values for $K_e$ are substituted into the equation representing $t_{1/2}$ of 8, 15, 20 and 24 hours.

where $$K_e = \frac{0.693}{t_{1/2}}$$

Values for $K_e$ = 0.087, 0.046, 0.035 and 0.029 $hr^{-1}$ respectively.

The most practical dose in the median of the range is chosen, initiated, and the 12-hour standard serum lithium level is measured one week later. Doses are adjusted where necessary, until the level is within the desired therapeutic range. The relationship between maintenance dose and steady state serum lithium concentration is linear, i.e. doubling the dose will double the concentration.

## LITHIUM CLINIC - INITIATION OF LITHIUM THERAPY

Name Unit no Consultant DOB

Weight = kg

Desired therapeutic range = to mmol/l.....($C_p$ des)

Test dose = 16mg/kg body weight

= 16 x

= mg

Test dose chosen = mg.....(D)

Test dose given at = on

Blood sample drawn at = on

Time interval = hours.....(t)

Lithium level = mmol/l.....($C_p$ stat)

$$\text{Maintenance dose} = \frac{C_p \text{ des} \times K_e \times T \times D \times e^{-K_e t}}{C_p \text{ stat}}$$

Values for $K_e$ = 0.087, 0.046, 0.035 & 0.029 $hr^{-1}$

T = maintenance dose interval = 24 hours

Calculated maintenance doses for $C_p$ des of mmol/l

$K_e$ = 0.087 $hr^{-1}$ ($t_{1/2}$ = 8 hr) Dose = mg

$K_e$ = 0.046 $hr^{-1}$ ($t_{1/2}$ = 15 hr) Dose = mg

$K_e$ = 0.035 $hr^{-1}$ ($t_{1/2}$ = 20 hr) Dose = mg

$K_e$ = 0.029 $hr^{-1}$ ($t_{1/2}$ = 24 hr) Dose = mg

$K_e$ = $hr^{-1}$ ($t_{1/2}$ = ) Dose = mg

Maintenance dose = mg

Started at = on

# APPENDIX III

A representation of the modified RPSGB lithium information card which was given to all patients attending the lithium clinic.

**How should I take the tablets?**
Swallow each tablet whole or broken in half,with water.Do NOT chew or crush it.Try to take the dose at the same time each day.

**What should I do if I miss a dose?**
Do NOT double your next dose.If you find you have missed a few doses,start taking your usual dose on the day you remember and tell your doctor.

**Why must I have a blood test?**
This is to check the amount of lithium in your blood.It is very important to have the correct amount because too much can be dangerous.Take the blood test ABOUT 12 HOURS AFTER the last dose of lithium.

**Can I drink alcohol?**
It is safe to drink SMALL quantities.

**Can I take other medicines with lithium?**
Some medicines can change the amount of lithium in the blood. These include diuretic (water) tablets and capsules,some pain killers and some indigestion mixtures and laxatives.So check with your doctor or pharmacist before taking other medicines. Please note: It is safe to take aspirin and paracetamol but not ibuprofen.

**What else alters the lithium level?**
The level can be altered by the amount of fluids you drink, changes in the amount of salt in your food,sweating more than usual (in hot weather,fever or infection),severe vomiting,severe diarrhoea and a low salt diet. Check with your doctor if any of these things happen.

**Signs of a high lithium level**
Vomiting,severe diarrhoea,unusual drowsiness,muscle weakness and feeling very giddy may mean that your level of lithium is too high.Stop taking the tablets and talk to your doctor IMMEDIATELY.

**Does lithium have side effects?**
Some slight effects (such as sickness, shaking) may occur at first but they usually wear off if blood tests are normal.Discuss this with your doctor. Some patients may gain weight but this can be prevented with a sensible diet.

**How long will I have to take lithium?**
Lithium is a way of preventing illness so you may have to take it for many years.Never stop taking the tablets without asking your doctor.

**Thinking about starting a family?**
Because lithium can affect the unborn baby do NOT become pregnant without first talking to your doctor.If you are pregnant tell your doctor now.

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**KEEP YOUR TABLETS IN A SAFE PLACE WELL OUT OF THE REACH OF CHILDREN.**

*Lithium Clinic*
City General Hospital
Tel. (0782) 718834
Consultant:
*Tuesdays 9 - 12*

| Next visit | Current dose | Time of dose |
|---|---|---|
| | | |

## LITHIUM TREATMENT CARD

CARRY THIS CARD WITH YOU AT ALL TIMES. SHOW IT TO ANY DOCTOR OR NURSE WHO TREATS YOU AND ANY PHARMACIST YOU BUY MEDICINES FROM.

NAME.....

PREPARATION
OF LITHIUM.....

Should a different proprietary product be prescribed,the card must be suitably endorsed.

# APPENDIX Ⅳ

## LITHIUM CLINIC - SUMMARY OF MEDICAL RECORDS

Name Unit no Consultant Date

| |
|---|
| Family/social history<br><br>Occupation |
| Past psychiatric history |
| Past medical history |
| Diagnosis |

| Thyroid function tests | | | Renal function tests | | |
|---|---|---|---|---|---|
| Date | Test | Result | Date | Test | Result |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

Lithium therapy

| Date | Serum Li | Date | Serum Li | Date | Serum Li |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

Drug history

| Date | Drug | Dose | Date | Drug | Dose |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

Abnormal U & E results

| Date | Test | Result | Normal range |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

# APPENDIX V

## LITHIUM CLINIC - INITIAL INTERVIEW QUESTIONNAIRE

Patients were interviewed using the following questions as a guide. The atmosphere was kept as informal as possible, and patients were told that this was not a test, merely a way of seeing what they already knew, and to find out whether there was anything else they would like to know about lithium.

1. When did you start taking lithium?
2. Why are you taking lithium?
3. Which brand of lithium tablet are you taking?
4. How much lithium are you taking?
5. Has anyone talked to you about lithium?
6. Have you had any leaflets on lithium?
7. Have you experienced any side-effects with lithium?
8. Is there a particular way to take the lithium tablets?
9. Have you ever missed any doses, and what did you do then?
10. Why do you need blood tests while taking lithium?
11. Do you know of anything that can alter the amount of lithium in the body?
12. Are there any medicines you should avoid when taking lithium?
13. Is it safe to drink alcohol with lithium?
14. Do you know of any of the the symptoms to look out for when the lithium level gets too high?
15. Are there any special diets to follow when taking lithium?
16. Are you taking any other medicines?

LITHIUM CLINIC - INITIAL INTERVIEW QUESTIONNAIRE

INITIAL COUNSELLING INFORMATION

The following were the basis of the verbal answers given to patients when they did not know the answers to the questions in the initial interview questionnaire. The aim was to keep the advice consistent and easily understandable.

**How to take tablets**

Take at the same time each day. Swallow whole with a glass of water or a cool drink. Tablets can be broken in half, but should not be crushed or chewed.

**Missed doses**

If you take lithium once a day, and you remember within three hours of the time you normally take the dose, then it is safe to take a dose. If you remember more than three hours late, then take your normal dose at the usual time on the next day. If you take lithium in two or three doses during the day, then take your next dose at the usual time. Do not double the dose. If you have missed a few doses, start taking the usual dose when you remember, and tell the clinic on your next visit.

**Reason for blood tests**

Blood tests are used to check the amount of lithium in the blood. If the level gets too high this can lead to side-effects, and if it is too low then the lithium may not be effective. The level giving the best result varies from one patient to another. The blood sample is taken 12 hours after the evening dose of lithium.

**Factors affecting the lithium level**

Too little salt or water in the body will increase the lithium level which can be dangerous. This can occur when sweating too much, if you have flu, or with severe

sickness and diarrhoea. Too much salt can reduce the lithium level, making it ineffective.

### Medicines to avoid

Some medicines such as diuretics (water tablets) and some pain killers can increase the level of lithium in the blood. Check with the clinic, GP or pharmacist before taking any other medicines, including ones you have bought without prescription. It is safe to take aspirin or paracetamol, but not ibuprofen. Some indigestion remedies can reduce the lithium level if they contain too much salt.

### Alcohol with lithium

It is safe to drink alcohol in small amounts e.g. 1 or 2 pints of beer (less for women). Do not drink to excess as this may cause dehydration which could lead to lithium poisoning.

### Signs of lithium toxicity

Some of the signs are: blurred vision, drowsiness, sluggishness, diarrhoea and vomiting, unsteadiness, difficulty in speaking, and severe tremor of the hands and lower jaw. If you get any of these symptoms, stop taking the lithium tablets and contact the clinic to arrange a blood test as soon as possible.

### Dietary precautions

There are no special diets to follow, but it is important not to vary the amount of salt in your diet by too much, or the amount of fluid. Always drink if you feel thirsty, and try to keep your diet consistent.

## LITHIUM CLINIC - INITIAL INTERVIEW QUESTIONNAIRE

Name Unit no Consultant Date

| Question | Answer |
|---|---|
| Lithium treatment started | years months |
| Reason for lithium therapy | □ MD □ D □ Other □ ? |
| Lithium preparation | □ Priadel □ Camcolit □ ? |
| Dose and frequency | |
| Verbal information | □ Doctor □ Pharm □ Nurse □ Other □ None |
| Written information | □ Doctor □ Pharm □ Nurse □ Other □ None |
| Side-effects | □ Ur □ Trem □ Diarr □ Wt □Thir □ Other □ None |
| How to take tablets | □ Whole □ Water □ Time □ ? |
| Missed doses | □ Not double □ Next dose □ ? |
| Reason for blood tests | □ Check level □ ? |
| Factors affecting Li level | □ Drugs □ Alcohol □ Water □ ? |
| Medicines to avoid | □ Diuretics □ NSAIDs □ Other □ ? |
| Alcohol with lithium | □ Avoid □ Small □ OK □ ? |
| Signs of lithium toxicity | □ Trem □ Vis □ Dizz □ N&V □ Diarr □ Conf □ ? |
| Dietary precautions | □ None □ Na/$H_2O$ balance □ ? |
| Concurrent medication | |

# APPENDIX VI

## LITHIUM CLINIC - SECOND INTERVIEW QUESTIONNAIRE

Patients were questioned for a second time using the following questions as a guide. They were told that they would first be asked some of the questions that they had been asked previously, then some questions on their opinion of the clinic. They were asked to be as honest as possible, so that we could see what improvements we could make.

1. What can change the amount of lithium in the blood?
2. Are there any medicines you should avoid when taking lithium?
3. What are the signs when the lithium level gets too high?
4. Is the place where the clinic is held convenient?
5. Is the time of the clinic convenient?
6. How do you find the surroundings of the clinic?
7. Do you find the ECT equipment disturbing in any way?
8. Is the length of time you have to wait acceptable?
9. Have you telephoned the clinic?
10. Do you refer to the information on the appointment card?
11. Would you like more information than is contained on the card?
12. Do you feel you have learned anything about lithium since coming to the clinic?
13. How would you describe the attitude of the staff?
14. How would you describe the general atmosphere of the clinic?
15. What is the job of the different staff in the clinic?
16. Do you have any suggestions on ways to improve the clinic?

## LITHIUM CLINIC – SECOND INTERVIEW QUESTIONNAIRE

Name Unit no Consultant Date

| | |
|---|---|
| Change in Li level | □ Drugs □ $Na/H_2O$ □ Alcohol □ ? |
| Medicines to avoid | □ NSAIDs □ Diuretics □ ? |
| Signs of Li toxicity | □ Drowsiness □ Nausea □ Vomiting<br>□ Diarrhoea □ Dizziness □ Tremor □ ? |
| Place convenient | □ Yes □ No Prefer: |
| Time convenient | □ Yes □ No Prefer: |
| Surroundings | |
| ECT equipment OK | □ Yes □ No |
| Waiting time OK | □ Yes □ No |
| Telephoned clinic | □ Yes: □ No |
| Information used | □ Yes: □ No |
| Further information | □ Yes: □ No |
| Learned about Li | □ Yes □ No |
| Attitude of staff | |
| Atmosphere of clinic | |
| Clinic staff | Doctor |
| | Nurse |
| | Pharmacist |
| Improvements | |