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From initial prescribing to long-term management: what is the role of lithium monitoring?

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Abstract

Lithium is currently licensed for the treatment and prophylaxis of recurrent affective disorders, treatment of bipolar depression where the use of antidepressants has been ineffective, and the treatment of aggressive or self-mutilating behaviour. Lithium requires therapeutic drug monitoring (TDM) during treatment and evidence is lacking to support the recommended monitoring frequencies of lithium levels. A retrospective analysis of a monitoring database was run to establish the association of single and double exposures of various lithium levels on renal function. Interviews were also conducted with prescribers to establish the factors affecting prescribing decisions related to lithium.

This study suggests there is a short-term negative association on renal function after exposures to single, high lithium levels but due to the small patient groups in the multiple exposures analysis the results from this are not statistically reliable. These results did, however, raise the considerations that changes in lithium levels may impact on renal function.

This work added to the factors influencing prescribing decisions surrounding knowledge, learning and competence of prescribers with concerns around a lack of knowledge of older drugs seen in newer doctors. Guidance surrounding at what points during the patient's journey the initial prescribing choice and a decision should be made is also needed. This would help overcome the barrier of split services within mental health and give clearer roles to the various consultants involved in a patient's care and aid in the involvement of the patient with their treatment.

The roll out of a centralised lithium monitoring system with access for all those involved in the patients care could be considered to aid in the long-term monitoring of lithium. . This sort of system would also allow for all those involved being able to retain oversight over patients whether or not they are still directly under their care.

Contents

List of figures

List of tables

List of Appendices

Glossary

5HT	Serotonin
^{51}Cr-EDTA	^{51}Cr-EDTA = chromium-51 labeled ethylenediamine tetraacetic acid
AA	Arachidonic acid
AAS	Atomic absorption spectrophotometry
ACE inhibitor	Angiotensin-converting-enzyme inhibitor
AMI	Affective morbidity index
AMPT	A-methyl-p-tyrosine
AQP2	Aquaporin-2
ATPase	Adenosinetriphosphatase
BAP	British Association for Psychopharmacology
Bcl-2	B-cell lymphoma/leukaemia 2-gene
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
cAMP	Cyclic adenosine 3',5'-monophosphate
CCG	Clinical Commissioning Group
CKD	Chronic Kidney disease
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CrCl	Creatinine clearance
DSM	Diagnostic and Statistical Manual of Mental Disorders:
eGFR	Estimated glomerular filtration rate
EPAC	Exchange protein activated by cAMP
FDA	Food and Drug Administration
FES	Flame emission spectroscopy
FSGS	Focal global and segmental glomerulosclerosis
GABA	Gamma-aminobutyric-acid
GFR	Glomerular filtration rate
GP	General Practitioner
GSK3β	Glycogen synthase kinase-3, β-isoform
GTP	Guanine triphosphate

ICD	International Classification of Diseases
IMPase	Inositol monophosphatase
Li-ISE	Lithium-ion selective electrode technology
MDRD	Modification of Diet in Renal Disease
mRNA	Messenger ribonucleic acid
NAA	N-acetyl-aspartate
NDI	Nephrogenic diabetes insipidus
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMDA	N-methyl-D-aspartate
NNUH	Norfolk and Norwich University Hospital
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
NSAID	Non-steroidal anti-inflammatory drug
NSFT	Norfolk and Suffolk NHS Foundation Trust
NTR	Narrow therapeutic range
PCT	Primary Care Trust
PKC	Protein kinase C
PLA_2	Phospholipase-A_2
POMH-UK	Prescribing Observatory for Mental Health UK
Primary researcher	PhD student
QIP	Quality Improvement Programme
QOF	Quality and Outcomes Framework
REC	Research Ethics Committee
RPsychCCQI	Royal College of Psychiatrists College Centre for Quality Improvement
SIGN	Scottish Intercollegiate Guidelines Network
T4	Thyroxine
TDM	Therapeutic Drug Monitoring
TSH	Thyroid Stimulating hormone
UMax	Urinary concentrating ability
WMD	Weighted mean difference

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Chapter One

1: Introduction to lithium

1.1 General introduction

Lithium was initially discovered in the 5th century AD but it did not become routinely used in the field of medicine until 1847, when it was used to treat gout. It had no role in psychiatry until the late 1800s (Clouston, 1892). During this time clinical trials were not performed in the controlled manner as expected today, but small cohort studies were conducted by independent physicians in the various hospitals at which they worked. Since the 1800s there have been more clinical studies performed which have led to several theories about lithium's mode of action (Marmol, 2008).

Lithium is currently licensed for the treatment of mania and hypomania, treatment and prophylaxis of recurrent affective disorders, treatment of bipolar depression where the use of antidepressants has been ineffective, and for the control of aggressive or self-mutilating behaviour (Norgine, 2011, Rosemont, 2011, Sanofi-Aventis, 2012). The National Centre for Health and Care Excellence (NICE) guidelines do not recommend the use of lithium in mania or hypomania as an acute treatment and the manufacturers also state that treatment with lithium should be focussed on stabilising bipolar disorder rather than used to establish control of acute episodes (Norgine, 2011, Rosemont, 2011, Sanofi-Aventis, 2012, NICE, 2014a).

Lithium also requires therapeutic drug monitoring (TDM) during treatment. TDM is used to prevent toxicity from high blood levels, and to ensure that the therapeutic level is maintained above the minimum effective level for the drug. Lithium is initially prescribed at a set dose depending on the condition being treated and the age of the patient, and

then this dose is adjusted over the first week of treatment to achieve a serum-lithium concentration of generally between 0.4-1.0mmol/L (Joint Formulary Committee, 2015). The potential for side effects and toxicity from lithium increases at higher blood levels and it is not thought to hold efficacy at lower levels. There remains a level of uncertainty over the long-term side effects of various lithium levels, specifically on renal function. As lithium is primarily renally excreted this is an area of interest due to the potential for accumulation with a declining renal function (McKnight et al., 2012).

Within Norfolk a county-wide therapeutic drug monitoring database was set up to improve the standards of lithium monitoring throughout the area following several incidents in primary care surrounding lithium therapy and inadequate monitoring (Holmes, 2005). The focus of this research is on the impact of this database on lithium testing rates and the relationship of a range of lithium levels on renal function, in addition to an exploration of doctors' perspectives of lithium and the factors that influence their prescribing practice.

1.2 Discovery and the 1800s

In the 5th century AD a Roman physician recommended the use of alkaline waters to people suffering with mental disorders. The beneficial effect of these waters on their mental state was thought to be due to the lithium content but further investigation was not undertaken at the time (Marmol, 2008). Lithium as an element was discovered by Arfwedson, a student of chemistry, in 1817 while he was analysing petalite ore. What he found was a lithium aluminium tectosilicate mineral which appeared to form similar compounds to those of sodium and potassium (Hu, 2012). Lithium salts however did not become recognised in a clinical capacity until the mid-19th century when they started to be used to treat gout due to lithium's ability to dissolve uric acid (Marmol, 2008). Garrod had used lithium carbonate as an internal remedy since 1847 for reducing the formation of uric acid deposits in patients that he encountered suffering from gout. He noted that in those patients who had been administered lithium carbonate the frequency of gout attacks reduced. Lipoeitz and Garrod demonstrated that lithium carbonate, once boiled with water and added to uric acid, formed the bi-urate of lithium in vitro. This bi-urate of lithium is the same salt formed in the blood and tissues of patients with gout (Garrod, 1859, Clouston, 1892). At this time the terms *'gouty or podagrous insanity or mania'* started to be used to describe a type of mental illness associated with gout which commonly had symptoms including *'irritability, incapacity for mental exertion, and depression'* (Clouston, 1892). It was also noted by Clouston, that in patients suffering from gout, *'deep melancholia is a common accompaniment of the gouty diathesis'*, suggesting that there was another side to the insanity, presenting mainly with irritability and changes in temper (Clouston, 1892).

1.3 Initial use in psychiatry and the recognition of bipolar disorder

In his 1885 treatise, Carl Lange started to formulate the idea of depression and mania existing as a cyclical state, this was 14 years before Kraeplin introduced the concept of *manisch-depressive irresein* (manic-depressive insanity) (Schioldann, 2011, Lange, 1885). Before this there had been unpublished personal views of several students, and lesser known figures in psychiatry at the time on how '*melancholia*' and mania may be related to each other. In 1854 Jules Baillarger coined the term *la floie à double forme,* which was a disease characterised by separate phases of mania and '*melancholic depression'* occurring in regular periods. Two weeks later, as a response to the publication of Baillarger's theory, Jean-Pierre Falret described a similar condition which he claimed to have been discussing for ten years previously under the name *la folie circulaire* citing his publication in 1851 (Jackson, 1986). Such 'periodicity' of mental illness was a concept that had been discussed prior to Lange's publication, but more in terms of separate periods of depression or melancholy and mania, rather than being part of the same illness (Schioldann, 2011). A milder form of a cyclical disorder than the manic depressive illness later described by Lange and Kraeplin was introduced by Kahlbaum in 1882, this included depressive, hypomanic and mixed hypomanic-depressive disorders (Hecker, 2003).

Prior to the late 1800s the existence of a cyclical state combining both mania and depression had not been considered. However since the 2nd century AD both mania and '*melancholia'*, the term used at the time for what would now be considered depression, had been written about in either the same chapters or adjacent chapters in medicinal books as contrasting diseases or conditions. The first accounts which provided significant detail were those by Soranus of Ephesus and Aretaeus of Cappadocia whose descriptions

can clearly be linked to modern day accounts of mania (Pargeter and Jackson, 1792). Both of these authors placed their chapters on '*melancholia'* and mania adjacent to each other demonstrating the belief at the time that the two conditions were somehow linked by their contrast. This connection and alignment of chapters was to become a longstanding tradition until the concept of a cyclical manic/depressed state came into existence and there was a wider understanding of mental illnesses in general (Pargeter and Jackson, 1792). In 1886 Lange theorised, in his study of emotional illnesses, that an excess of uric acid in the body led to what he termed '*periodical depressions'*, linking back to the early 1800s terms of *'gouty or podagrous insanity'* and *'melancholia'* (Lange, 1886). This illness was considered to be separate from the long standing diagnosis of '*melancholia'* since, in many cases of these periodic depressions observed by Lange, the particular delusions seen in melancholic patients never occurred (Schioldann, 2011, Jackson, 1986).

The treatise written by Lange in 1886 was later made available with a fuller title encompassing his idea of the uric acid diathesis (Lange, 1896). This is the theory that uric acid excess led to these depressions, and therefore the breakdown and subsequent elimination of the excess uric acid through treatment with lithium was a logical choice (Schioldann, 2011). However, by the end of the 1800s the theory of excess uric acid and its associations with mania and depression had not been readily accepted by the medical community and in the publication of Emil Kraeplin's milestone textbook of psychiatry in 1899 was dismissed as a theory (Schioldann, 2011).

1.4 The 1900s to present day

Despite the dismissal of the uric acid diathesis by Kraeplin, in the 1930s a number of lithium containing products remained on the market for the control of kidney stones utilising lithium's ability to break down uric acid (Shorter, 2009). There was however virtually no reference to lithium being used in psychiatry in the first half of the 20th century (Shorter, 2009). The interest in the use of lithium for affective disorders started after the 1949 publication by John Cade showing that lithium had a significant effect in a case series of ten manic patients presenting with '*psychotic excitement*' (Cade, 1949). Six months before the publication of Cade's review however, the salt lithium chloride had been introduced to the American public as a substitute to the table salt sodium chloride (Corcoran and Taylor, 1949). This came after the discovery that a sodium-free diet was helpful to patients with a cardiac or hypertensive history (Talbott, 1950). Unfortunately, there were reports of poisonings and deaths after the widespread use of this salt substitute (Noack and Trautner, 1951, Hanlon et al., 1949, Corcoran and Taylor, 1949). Due to this, even though there were positive reports of lithium's effect in affective disorders, it was not speedily taken up by the medical community. However work continued to establish the safe and effective use of lithium for the treatment of affective disorders.

In 1951 Noack and Trautner added to the evidence for the anti-manic effect of lithium as well as initiating the development of indicators for safe lithium levels and initial signs of toxicity (Malhi and Gershon, 2009, Ashburner, 1950, Noack and Trautner, 1951). They saw in their small hospital based trial that only some treated patients experienced side effects or early signs of toxicity and that these emerged within three to four days of treatment

(Noack and Trautner, 1951). These signs of early toxicity included gastric disturbances, motor disturbances, blurred vision and dizziness. This range of symptoms were similar to those previously documented in case reports by Cleaveland, Corcoran and Hanlon who related the similarity of the symptoms described above to those of Addison's disease or sodium depletion (Cleaveland, 1913, Corcoran and Taylor, 1949, Hanlon et al., 1949). That lithium owes its effect, at least in part, to the displacement of sodium in the body was then suggested due to the similarity of the symptoms of toxicity to disorders of sodium dysregulation.

Small trials throughout the 1950s and 1960s established the efficacy of lithium in both the manic and depressed stages of bipolar disorder and by 1972 the evidence was compelling for the use of lithium in affective disorders. The USA became the 50th country to register and license lithium with the Food and Drug Administration (FDA) approving its use for the long-term treatment of bipolar disorder as the lithium carbonate salt in 1980, with approval for lithium citrate following close behind (FDA, 2012 (a), FDA, 2012 (b)). By this time lithium had already been registered for medicinal use elsewhere, including France (1961), UK (1966), Germany (1967) and Italy (1970) (Shorter, 2009). Lithium has since been licensed for the treatment and prophylaxis of mania and hypomania, prophylactic treatment of recurrent affective disorders, treatment of recurrent bipolar depression where the use of alternative antidepressants has been ineffective, and the treatment of aggressive or self-mutilating behaviour (Sanofi-Aventis, 2012, Norgine, 2011, Rosemont, 2011).

Lithium sits currently in the NICE guidelines as the first line option to be offered to people with bipolar disorder as a long-term pharmacological intervention protecting against both

depression and mania as well as reducing the risk of suicide and self-harm (NICE, 2014a, McKnight et al., 2012). If this is not tolerated or not suitable for the patient, including reasons such as they will not agree to routine monitoring, then other options should be considered – currently olanzapine or valproate are suggested. However lithium is the most effective long-term treatment for bipolar disorder (NICE, 2014a). For bipolar depression, although lithium is licensed for this indication, other drugs are suggested as first line pharmacological options by NICE, such as olanzapine or lamotrigine.

As seen in NICE guidelines, anticonvulsants are now also mentioned as alternatives to lithium and are also referred to as mood stabilisers. A systematic review from 2004 noted that the vast majority of the high quality evidence published or reported on lithium and its use in bipolar disorder has been published since 2000, with the inclusion of placebo and lithium arms inn studies. The results from this review support the licensed indications of lithium in that it is shown to be more effective than placebo in preventing relapse, particularly against manic episodes (Geddes et al., 2004).

1.5 Main proposed mechanism(s) of action of lithium as a mood stabiliser

Lithium is a monovalent cation and shares many physico-chemical properties with other alkaline metals, including sodium and potassium, and it is handled in a similar way in the body to these other metals (Amari et al., 1999). These similarities to other commonly found bodily metals is, in part, why it has been so difficult to ascertain the key mechanism(s) of action when used as a mood stabiliser (Taylor, 2012, Mitchell, 2000). There are several main areas of interest for the mechanism of action of lithium, however the exact mechanisms by which lithium exerts its therapeutic effects are not completely understood (Marmol, 2008, Malhi et al., 2013, Brown and Tracy, 2013).

1.5.1 The ionic mechanism

Within the body all tissues retain a sodium electrochemical gradient which is needed for the transportation functions of electrolytes and ions as well as being key to cell excitation. Before lithium became well established in psychiatry clinicians had noted that there were alterations in the intracellular sodium levels of psychiatric patients. Shaw reported that in patients suffering from affective disorders there appeared to be higher intracellular sodium levels in both manic and depressed states with lower potassium levels in depressed states (Shaw, 1966). An altered response by lymphocytes has also been shown in patients suffering from bipolar disorder. In healthy subjects lymphocytes exposed to lithium showed an increase in Na^+, K^+-A Adenosinetriphosphatase (ATPase) molecules. This response was not mimicked in currently euthymic patients with bipolar disorder either taking lithium or on no medications (Wood et al., 1991, Wood and Goodwin, 1987).

Studies throughout the 1970s to 1990s investigated Na^+, K^+-ATPase activity in patients at various phases of bipolar disorder. Although there were a variety of methods used in these studies to measure the activity of the Na^+, K^+-ATPase pump all intra-study comparisons used the same method. El-Mallakh et al reviewed the evidence for the altered Na^+, K^+-ATPase activity. Several studies did not distinguish patients with unipolar depression from those with bipolar depression or clarify if patients were acutely ill or euthymic at the time of the study. The 12 studies reviewed by El-Mallakh et al indicate overall that in patients with bipolar disorder who are acutely unwell, in either manic or depressed phases of the illness, the activity of Na^+, K^+-ATPase is decreased compared to euthymic bipolar patients (Scott and Reading, 1978, Naylor et al., 1976, Hokin-Neaverson and Jefferson, 1989b, Hokin-Neaverson and Jefferson, 1989a, Naylor et al., 1980, Reddy et al., 1992, Reddy et al., 1989, Akagawa et al., 1980, Chio et al., 1977, Hesketh et al., 1977, Nurnberger et al., 1982, Rybakowski et al., 1981). El-Mallakh et al theorised that the decrease in Na^+, K^+-ATPase activity is therefore a 'mood-state related' marker of the disease and not a trait marker.

Due to lithium's similarity to sodium, in electrically activated cells each sodium ion is replaced by one lithium ion. With long-term lithium treatment therefore there is an accumulation of lithium in these cells triggering an increase of Na^+, K^+-ATPase activity resulting in a decrease in intracellular calcium and sodium content (Marmol, 2008, Lenox and Frazer, 2002). High intracellular sodium levels have been linked to both phases of bipolar disorder with recovery similarly linked to decreased intracellular sodium concentrations. In addition high intracellular calcium levels have been shown to be

significantly elevated in ill, untreated bipolar patients in both phases of the disorder compared to both controls and treated bipolar patients (El-Mallakh, 1995).

1.5.2 Effects on neurotransmitter signalling

This proposed mechanism of action of lithium is dependent on the monoamine hypothesis which states that depression is in part caused alterations in monoamine function (including dopamine, serotonin and norepinephrine) in the central nervous system. Although studies are still not in agreement of the site of lithium's action, be it post- or pre-synaptic, they are in agreement that there is evidence of lithium's action at multiple sites involved in the modulation of neurotransmission. One of the main neurotransmitters implicated in depression is dopamine. A key finding which supports the monoamine hypothesis is the reduction of homovanillic acid levels which is a consistent finding in depression (Marmol, 2008). More recently studies have shifted to studying the catecholamine depletion effects by the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine (AMPT) to further explore the roles of both dopamine and noradrenaline related substances in bipolar disorder. Anand et al looked at the effects of AMPT administration on eight subjects, currently in remission from bipolar disorder who had all been prescribed lithium for >3months. In this double blind study subjects were given either AMPT or placebo for four days each. Although no noticeable differences in mood were shown during treatment with AMPT once it was stopped a significant percentage of subjects showed a transient relapse of hypomanic symptoms which did not correlate with increases in homovanillic acid levels. These results are thought to be compatible with a dysregulated signalling system and compensatory overshoots rather than direct effects of one neurotransmitter system (Anand et al., 1999).

Another hypothesis for the mechanism of lithium in mood disorders revolves around effects on serotonin (5HT). Although 5HT has been extensively studied in unipolar depression and its effects are relatively well known in this illness this is not the case for bipolar disorder. It has been shown both in vivo and in vitro that lithium can, at a synaptic level, cause an increase in 5HT. As well as this biochemical observation, lithium has been shown to interact with different 5HT receptors at both molecular and functional levels, in particular $5HT_{1B}$ receptors at low concentrations of lithium (Mori et al., 1996, Glue et al., 1986, Marmol, 2008). This effect on 5HT function is thought to be caused by either lithium having partial agonist activity or modulatory action on $5HT_{1B}$ receptors which possibly explains the anti-manic effect of lithium (Chenu and Bourin, 2006).

1.5.3 Effects on the adenyl cyclase system, inositol phosphate and protein kinase C signalling

Cyclic adenosine 3',5'-monophosphate (cAMP) was the first second messenger identified in mammals and has been shown over the past 30 years to have a key role in the cellular response to multiple hormones and neurotransmitters (Fimia and Sassone-Corsi, 2001). There are three main targets of cAMP: protein kinase A (PKA), the guanine triphosphate (GTP) exchange protein activated by cAMP (EPAC) and cyclic-nucleotide-gated ion channels (Fimia and Sassone-Corsi, 2001). It is the PKA target that has been of interest in relation to lithium's mechanism of action in mood disorders as it is a main mediator of cAMP action in the central nervous system (Marmol, 2008). Back in 1996 Mori et al had observed that the administration of lithium reduces the phosphotransferase activity of PKA (Mori et al., 1996). This action was thought to be caused by competition between lithium and magnesium at a subunit of PKA, due to the similarity in the ionic radii of

lithium and magnesium (Mori et al., 1996, Jope, 1999, Gould et al., 2004). It is thought that lithium can stabilise the cAMP level fluctuations by increasing the lowest basal levels and decreasing the highest stimulated increases, thereby stabilising the system (Jope, 1999, Marmol, 2008). In laboratory studies in rat cerebral cortex α_{2D}-adrenoceptors are related to this effect of lithium on cAMP stabilisation. The recovery of these receptors after irreversible inactivation is related to the stabilising effect of lithium on cAMP production (Marmol, 2008). Lithium has also been shown to affect cAMP levels outside of the CNS. Studies have shown alterations in the bovine thyroid gland, kidney tissues of multiple animals and guinea pig ileum (Marmol, 2008). Interestingly this effect of lithium on cAMP phosphorylation only appears to occur in bipolar patients. Zanardi et al reported that after only 15 days of treatment with lithium in bipolar patients' cAMP-stimulated phosphorylation to Rap1, a small Guanosine-5'-triphosphate -binding protein present in different tissues was enhanced. This modifications of cAMP dependent phosphporylation was not mirrored in healthy controls (Zanardi, 1997).

Inositol phospholipids are also important in the receptor mediated signal transduction pathways and are involved in neuronal excitability, secretion and cell division. The inositol depletion hypothesis states that the therapeutic effect of lithium is due to it depleting the neuronal levels of myoinositol. It appears that lithium decreases inositol monophosphatase (IMPase) activity and inositol levels in vitro and animal models and decreases myoinositol levels in humans however this has been difficult to replicate in clinical studies (Marmol, 2008).

Two primary second messengers produced by the phosphoinositol signal transduction system are inositol triphosphate and diacylglycerol which activates protein kinase C.

Modulation of protein kinase C (PKC) by lithium and other mood stabilisers has been extensively studied. Early studies in the late 80s/early 90s found decreased levels of PKC signalling activity in lithium treated tissues and evidence of an activation of PKC in cases of mania (Jope, 1999). The inhibition of IMPase may represent an initial action of lithium which triggers a cascade of secondary changes in the PKC signalling pathway which may be responsible for the therapeutic effects of lithium in bipolar disorder (Marmol, 2008, Manji and Lenox, 2000, Quiroz, 2004, Einat et al., 2007, Manji and Chen, 2002).

1.5.4 Arachidonic acid metabolism

Arachidonic acid (AA) is an important mediator of second messenger pathways in the brain, Chang et al reported that lithium produced am 80% reduction in AA turnover. Subsequent trials showed that lithium decreased gene expression and protein levels of an AA-specific phospholipase-A_2 (PLA_2) and the protein levels of cyclooxygenase-2 (COX-2). COX-2 production is also stimulated by PLA_2 activation (Chang and Jones, 1998, Chang et al., 1996). Similar effects to this have also been found for other mood stabilisers including valproate and carbamazepine.

1.5.5 Neuroprotective and neuroproliferative effects through preservation of grey matter

The neuroprotective effects of lithium are thought to involve inactivation of N-methyl-D-aspartate (NMDA) receptors through multiple mechanisms including the induction of neurotrophic/neuroprotective proteins including B-cell lymphoma/leukaemia-2 gene (Bcl-2) which leads to antiapoptotic mechanisms (Marmol, 2008). Magnetic resonance imaging studies have also shown that the volume of grey matter in bipolar patients

administered lithium increases. Healthy subjects have also shown increased dorsolateral prefrontal cortex and cingulate gray matter volume (Brown and Tracy, 2013). Clinical studies have also reported that the administration of therapeutic doses of lithium not only led to increased gray matter volume in brain but also increased levels of N-acetyl-aspartate (NAA) which is a marker of neuronal viability and function) effects (Moore et al., 2000).

In summary multiple actions of lithium must be considered in the therapeutic response. Multiple actions of lithium, rather than a single site, are necessary due to its multiple effects in affective disorders as antimanic, antidepressant and prophylactic stabilising actions (Jope, 1999). By modulating neurotransmitters, lithium has a regulatory effect on their excitatory and inhibitory functions. Its proposed effects on second messenger systems, including cyclic adenosine 3',5'-monophosphate (cAMP) and PKC are thought to aid in the neural plasticity needed for its stabilising effect on mood.

1.6 Pharmacokinetics of lithium

Lithium is a naturally occurring ion that does not bind to plasma proteins and is able to cross the blood-brain barrier. It is absorbed through the stomach and does not undergo metabolism, it is filtered by the glomeruli and eliminated as the free ion by the kidneys (Malhi et al., 2012, Cates and Sims, 2005). The clearance of lithium is directly proportional to the glomerular filtration rate of the patient and renal blood flow. It is predicted that 80% of lithium filtered by the glomeruli is reabsorbed in the proximal tubules (by the apical epithelial sodium channel) of the kidneys. Of the filtered lithium 60% is reabsorbed in the proximal tubule and 20% between the Loop of Henle and the collecting duct. The clearance of lithium is about 20% of the patient's glomerular filtration rate (Cates and Sims, 2005, Kishore and Ecelbarger, 2013, Ratkovi-Gusic et al., 2002).

As lithium is treated by the kidneys as if it were sodium, a decreased sodium balance would be expected to result in increased serum lithium concentrations, whereas an increased sodium balance would be expected to result in decreased serum lithium concentrations (Kishore and Ecelbarger, 2013, Cates and Sims, 2005).

The half-life of lithium varies depending on the age and renal function of the patient taking it from 24 hours in adults, 36 hours in the elderly to 40-50 hours in patients with impaired renal function (Cates and Sims, 2005).

1.7 Lithium's effects on the kidney

There are several ways of measuring kidney function. One commonly quoted method is by calculating the glomerular filtration rate (GFR) which is equal to the total of the filtration rates of the functioning nephrons in the kidney. This cannot be measured directly and so the urinary or plasma clearance of a filtration marker such as inulin is used. This is not often done in clinical practice as it is not a simple process and instead serum levels of endogenous markers such as creatinine are used to estimate the GFR. Serum creatinine alone is known to be a poor measure of renal excretory function as its relationship with GFR is not linear and so it only rises outside of what is considered the normal laboratory range once substantial loos of renal function has occurred. Mild and moderate kidney injury is therefore poorly inferred from serum creatinine alone and so clinical laboratories are recommended to report an estimated GFR calculated from serum creatinine levels alongside serum creatinine concentrations (Renal Association, 2011).

A stable volume of extracellular fluid as well as a stable composition is needed for normal functioning of the body. The kidney is the primary organ responsible for regulating this extracellular fluid therefore any loss of kidney function can have severe consequences on the body (Schrier, 2006). In addition to the regulation of extracellular fluid the excretory, metabolic, and endocrine functions of the kidney mediate essential interactions with several organs, sustaining an array of vital functions. These include regulation of body water and thirst, blood pressure, cardiac rhythm, ventilation, drug metabolism, potassium balance, erythropoiesis, calcium and phosphate metabolism, tissue oxygenation and acid-base homoeostasis (Eckardt et al., 2013).

1.7.1. Effects on tubular function

One well documented side effect of lithium use is polyuria which is associated with a decrease in urinary concentrating ability resistant to arginine vasopressin, otherwise known as acquired nephrogenic diabetes insipidus (NDI) (Turan et al., 2002). The mechanisms underlying this effect are not completely understood but is thought to be associated with the inhibition of glycogen synthase kinase-3, β-isoform (GSK3β), impaired cAMP production, dysregulation of renal prostaglandins, altered purinergic signalling, and changes in renal architecture and possibly other methods (Kishore and Ecelbarger, 2013). Studies have also suggested that the ability of lithium to produce NDI may related to decreased aquaporin-2 (AQP2) messenger ribonucleic acid (mRNA) levels therefore inhibiting water channel delivery and reducing water permeability.

1.7.2. Effects on glomerular function

Lithium-induced nephrotic syndrome is thought to be due to lithium-induced epithelial toxicity leading to minimal change disease, meaning it will resolve after discontinuation of lithium, or focal global and segmental glomerulosclerosis (FSGS). A higher prevalence of glomerular changes correlated with a higher prevalence of proteinuria which is an uncommon result of lithium toxicity (Alexander et al., 2008). Chronic interstitial changes have also been shown in patients with psychiatric disorders who were not treated with lithium so the changes cannot be definitely attributed to treatment with lithium (Gitlin, 1999). Glomerular function itself seems to remain relatively untouched with a mild to moderate decrease in glomerular filtration rate being seen correlated with age (Johnson, 1998).

1.8 Therapeutic drug monitoring

The practice of therapeutic drug monitoring (TDM) has been around since the early 1970s allowing for individual patients to have, where required, their drug therapy tailored to their needs and responses (Touw et al., 2005). The principal aim of TDM is to increase the effectiveness of drug treatment whilst reducing the risk of serum level related adverse effects for those drugs where the concentration of the active drug or its metabolites are a better predictor of effect than dose alone. There are several drugs which have the potential to be highly toxic if serum levels are not closely monitored in order to obtain the desired clinical effects whilst minimising the risk of any avoidable adverse effects and these are termed narrow therapeutic range (NTR) drugs (Raebel et al., 2006). Sample populations are used to determine therapeutic ranges for medications, so there may be variations in these ranges for individual patients (Hitchings, 2012).

There is no comprehensive and recognised list of drugs with a NTR available, but the following are usually considered to be NTR-drugs: aminoglycosides, carbamazepine, digoxin, digitoxin, flecainide, lithium, phenytoin, phenobarbital, ciclosporin, rifampicin, theophylline, tacrolimus, aminophylline and warfarin (Blix et al., 2010, Benet, 1999, UKMI, 2011). There are other drugs in use for which TDM is not routine, but can be used when adherence is doubted or the response to treatment or side effects experienced are not as expected, for example, clozapine and olanzapine (Taylor, 2012).

The measurement of one single blood serum concentration from a patient sample is not the whole process of TDM. Interpretation of the value(s) reported, leading to appropriate conclusions and advice on clinically relevant and suitable treatment options, is needed. In

order for TDM to be clinically relevant and effective there are three things that need to be known about the drug and the illness as defined by McInnes 1989, p. 281:

1) A definitive therapeutic target range for serum levels of the drug where the maximum therapeutic effect is expected with a minimum risk of toxicity,
2) Dose alterations purely based on serum drug levels diminishes variations occurring between individuals,
3) Altering the dose of a drug based solely on clinical judgement does not lead to as great a patient benefit as keeping drug levels within the therapeutic range previously determined.

(McInnes, 1989)

There is limited to no clinical benefit for TDM of drugs whose toxic or therapeutic benefits can be measured directly. However, where this is not the case then plasma concentration measurements can help to adjust the dose to within the therapeutic range required (Aronson and Hardman, 1992). With drugs where both the parent drug and the metabolite have a clinical effect then the concentrations of both in the blood of the patient need to be ascertained to give an accurate value for the overall drug plasma level responsible for the clinical effect.

In recent years, analysis and interpretation of results considering all aspects of drug therapy has become more prominent, including patient response, adverse effects, dosing information, blood sampling times, pharmacokinetic behaviour, drug level interpretation and dose optimisation (Touw et al., 2005). For those patients for whom population-determined therapeutic ranges are not appropriate, this is increasingly important for understanding their responses to drugs and adapting their treatments appropriately

(McInnes, 1989). There is the potential with TDM that requests for blood levels may be inappropriate and therefore lead to results being interpreted incorrectly and doses changed inappropriately (Vuille, 1991, Clague et al., 1983).

As previously mentioned, there may be patients for whom a population-based therapeutic range is not appropriate, and there may also be external factors which modify the therapeutic range in a particular patient. In light of this, the context of the result reported needs to be considered for any therapeutic decisions made, not just the result in isolation. For CNS (central nervous system) drugs TDM assumes that blood concentrations are proportional at a set ratio to that in the CNS, this may not be necessarily true in all patients and therefore toxicity could occur at therapeutic levels (Walbridge and Bazire, 1985). The serum level of a drug can only be useful when considered alongside the clinical picture of the patient and treatment needs to be tailored to the patient's needs, the clinician(s) responsible for the patient need to be able to interpret the plasma level result in light of this (Brodie and Feely, 1988, Vestergaard et al., 1982).

1.9 Serum lithium analysis

Both serum (prepared from clotted blood) and plasma (prepared from anticoagulated blood), can be used for many TDM measurements. Serum is used routinely for the measurement of lithium to avoid any possible interaction with lithium heparin, which is used as an anticoagulant (Aronson and Reynolds, 1992). The pharmacokinetics of lithium varies from person to person, making it difficult to accurately predict dosage requirements. Serum levels of lithium also vary widely between doses and there is a diurnal variation in the way the body handles lithium, with it having a longer half-life throughout the night than during the day (Aronson and Reynolds, 1992). Due to this variation in serum levels between doses it is recommended that the sample is taken 12 hours after the last dose. Diurnal variation is not currently taken into account as modified release formulations go some way to ameliorating these variations (Aronson and Reynolds, 1992). Due to the renal elimination of lithium, any adjustments in dose need to take into consideration not only the absolute serum lithium level, but also the changes in renal function. A change in serum lithium level may be indicative of a change in renal function which requires further investigation (Vestergaard et al., 1982).

There are several methods of monitoring serum lithium levels, which is an important variable for the generalisability of population-based therapeutic drug ranges. Difficulties in interpretation may also occur if different laboratories use a variety of methods for lithium level analyses on the same patient. The main methods of lithium serum level analysis are flame emission spectroscopy (FES), atomic absorption spectrophotometry (AAS) and lithium-ion selective electrode technology (Li-ISE) (International Group for The Study of Lithium Treated Patients, 2010). At pathology laboratories within Norfolk and

Suffolk, a spectrophotometric method is used, with a direct colorimetric endpoint reaction. (Eastern Pathology Alliance, 2013 (a), Eastern Pathology Alliance, 2013 (b)). Lithium found within the serum sample reacts with a lithium-specific chromoionophore in an alkaline solution forming a lithium ion complex, changing the absorbance of the sample. The concentration of lithium in the sample is proportional to the increase in absorbance (Eastern Pathology Alliance, 2013 (b)). As with any chemical reaction there is the potential for interfering substances which can cause physiological changes in either the serum or plasma analyte concentrations, and results must therefore be interpreted in light of these and the clinical presentation of the patient.

1.10 Diagnosis, treatment and management of bipolar disorder

Bipolar disorder is characterised by recurrent changes in mood. There are also however, cognitive, psychotic and anxiety symptoms which account for some of the disability associated with it (Altamura et al., 2011). It is estimated that the lifetime prevalence of bipolar disorder is between 1-5%. Due to the complexities in diagnosis when this is expanded to encompass all bipolar spectrum disorders this can vary between 2.8-6.5% (Bauer and Pfennig, 2005). There is a suggestion that these estimates possibly underestimate the overall prevalence as a consequence of frequent misdiagnoses due to an overlap of psychiatric symptoms and comorbid conditions (Bauer and Pfennig, 2005). A diagnosis of bipolar disorder is associated with high rates of other medical, psychiatric and substance misuse disorders which contribute to a lower life expectancy and overall quality of life (Connolly, 2011).

Bipolar disorder is, in most patients, a chronic and recurrent illness and the main aim of treatment is maintenance of euthymia which is best achieved by the long- term treatment to prevent future episodes and further functional impairment. The impairment seen in patients who have recovered from acute episodes of mood fluctuation and are asymptomatic is related to the number of previous episodes experienced (NICE, 2006).

There are two main diagnostic schemes in use in the field of psychiatry: the International Classification of Diseases of the World Health Organisation (10th edition ICD-10) and the Diagnostic and Statistical Manual (5th edition DSM-5) of the American Psychiatric Association (American Psychiatric Association, 2013, World Health Organisation, 2010). There are differences in these two systems for the diagnosis of bipolar disorder, details of

which can be found on pages 5 and 6 of the Scottish Intercollegiate Guidelines Network (SIGN) Clinical Guideline 82 (SIGN, 2005).

Current guidance from the National Centre for Health and Care Excellence (NICE) which produces guidelines and advice for health services within England and Wales is that lithium should be offered first line for the long-term treatment of bipolar disorder. Where lithium is not tolerated, or is not considered suitable, then olanzapine or valproate should then be considered (NICE, 2014a). If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder then lithium is not recommended as mono-therapy, with other drugs not currently holding UK marketing authorisation for this use also being recommended. If lithium is already prescribed and measuring at a maximum serum level, then it can be augmented with other agents such as fluoxetine or olanzapine (NICE, 2014a).

The differences in diagnostic criteria and the complexities of co-morbid conditions impact on the ability to effectively treat bipolar disorder.

1.11 Decision making in the prescribing of lithium

Although there is a great deal of evidence in support of lithium as a treatment in affective disorders, it does come with safety concerns, and it has had several 'renaissances' in its long history (Malhi and Gershon, 2009). In some countries, the use of lithium has been declining in recent years, particularly in the Americas. This is thought to be in part due to the ongoing and recurrent doubts about its efficacy in affective disorders and also concerns around its safety as a long-term treatment option.

Although there have been several studies in recent years on decision-making in prescribing these have focussed on the prescribing of newer medications rather than well-established drugs such as lithium (Prosser and Walley, 2006, Cutts and Tett, 2003, Denig et al., 2002a, Jones et al., 2001, Jaye and Tilyard, 2002). It is not clear if the influencing factors on prescribing are the same for older drugs.

1.12 Conclusion

Since its initial discovery, lithium has experienced oscillations between a positive and negative reputation within the medical community. It is currently considered the gold standard treatment for bipolar disorder and is recommended in the UK as a first line, long-term treatment. It does, however, require therapeutic drug monitoring to ensure that the risks of toxicity are minimised whilst still maximising its efficacy. There are also still unanswered questions about the long-term side effects of lithium, particularly on renal function.

This thesis starts with a comprehensive literature review to firmly establish the evidence base before this work, on the development of a therapeutic drug level, monitoring parameters and the established effects on renal function of lithium. This then leads into the research conducted investigating the gaps in the evidence specifically around the effects lithium, and lithium levels on renal function. One complexity inherent in the prescribing of lithium is the difficulty in diagnosing the condition it is intended to treat. Bipolar disorder is known to be difficult to diagnose with differences in diagnostic criteria even existing in the US and European manuals for diagnosis (DSM-5 and ICD-10). One idea which is consistent across diagnostic criteria and guidelines surrounding prescribing is that bipolar spectrum disorders are long-term, chronic conditions requiring long-term treatment with medication to minimise relapses and to maintain a euthymic state. The safety and long-term implication of the chosen treatment are a consideration for prescribers.

With research on prescribing decisions having focussed on new medications it is not clear if these complexities of lithium have a different impact on prescribing decisions. In association with investigating the relationship of lithium levels on renal function the long-term prescribing decisions will be investigated for this well-established drug to add to the evidence base in this area.

Chapter Two

2: Literature review

2.1 Literature review background

When lithium was first used in medicine there was no routine monitoring for therapeutic effects or toxicity, doses were increased until side effects occurred then reduced until the side effects reduced and there was no clear indication of what was causing them (Schou, 1988). It was not known what lithium level proved the most efficacious in preventing both poles of bipolar disorder. In early studies of lithium as a prophylactic medication in bipolar disorder, patients were maintained at lithium levels of 0.6-1.3mmol/L and these levels were therefore recommended for use in clinical practice (Maj et al., 1986). Since then there have been several studies which have tried to narrow down this therapeutic range to maximise efficacy of treatment whilst minimising the risk of adverse effects.

The custom in the late 1980s for determining serum levels at two, four or 12 months was based on what was being done in practice (Schou, 1988). Up until 1995, the British National Formulary (BNF) advocated monthly monitoring of lithium as routine. There have however been several debates in the literature about the merit in regularly checking serum lithium concentrations, and so the BNF recommendations were changed to three monthly monitoring (Joint Formulary Committee, 1995).

Current guidelines for lithium monitoring have not veered far from this, with recommendations at the time of writing being for serum lithium levels every three months (NICE, 2006, SIGN, 2005). Since the background work for this thesis was conducted, national guidelines within England and Wales have been updated and now

recommend three monthly lithium levels for the first year of treatment and then every six months, or every three months for some patient groups (NICE, 2014a).

Renal function is important for the elimination of lithium as a declining glomerular filtration rate (GFR) will increase any risks of lithium toxicity due to accumulation. Although there is evidence that lithium is effective in affective disorders, until the publication of the McKnight review in 2012 there was no systematic review of the toxicity profile of lithium (McKnight et al., 2012). Even after this publication there remain uncertainties surrounding the renal toxicity profile of lithium in relation to its potential effects on eGFR, urinary concentrating ability and end stage renal failure. There is also no background detail in the published guidance for the recommended frequency of lithium monitoring, or evidence for effective lithium levels which would further enable risk-benefit decisions to be made by prescribers.

2.2 Aims and Objectives

2.2.1. Aim

A literature search was performed to identify published research articles that looked at the development of therapeutic lithium level ranges, the rationale behind the frequency of monitoring currently recommended and the effects of lithium on renal function.

2.2.2. Objectives

To determine the:

- relative efficacy and toxicity of different lithium levels in the prevention of relapse in recurrent mood disorders,
- evidence behind the current recommendations of the frequency of lithium monitoring,
- association between lithium use and renal function in adults with recurrent mood disorders.

2.3 Methods

This review will be separated into three sections running throughout the method and results relating to the three areas covered in the objectives.

The following databases were searched for relevant articles: Embase, Medline, PsychINFO, CINAHL, and the Cochrane database. These databases were chosen as they are the specialist ones for allied health professionals, nursing and medicine as well as being the general literature databases that are likely to have major published articles in this field. The research team did not have the facilities to translate articles that were published in a foreign language and so these were excluded if an English version could not be found. If full texts were readily available these were accessed, where these were not immediately available abstracts were checked to see if they made mention of the methods in enough detail for the studies to be eliminated, and all others were requested in full to be reviewed. The literature search was performed up to and including March 2014.

2.4 Included studies

2.4.1. Development of a therapeutic lithium level

To focus on the development of a therapeutic lithium level this section of the literature review needed to include articles which reported on the long-term treatment of mood disorders where patients were assigned to specified target ranges of lithium levels. The Embase search was performed first and bought up a review article which had looked at this same issue covering the period from 1966 to March 2006 (Severus et al., 2008) and so when the Medline search was performed the same search terms were used as this review and the results were limited from 2006 onwards to find new articles which had since been published. Original articles included in the 2008 review by Severus et al., were also obtained. This was a pragmatic method of searching due to time constraints on the need to do multiple literature reviews for the topics covered in the thesis.

After detailed searching of the abstracts found from the literature review, 12 articles were included for further reading in addition to the five original reports mentioned in the review found from 2008 (Severus et al., 2008). From reference list reviews of these initially selected articles a further nine articles were included for further reading. Of these articles ten were subsequently deemed appropriate for inclusion (Jerram and McDonald, 1978, Waters et al., 1982, Coppen et al., 1983, Maj et al., 1986, Gelenberg et al., 1989, Vestergaard et al., 1998, Stokes et al., 1976, Hullin, 1979, Goodnick and Fieve, 1985, Lewitzka et al., 2012). Articles were included if they compared at least two different lithium level ranges for the treatment of affective disorders.

2.4.2. Development of recommended monitoring frequency for lithium

To explore the rationale for the development of the monitoring frequency for lithium a search was carried out for published articles which mentioned both lithium and drug monitoring. No controlled trials were found from the literature search in this area so the inclusion criteria for all articles found was kept very broad and all articles which included guidance or advice on the monitoring frequency of lithium were considered suitable for inclusion. After detailed searching of the published abstracts, 57 were included for further reading. Two additional articles were found through reference list searching. Of these articles ten were subsequently deemed appropriate for inclusion (Dunner, 2000, Vestergaard and Licht, 2001, American Psychiatric Association, 2002, Hitchings, 2012, Grandjean and Aubry, 2009, Mitchell, 2001, Schou, 1988, Brodie and Feely, 1988, Delva and Hawken, 2001, Sachs et al., 2000).

2.4.3. Renal effects of lithium

The section of the literature review focussing on the renal effects of lithium needed to include articles which reported on the renal effects of lithium treatment in mood disorders. During the previous search performed when for the development of a therapeutic lithium level, a systematic review and meta-analysis had been found which reported the toxicity profile of lithium. This had screened all published articles, textbooks, conference abstracts and even contacted pharmaceutical companies for additional data up to 2010. A search was performed using a wide range of key words, as the search terms used in this review were not available, and only articles from 2010 onwards were included for further review.

From the previous search run for the development of therapeutic lithium levels a comprehensive systematic review and meta-analysis had been found (McKnight et al., 2012). The results from this literature search were screened to see if any additional articles had been published since 2010, which was the date up to which the McKnight review had searched. After detailed searching of the abstracts found from the literature review 13 articles were included for further reading in addition to the 28 original reports mentioned in the McKnight review. Of these articles 32 were subsequently deemed appropriate for inclusion (Janowsky, 2011, Preda, 2012, Rej et al., 2013a, Hullin et al., 1979, Bendz, 1985, Bendz et al., 1996, Bendz et al., 2001, DePaulo et al., 1986, Grof, 1980, Hetmar et al., 1987b, Hetmar et al., 1991, Jensen and Rickers, 1984, Johnson et al., 1984, Jorkasky et al., 1988, Kallner and Petterson, 1995, Muir et al., 1989, Nilsson and Axelsson, 1989a, Povlsen et al., 1992, Presne et al., 2003, Schou and Vestergaard, 1988, Smigana et al., 1984, Vaamonde et al., 1986, Waller et al., 1988, Åberg-Wistedt et al., 1988, Coşkunol et al., 1997, Hetmar and Rafaelsen, 1987c, Turan et al., 2002, Walker et al., 1982a, Walker et al., 1982b, Tredget et al., 2010, Vestergaard and Thomsen, 1981, Vestergaard et al., 1979). Articles were included if they were case-control, cohort or chart reviews comparing creatinine clearance, glomerular filtration rate (GFR), estimated GFR (eGFR), serum creatinine or urinary concentrating ability at baseline and follow-up, or between cases and controls. One study was also included as it looked at the relative risk of renal impairment or renal failure.

Since the original search was done several papers have been published on the effect of lithium on GFR which were found by an email alert set up when the initial search was done (Clos et al., 2015, Ott et al., 2016, Rodrigo et al., 2014).

2.5 Excluded studies

2.5.1. Development of a therapeutic lithium level

A number of studies were excluded as they focussed primarily on monitoring parameters of lithium or were critical reviews of the evidence for lithium prophylaxis (Nierenberg et al., 2009, Severus, 2010, Carney, 2005, Keck, 2003, Maj, 2000, Grandjean and Aubry, 2009, Schou, 1988, Prien et al., 1972, Goodwin and Goldstein, 2003, Amdisen, 1980). Several other studies did not assign patients to precisely specified target ranges of lithium levels, or had no differences in lithium levels used in the studies therefore not allowing comparisons to be made (Calabrese et al., 2006, Smith et al., 2007, Burgess et al., 2001, Stallone et al., 1973, Nilsson and Axelsson, 1989b, Lewitzka et al., 2012). The study by McKnight et al., was a clinically informative, systematic toxicity profile of lithium not focussing on differing lithium levels (McKnight et al., 2012).

2.5.2. Development of recommended monitoring frequency for lithium

Those articles which had no mention of monitoring frequency or were audits on how well areas comply with guidelines or the current rates of testing were not included along with articles which contained material pertinent to another section of the literature review or those which were letters or replies (Paton et al., 2010, Collins et al., 2010, Jefferson, 2010, Sharma, 1992, Lewis, 2004, Gupta and Eagles, 2001, Guscott and Taylor, 1993, Kehoe, 1993, Hullin et al., 1993, Hellewell and Pugh, 1992, Rowlands, 1992, McKean and Vella-Brincat, 2012, Anderson and Bazire, 2011, Udumaga E., 2010, Shaw, 2004, Butler and Taylor, 2000, Brown, 2012, Frings, 1987, Marcus et al., 1999, Kehoe and Mander, 1992, Tjia et al., 2010, Schrader, 2002, Myers and Hallworth, 1996, Friedman and Greenblatt,

1986). Several articles also focussed on the reliability processes to estimate drug concentrations and dosing strategies or the appropriateness of requests for the drug monitoring of lithium which were also not included in this review (Hoegberg et al., 2012, Ratanajamit et al., 2006, Mann et al., 2006, Aishah and Foo, 1995, Amdisen, 1980).

2.5.3. Renal effects of lithium

Any articles which were personal reflections, discussion only, single case studies, editorials, letters or reviews of methods of measuring renal function or those with non-comparable outcomes measured (Jefferson, 2010, Dhavaleshwar and Spencer, 2010, Rybakowski et al., 2012, Werneke et al., 2012, Jean-Noel and Lapid, 2011, Pradhan et al., 2011, Svedlund et al., 2012, Abramowicz et al., 2012, Bendz et al., 2010).

2.6 Results

2.6.1. Development of therapeutic lithium level

Table 2.1 details the analysis of included studies and their results.

Study	Method	Diagnosis	Prior use of lithium	Characteristics of participant at study entry	Number of cases	Follow up	Specific outcomes measured	Lithium levels used	Results
Stokes, Kocsis et al., 1976	Blinded, randomised, controlled trial using three separate lithium level ranges*	Manic states	Unknown	On-going symptoms or episodes before entry	68 (42 completed)	10 days for each lithium level range, 40 days total	Behavioural ratings	Placebo Low dose: 0.24MEq/Kg/day Medium dose: 0.50mEq/Kg/day High dose: 0.72mEq/Kg/day	High and medium doses more efficacious ($p<0.01$ and $p<0.05$ respectively) High dose only significant in achieving euthymia $p<0.005$)
Jerram and McDonald, 1977	Randomised controlled trial using three separate lithium level ranges	Definite affective disorder, currently in remission	Yes	Stability of mood on study entry	80 (73 completed)	12 months	Necessity for additional psychotropic medication and/or admission	Low: <0.49mmol/L Medium: 0.50-0.69mmol/L High: >0.70mmol/L	No significant difference in outcomes in the three groups ($p=0.98$)
Hullin, R.P., 1979	Randomised controlled trial using three separate lithium level ranges	Definite affective disorder, currently in remission	Yes	Stability of mood on study entry	73 (70 completed)	12 months	Hospitalisation OR relapse	Low: 0.25-0.39mmol/L Medium: 0.40-0.59mmol/L High: 0.60-1.0mmol/L	Non-significant difference in relapse rate between groups ($p=0.76$)

*Cross over trial, DSM - Diagnostic & Statistical Manual of Mental Disorders, ICD - International Classification of Diseases, BPRS - brief psychiatric assessment rating scale
MEq = milliequivalent (For monovalent ions including lithium, 1 MEq = 1 mmol)

Table 2.1: Results of included studies - development of therapeutic lithium levels, continued on the following pages

Study	Method	Diagnosis	Prior use of lithium	Characteristics of participant at study entry	Number of cases	Follow up	Specific outcomes measured	Lithium levels used	Results
Waters, Lapierre et al., 1982	Blinded, randomised, controlled trial* Two lithium level ranges	DSM III defined bipolar disorder	Yes	Residual mood swings in preceding 24 months	36 (29 completed)	6 months for each stage of crossover, 12 months in total	Global clinical assessment and brief psychiatric assessment rating scale (BPRS) Relapses	Low dose: 0.30-0.80mEq/L High dose: 0.80-1.4mEq/L	Significantly more relapses in low dose phase ($p<0.01$) Significantly higher BPRS scores in low dose phase ($p<0.01$)
Coppen, Abou-Saleh et al., 1983	Blinded, randomised, controlled trial Previous lithium level or 25 or 50% reduction.	Unipolar or bipolar patients	Yes	Unknown	88 (72 completed)	≥12 months	Affective morbidity	Group 1: 0.45-0.59mmol/L Group 2: 0.60-0.79mmol/L Groups 2 and 3: ≤0.79mmol/L Group 4: ≥0.80mmol/L	Significant decrease in morbidity for all patients with lithium level ≤0.79 mmol/L ($p<0.02$)
Goodnick and Fieve, 1985	Prospective	Bipolar disorder diagnosed according to modified Feighner et al criteria	Unknown	Stability of mood on study entry	44	Group 1 = 42.0±19.5months Group 2 = 39.1±22.9months	Deviation of mood from normal (7 point scale)	Group 1: 0.87±0.10mEq/L Group 2: 0.58±0.12mEq/L	No significant differences in episodic functioning between groups

*Cross over trial, DSM - Diagnostic & Statistical Manual of Mental Disorders, ICD - International Classification of Diseases, BPRS - brief psychiatric assessment rating scale, MEq = milliequivalent (For monovalent ions including lithium, 1 MEq = 1 mmol)

Table 2.1 continued: Results of included studies - development of therapeutic lithium levels

Study	Method	Diagnosis	Prior use of lithium	Characteristics of participant at study entry	Number of cases	Follow up	Specific outcomes measured	Lithium levels used	Results
Maj, Starace et al 1986	Controlled trial Four lithium level ranges	DSM III defined bipolar disorder	Yes	At least one affective episode in preceding 24 months	80 (69 completed)	24 months	Number of affective episodes and total morbidity	Group A: 0.30-0.45mEq/L Group B: 0.46-0.60mEq/L Group C: 0.61-0.75mEq/L Group D: 0.76-0.90mEq/L	Significant decrease in mean number of affective episodes and mean total morbidity in groups B, C and D ($p<0.002$)
Gelenberg, Kane et al 1989	Blinded, randomised, controlled trial Two lithium level ranges	DSM (or equivalent) diagnosis for bipolar disorder	Yes	Stability of mood	94 recruited (33 completed)	6 months	Relapse	Low: 0.40-0.60mmol/L Standard: 0.80-1.0mmol/L	2.6 times increased risk of relapse for low dose group (95% CI 1.3-5.2)
Vestergaard, Wentzer Licht et al 1998	Randomised controlled trial Two lithium level ranges	DSM (or equivalent) diagnosis for bipolar disorder, currently hospitalised	Unknown	Unknown	101 recruited with 91 randomised (49 completed)	24 months	Recurrence of symptoms which required hospitalisation	Low: 0.50-0.80mmol/L High: 0.80-1.0mmol/L	No statistically significant difference in outcome between high/low serum levels ($p=0.83$)
Lewitzka et al., 2012,	Prospective	ICD-10 diagnosed recurrent unipolar or bipolar affective disorder	Yes	1 euthymic interval during observation period	54	2 years	Psychopathol-ogical features	<0.40mmol/L <0.50mmol/L Mean level for all patients: 0.72±0.16mmol/L	No generally occurring significant correlations between lithium serum levels

*Cross over trial, DSM - Diagnostic & Statistical Manual of Mental Disorders, ICD - International Classification of Diseases, BPRS - brief psychiatric assessment rating scale, MEq = milliequivalent (For monovalent ions including lithium, 1 MEq = 1 mmol)

Table 2.1 continued: Results of included studies - development of therapeutic lithium levels

Seven studies were found dating from the 1970s and 1980s when there was a significant amount of research being conducted around lithium treatment for affective disorders; the remaining two included studies are more recent from the 1990s and 2000s (Stokes et al., 1976, Jerram and McDonald, 1978, Hullin, 1979, Waters et al., 1982, Coppen et al., 1983, Maj et al., 1986, Gelenberg et al., 1989, Vestergaard et al., 1998, Lewitzka et al., 2012).

There was no significant difference seen for the different lithium levels used in patients whose mood was stable at study entry or were assessed whilst euthymic apart from Gelenberg, Kane et al which did show an increased risk of relapse for those in the low dose group (Jerram and McDonald, 1978, Hullin, 1979, Lewitzka et al., 2012, Gelenberg et al., 1989). There was also no significant difference seen when the outcome measure required relapse or increase in symptoms severe enough to require hospitalisation (Vestergaard et al., 1998). There was a majority agreement that levels ≤0.79mmol/L held an increased risk of both relapse and symptom increase (Waters et al., 1982, Coppen et al., 1983, Gelenberg et al., 1989, Maj et al., 1986, Stokes et al., 1976). With levels >0.79MEq/Kg/day or 1mmol/L significant decreases in the mean number of affective episodes were seen (Maj et al., 1986, Waters et al., 1982) and between 0.45-0.9mmol/L significant decreases in the mean total morbidity were seen (Maj et al., 1986, Coppen et al., 1983) and this was the only level at which significance was shown for achieving euthymia (Stokes et al., 1976).

These single studies have ranges of numbers of participants from 36 to 101 and as such each will have a different statistical power. Meta-analysis can help to increase the statistical power by combining studies however in this case the differences in the

methods, population characteristics and specific outcomes measured meant that a meta-analysis would not be beneficial or appropriate to use.

2.6.2. Development of recommended monitoring frequency for lithium

Table 2.2 details the analysis of included studies and their results.

Study	Type of article	Recommendations	Based on	Reasons for frequency
Schou, 1988	Review	For dose adjustment at the start of treatment and for control after dose changes	Unclear	Nephrotoxic effects
Brodie and Feely, 1988	Review	Start of treatment, then twice weekly for a week, then weekly for first month then monthly for next six. After this should be three monthly, repeated after dose changes.	Unclear	To anticipate the possibility of gradual renal function decline
Dunner, 2000	Review	1-2 weeks until satisfactory blood level achieved, then 2-3 months for first 6 months, at least 6-12 months thereafter	Expert consensus guidelines	Side effects
Sachs et al., 2000	Practice guideline	Periodic	Unclear	Side effects and early prevention of decline in renal and thyroid function
Vestergaard and Licht, 2001	Review/Mini-review	Serum lithium determined at steady state, then four times a year	Hospital guidelines from a lithium clinic	Side effects and toxicity
Mitchell, 2001	Review	Once dose stabilised frequency of test depends on the individual patient's clinical situation but should be no less frequency than every 6 months	Expert consensus guidelines	Toxicity potential due to narrow therapeutic range
Delva and Hawken, 2001	Continuing medical education article	5 days after dose change and then one monthly later. Routinely every 3 months.	Unclear	Side effects and toxicity

Table 2.2: Results of included studies - Recommended monitoring frequency for lithium, continued on the following page

Study	Type of article	Recommendations	Based on	Reasons for frequency
American Psychiatric Association, 2002	Practice guideline	At steady state (~5 days unless rapid schedule), after each dose increase, before the next Generally should be no less than every 6 months for stable patients. The optimal frequency of serum level monitoring in an individual patient depends on the stability of lithium levels over time for that patient and the degree to which the patient can be relied upon to notice and report symptoms	The decision to recommend a test is based on the probability of detecting a finding that would alter treatment as well as the expected benefit of such alterations in treatment.	Laboratory measures and other diagnostic tests are generally recommended on the basis of pathophysiological knowledge and anticipated clinical decisions rather than on empirical evidence of their clinical utility.
Grandjean and Aubry, 2009	Review	Recommended interval for routine serum concentration checking varies from 6-12 weeks to 6 months in stable patients At a minimum: after initiation of lithium therapy, after any change in dosage, and when there has been concurrent disease or any change in medication	Previous review articles	Narrow therapeutic range
Hitchings, 2012	Practice article	Weekly after initiation and dosage changes until concentrations are stable, then every 3 months thereafter	Unclear	Side effects and toxicity

Table 2.2 continued: Results of included studies - Recommended monitoring frequency for lithium

No controlled clinical trials or high quality evidence was found to support the recommendations for the frequency of lithium level testing. The most widely known frequency, and that currently recommended in UK national guidelines is based on expert consensus taking into consideration the clinical state of the patient and the expected utility of the results. The consensus guidelines do comment on the lack of empirical evidence of the clinical utility of laboratory tests for lithium treatment and emphasise that these recommendations should be adjusted to each individual patient:

> *"The optimal frequency of serum level monitoring in an individual patient depends on the stability of lithium levels over time for that patient and the degree to which the patient can be relied upon to notice and report symptoms"*
>
> (American Psychiatric Association, 2002).

Other recommendations, such as the increased frequency of monitoring at the start of treatment are based on what happens in practice.

2.6.3. Renal effects of lithium

Table 2.3 details the analysis of included studies and their results.

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Hullin et al., 1979,	Comparative study: Patients admitted overnight and measurements taken from 18hour urine collection	Affective disorders	Affective disorders, patients matched for age, sex and diagnosis not on lithium	30	30	Compared GFR and Umax between cases and controls	-	Non-significant reduction in GFR. WMD -20.20 (CI -41.72-1.32) Non-significant decrease in Umax. WMD -70.00 (CI -171-31.27)
Vestergaard et al., 1979	Prospective cohort: Determination of 24-hour creatinine clearance and serum creatinine	Unipolar depression, bipolar disorder	-	184	-	Measured GFR at baseline and follow-up	15 months	Significant decrease in GFR Significant reduction in Umax
Grof, 1980,	Retrospective chart review: Measuring creatinine clearance, maximum urinary osmolality and 24 hour urine volume	Affective disorders	-	50		Measured GFR at baseline and follow-up	68 months	Non-significant decrease in GFR
Walker et al., 1982a,	Case-control study: studied the renal histology and the renal function measured by biopsy and urinary concentrating ability	Unipolar depression, bipolar depression, Schizoaffective disorder	Affective disorders patient matched for age and sex	47	32	Compared GFR and Umax between cases and controls	-	Excluded from analysis as no standard deviations available from any source
Walker et al., 1982b,	Case-control study: biopsies of lithium treated patients when compared with cadaveric donor kidneys	Unipolar depression, bipolar depression	Bipolar disorder/unipolar depression not taking lithium	25	19	Compared GFR and Umax between cases and controls	-	Excluded from analysis as no standard deviations available from any source

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3: Results of included studies - Renal effects of lithium, continued on following pages

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Jensen and Rickers, 1984,	Prospective cohort: longitudinal GFR measurements by ^{51}Cr-EDTA plasma clearance	Unknown	-	13	-	Measured GFR and Umax at baseline and follow-up	16.5 months	Significant decrease in GFR
Johnson et al., 1984b,	Prospective cohort: repeated renal function tests	DSM III diagnosed bipolar disorder	-	61	-	Measured GFR and Umax at baseline and follow-up	24 months	Significant increase in GFR
Smigana et al., 1984,	Prospective cohort: tubular function studied by the desmopressin test and the GFR measured by creatinine clearance	Unipolar depression, bipolar depression, Schizoaffective disorder	-	53	-	Measured GFR and Umax at baseline and follow-up	12 months	Significant decrease in GFR, significant reduction in Umax
Bendz, 1985,	Case-control study: longitudinal GFR measurements by ^{51}Cr-EDTA plasma clearance, urine osmolality and urine volume	Unipolar depression, bipolar depression, Schizoaffective disorder	Healthy, matched for age and sex	32	32	Compared GFR and Umax between cases and controls	-	Non-significant reduction in GFR. WMD -4.00 (CI -20.69-12.69). Non-significant decrease in Umax. WMD -68.00 (CI -162.06-26.06)
Vaamonde et al., 1986,	Prospective cohort: measurement of creatinine clearances	Bipolar disorder	-	7	-	Measured GFR at baseline and follow-up	90 months	Non-significant decrease in GFR

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference, ^{51}Cr-EDTA = chromium-51 labeled ethylenediamine tetraacetic acid

Table 2.3 continued: Results of included studies - Renal effects of lithium

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
DePaulo et al., 1986,	Prospective cohort: GFR measured creatinine clearance from serum creatinine levels	DSM III diagnosed bipolar disorder	-	40	-	Measured GFR at baseline and follow-up	18 months	Non-significant increase in GFR
Hetmar et al., 1987b,	Prospective cohort: 24 hour urine volume, ^{51}Cr-EDTA plasma clearance and 26hr water deprivation test	Affective disorders	-	32	-	Measured GFR and Umax at baseline and follow-up	24 months	Non-significant decrease in GFR, significant reduction in Umax
Hetmar and Rafaelsen, 1987c,	Case-control study: 24 hour urine volume, ^{51}Cr-EDTA plasma clearance and 26hr water deprivation test	Affective disorders	Affective disorder patients not taking lithium	32	53	Compared GFR and Umax between cases and controls	-	Significant decrease in GFR. WMD -12.60 (CI-22.34 - -2.86) Excluded from Umax analysis as no standard deviations available from any source
Åberg-Wistedt et al., 1988,	Case-control study: measurement of urine osmolality only	Unipolar depression, bipolar depression, Schizoaffective disorder	Unknown	60	30	Compared Umax between cases and controls	-	Excluded from Umax as experimental group did not fit profile of patients in other studies
Jorkasky et al., 1988,	Prospective cohort: repeated urinalysis, repeated serum creatinine levels and creatinine clearance	Bipolar disorder	-	65 (18 at follow-up)	-	Measured GFR and Umax at baseline and follow-up	36 months	Significant decrease in GFR, significant reduction in Umax

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3 continued: Results of included studies - Renal effects of lithium

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Schou and Vestergaard, 1988,	Prospective study: Measuring creatinine clearance, maximum urinary osmolality and 24 hour urine volume and desmopressin test	Unipolar depression Bipolar depression	-	346 39	-	Measured CrCl at baseline and follow-up	84 months	Non-significant decrease in GFR, significant reduction in Umax
Waller et al., 1988,	Prospective cohort: GFR, assessed by creatinine clearance and serum creatinine concentrations	Unknown	-	28	-	Measured GFR and Umax at baseline and follow-up	56 months	Significant decrease in GFR, significant reduction in Umax
Muir et al., 1989,	Prospective cohort: repeated assessments of serum creatinine	DSM III diagnosed bipolar disorder	-	18	-	Measured GFR and Umax at baseline and follow-up	7.5 months	Non-significant decrease in GFR, significant reduction in Umax
Nilsson and Axelsson, 1989a,	Prospective cohort: repeated assessments of serum creatinine	Affective disorders	-	37	-	Measured Umax at baseline and follow-up	84 months	Significant decrease in Umax
Hetmar et al., 1991,	Prospective cohort: 24 hour urine volume, serum creatinine and ^{51}Cr-EDTA plasma clearance	Affective disorders	-	27	-	Measured GFR and Umax at baseline and follow-up	120 months	Significant decrease in GFR, significant reduction in Umax

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3 continued: Results of included studies - Renal effects of lithium

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Povlsen et al., 1992,	Prospective cohort study: endogenous creatinine clearance from 24hour urine collection	Affective disorders	-	53 (13 at follow up)	-	Measured GFR and Umax at baseline and follow-up	84 months	Non-significant change in GFR and Umax
Kallner and Petterson, 1995,	Retrospective chart review: serum creatinine, ^{51}Cr-EDTA plasma clearance and desmopressin test	Unipolar depression Bipolar disorder	-	207	-	Compared baseline GFR and Umax to measurements after lithium stopped	186 months	Non-significant decrease in GFR, significant reduction in Umax
Bendz et al., 1996,	Case-control study: serum creatinine, desmopressin test and urine volume measurements	Unipolar depression, bipolar depression, Schizoaffective disorder	Healthy, matched for age and sex	13	13	Compared GFR and Umax between cases and controls	-	Significant decrease in GFR. WMD -9.00 (CI -12.08—5.92). Significant reduction in Umax. WMD -211.00 (CI -254.76- -167.24)
Coşkunol et al., 1997,	Case-control study: 24hour urine collection, b -microglobulin (b -Mg) excretion, glycosaminoglycan levels and serum creatinine	DSM III diagnosed bipolar disorder	Healthy, matched for age and sex	109	109	Compared GFR and Umax between cases and controls	-	Non-significant increase in GFR. WMD 2.60 (CI -36.09 – 41.29). Significant reduction in Umax. WMD -229.00 (CI -269.41- -188.59)

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3 continued: Results of included studies - Renal effects of lithium

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Bendz et al., 2001,	Retrospective chart review: serum creatinine, ^{51}Cr-EDTA plasma clearance and desmopressin test	Unipolar depression, bipolar depression, Schizoaffective disorder	-	149	-	Compared CrCl or GFR and Umax recorded prior to lithium treatment	180 months	Non-significant decrease in GFR Significant reduction in Umax
Turan et al., 2002,	Case-control study: Serum blood urea nitrogen (BUN), creatinine, urine creatinine and desmopressin test	DSM IV diagnosed bipolar disorder	Bipolar patients prior to starting lithium	10	10	Compared GFR and Umax between cases and controls	-	Significant increase in GFR. WMD 24.94 CI 3.29- 46.59) Excluded from Umax analysis as no standard deviations available
Presne et al., 2003,	Prospective cohort: kidney biopsy, serum creatinine levels and creatinine clearance	Unknown	-	74	-	Measured CrCl at baseline and follow-up	120 months	Significant decrease in GFR
Tredget et al., 2010,	Case-control study: creatinine levels and calculated eGFR	Affective disorders	Severe affective disorders who had not received lithium	61	62	Compared eGFR between cases and controls	Mean of 11.5 years	Significant decrease in eGFR p=0.003
Janowsky, 2011,	Retrospective chart review:	Aggression, self-injurious behaviours	Previous cases: no indication of renal insufficiency	16	36	Serum creatinine	Mean of 3.2 years	Increases in creatinine levels seen

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3 continued: Results of included studies - Renal effects of lithium

Study	Method	Diagnosis	Characteristics of controls	Number of cases OR participants	Number of controls	Specific outcomes measured	Follow up	Results
Rej et al., 2013,	Retrospective Longitudinal Study: historic eGFR and serum creatinine levels	Unclear	-	42	-	Change in eGFR between baseline and follow-up	2 and 4 years	No significant correlation of lithium levels and change in eGFR p>0.57)
Close et al., 2014,	Retrospective cohort study: diagnostic codes for renal failure or renal impairment	Bipolar disorder	Bipolar disorder, no lithium use, adjusted for age and sex	2496 lithium users	3864 non-users	Relative risk of renal impairment or renal failure	Median of 5.4 years	Hazard ratio for renal failure 2.7 (CI 1.7 - 4.3), p=0.001
Rodrigo et al., 2014,	Comparative cross-sectional study: GFR from serum creatinine	ICD-10 clinical diagnosis of bipolar affective disorder	Matched patients without a psychiatric condition with respect to age, gender and co-morbidities	47	47	Mean eGFR compared to controls	-	Statistically significant impairment in eGFR in the group without co-morbidities (p<0.05)
Clos et al., 2015	Population based cohort study: mean eGFR levels	Unclear	Patients with exposure to other first-line drugs	305	815	Mean annual decline in eGFR	-	No effect of stable lithium maintenance therapy (levels within therapeutic range) on the rate of change of eGFR over time
Ott ey al., 2016,	Population based retrospective cohort study: serum eGFR and creatinine levels	Bipolar affective disorder	Bipolar disorder, no lithium use, adjusted for age and sex	Episodes of lithium intoxication	-	Creatinine levels before, during and after lithium intoxication	-	No change in renal function from baseline

GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, CrCl = creatinine clearance, Umax = urinary concentrating ability, WMD = weighted mean difference

Table 2.3 continued: Results of included studies - Renal effects of lithium

From the meta-analysis and systematic review of studies published in 2012, a small reduction in GFR (0.5ml/min) was seen in lithium-treated patients over a mean observation time of one year. This was also reflected in case control studies where the GFR of lithium-treated patients was lower than that seen in controls. The maximum urinary concentrating ability was also reduced by about 15% in lithium-treated patients when compared to controls (McKnight et al., 2012, Hullin et al., 1979, Vestergaard et al., 1979, Grof, 1980, Walker et al., 1982a, Walker et al., 1982b, Jensen and Rickers, 1984, Johnson et al., 1984, Smigana et al., 1984, Bendz, 1985, Vaamonde et al., 1986, DePaulo et al., 1986, Hetmar and Rafaelsen, 1987c, Hetmar et al., 1987b, Åberg-Wistedt et al., 1988, Jorkasky et al., 1988, Schou and Vestergaard, 1988, Waller et al., 1988, Muir et al., 1989, Nilsson and Axelsson, 1989a, Hetmar et al., 1991, Povlsen et al., 1992, Kallner and Petterson, 1995, Bendz et al., 1996, Coşkunol et al., 1997, Bendz et al., 2001, Turan et al., 2002, Presne et al., 2003). The results found from published studies after the 2012 systematic review correlate with these results in the main with significant increases in creatinine or decreases in eGFR being shown in addition to an increased hazard ratio for renal failure (Tredget et al., 2010, Janowsky, 2011, Close et al., 2014, Rodrigo et al., 2014). The studies by Rej et al., Clos et al., and Ott et al., which focussed more on different lithium levels or intoxication and the variation in effect on renal function, if any, did not show a significant correlation between lithium levels and change in eGFR (Rej et al., 2013b, Clos et al., 2015, Ott et al., 2016). A meta-analysis including the results of studies published since the McKnight review was not performed due to the small number of additional studies found and their different inclusion and exclusion criteria, and analysis methods (McKnight et al., 2012). These studies were collated and a general overview of

the results was considered for this thesis, therefore specifics such as the frequency of lowered GFR on lithium cannot be determined from these results. However the recently included meta-analysis by Rodrigo et al., comments that in an earlier comparative analysis by Bolton et al., not included in this thesis, a majority (85%) of patients on long term lithium had normal estimated glomerular filtration rates (eGFR), 15% had reduced eGFRs (Bolton, 2011, Rodrigo et al., 2014).

2.7 Discussion

2.7.1. Therapeutic level

The review article by Severus et al., from 2008 highlighted that there was still uncertainty about the most effective lithium level for the prophylactic treatment of bipolar disorder (Severus et al., 2008). Historically, the serum levels for the manic stage had been recommended as between 0.8-1.9mmol/L. The recommendations for the prophylactic range used appear to have been extrapolated from the anti-manic range suggested by Prien et al., and the idea that the plasma concentration thought to induce toxic effects in patients was >2.0mmol/L and so the treatment dose lay just below this (Prien et al., 1973, Hullin, 1979, Jerram and McDonald, 1978). Studies conducted in this area started to look at both the maximum and minimum effective ranges for the prophylactic use of lithium, using a variety of lithium level ranges from 0.24 to 1.4mmol/L.

Once lithium started to be used longer term as a prophylactic medication, the recommended levels for patients to be maintained at had not been clearly established, hence the number of research studies focussing on this at the time. The long-term side effects of lithium had also not yet been studied and concerns were raised in the design of these studies around what would happen to patients whose blood levels were held just below the toxic level. Evidence was needed to show the lowest lithium level which was effective in preventing relapses and lowering overall morbidity.

Stokes et al., showed that a low dose of lithium (0.24 mEq/kg/day) was not found to be more efficacious than placebo, but the proportion of patients with improved manic

ratings did increase markedly as a function of an increased steady-state serum lithium level (Stokes et al., 1976). As there was no difference seen between the lithium level groups in the study by Jerram and McDonald, they were the first authors to suggest that in some patients, lithium levels below 0.49mmol/L had the potential to still be effective (Jerram and McDonald, 1978). With a longer-term follow-up of these same patients by Hullin, with a further breakdown of the low levels used, a minimum effective serum lithium level of 0.4mmol/L is suggested. A higher relapse was rate seen in patients whose lithium levels were maintained between 0.25-0.39mmol/L (Hullin, 1979). This is further supported by Waters et al., and Vestergaard et al., who used lithium levels down to 0.3mmol/L and showed no significant difference between groups (Waters et al., 1982, Vestergaard et al., 1998). Abrupt changes in lithium level, seen in the trial designs of the cross-over studies, were also associated with relapses (Waters et al., 1982). Waters et al., commented that although the lower level lithium group in their study had more relapses they thought that this was due to the change in lithium level rather than the lower level itself. This is because there was a trend for relapse to occur within two months of an abrupt drop in plasma lithium level (Waters et al., 1982).

To find the evidence for the lithium levels above which no further efficacy is gained, Coppen et al., first mentioned that at levels >0.8mmol/L the beneficial effect in affective morbidity index (AMI) was not seen compared to levels of ≤0.79mmol/L (Coppen et al., 1983). Although patients held at 0.45-0.59mmol/L and 0.6-0.79mmol/L had a reduction in AMI and those at ≥0.80mmol/L had a slight increase in AMI, these changes were not significant. This significance seems to be due to the unipolar patients within the group as when the two diagnostic groups were analysed separately the unipolar patient groups

showed a significant reduction in AMI with a plasma lithium level on ≤0.79mmol/L but for the bipolar patients there was no significant difference in AMI for any of the different plasma lithium level ranges. This study seems to show that a reduction in lithium level from 0.86±0.2mmol/L to ≤0.79mmol/L in unipolar patients has a significant reduction in morbidity but it does not support the same effect in bipolar patients. At odds with the findings of the Coppen study, Maj et al., found that in their patients there was a numerically marked decrease in manic but not depressive symptoms in the 0.76-0.9mmol/L group compared to the 0.61-0.75mmol/L group. However evidence for the minimum effective plasma level agreed with the earlier studies, showing that reductions in morbidity started at levels ≥0.45mmol/L (Maj et al., 1986).

The only trial to look at the higher end of the lithium level ranges without the complicating effect of changing dose, and the potential rebound effect associated with this, concluded that doses resulting in serum levels from 0.8-1.0mmol/L were more effective than those in the lower range. After adjustment for stratifying variables (length of remission before study entry, number of previous episodes and polarity of recent episode) the low range group patients had a significantly shorter time to relapse according to Cox proportional-hazards regression analysis (Gelenberg et al., 1989). There was, however, a higher percentage of side effects such as tremor, dizziness, urinary frequency and weight gain in the high dose group, with borderline significance (p values: 0.05, 0.06, 0.06, 0.07 respectively).

Overall the optimal lithium level for the maintenance treatment of affective disorders appears to be between 0.4-0.79mmol/L. An increase in side effects without a consistent

reduction in AMI or reduction in relapses seems to occur at levels ≥0.80mmol/L. Levels greater than 0.8mmol/L may be effective in the short term for manic patient but are not therefore recommended for longer-term maintenance treatment of unipolar or bipolar disorder.

2.7.2. Monitoring parameters

No high quality evidence for the frequency of monitoring of lithium levels, either historically or currently, could be found in this literature review. The British National Formulary used to advocate routine monthly monitoring of serum lithium and currently recommends three monthly monitoring of lithium levels (Joint Formulary Committee, 2015). Current national guidelines recommend three monthly levels for the first year reducing to six monthly after that except for patients in the following groups, taken from NICE Clinical Guideline number 185, page 37:

- older people,
- people taking drugs that interact with lithium,
- people who are at risk of impaired renal or thyroid function, raised calcium levels or other complications,
- people who have poor symptom control,
- people with poor adherence,
- people whose last plasma lithium level was ≥0.8 mmol/L.

(NICE, 2014a)

The changes over time to the recommended frequency of monitoring of lithium comes from consensus agreement, behind which there is a lack of an evidence base. The concerns raised about the need for lithium monitoring from included studies are based on the prevention of side effects and to anticipate the possibility of gradual 'creeping' effects on renal function. The potential for external effects on lithium levels such as interacting medications, fluid intake or concurrent illness is enough to warrant continued monitoring. Further evidence, however, is required to confidently recommend any further changes in the frequency of monitoring from current guidance.

2.7.3. Renal effects

Renal function is important for the elimination of lithium and a declining GFR will increase any risks of lithium toxicity due to accumulation. Although some evidence supports the theory that lithium is responsible for progressive glomerular damage there is still evidence against this idea (McKnight et al., 2012). Most evidence suggests that although there is not a definitive correlation between treatment with lithium and glomerular function decline, leading to renal failure, there does appear to be some association between lithium treatment and urinary concentrating ability.

Due to the long time period over which the studies included were performed there have been changes, not only in diagnostic criteria but also the accuracy of laboratory testing. Most of the included studies did not use a patient group which was lithium naïve and the duration of follow-up was not always entirely clear, making the time between exposure to lithium and the onset of adverse renal effects difficult to define (McKnight et al., 2012).

Dose information was also inconsistently recorded, so any correlations between the renal side effects of lithium, serum lithium levels, and doses used in practice cannot be made.

A small reduction in GFR, 0.5ml/min over one year, does seem to be associated with lithium treatment. This reduction is, however, not considered clinically significant due to overall renal function decline over time in the general population (NICE, 2014b, McKnight et al., 2012). Progressive reductions in glomerular function do, however, have the potential to lead to end-stage renal disease. In the 1970s cases of chronic tubulointerstitial nephropathy were described in patients with lithium-related end-stage renal failure (Aurell et al., 1981, Hestbech et al., 1977). Only a small number of patients on long-term lithium therapy, however, go on to develop renal insufficiency or end stage renal disease thought to be caused by their lithium treatment (Markowitz et al., 2000, Coşkunol et al., 1997, Tredget et al., 2010).

2.8 Conclusion

The two decades of small trials investigating therapeutic lithium levels suggested that the optimal lithium level for the maintenance treatment of affective disorders appears to be between 0.4-0.79mmol/L. The association of levels above >0.8mmol/L and a small reduction in GFR, unwanted side effects, fluctuations of lithium level and non-compliance compared to those below 0.8mmol/L is replicated in modern guidance and contrasts with the earlier high level of 1.5mmol/L (Severus et al., 2008). Once these therapeutic ranges had been defined, and have since become common practice and are reflected in current guidelines, the practice of the routine monitoring was debated (NICE, 2014a, BAP, 2009). From the literature search and review conducted for this thesis there was no robust evidence to support any previously recommended monitoring frequencies, which have ranged from monthly to yearly.

The effect of lithium on renal function is still under debate and although there is increasing evidence of lithium's effect on urinary concentrating ability, there has only been a small effect on GFR seen which is not consistent across all studies. Further breakdown of any different impact of the range of lithium levels used in practice on GFR has not been clearly evidenced as the studies available do not consistently report doses or serum lithium levels. Although the risk of end-stage renal failure is low, lithium is primarily renally excreted and decreases in GFR could lead to accumulation, increasing serum levels and so this is an area which could warrant further investigation.

The current evidence base is not sufficient to draw conclusions on the effect of lithium in patients with previous histories of lithium toxicity or the different effects of doses, including low-dose lithium.

A quantitative section is needed to further establish the effects of lithium and lithium levels on renal function using the data collected from a lithium register and monitoring database in operation throughout Norfolk. Firstly a sense is needed of this data base and the type of impact, if any, it has had on lithium monitoring. The robustness of the data and a general sense of the data collected is needed in order to see if analysis of the database can add to these gaps in the current literature. Secondly, a disparity in the prescribing of lithium between the two counties covered by the one Mental Health Trust in the area has been shown from prescribing data and it is not yet known what factors are behind this disparity (Powell-Smith and Goldacre, 2015).

■■■ Chapter Three

3: An evaluation of the impact of active management of lithium monitoring within Norfolk

3.1 Introduction

Lithium is known to have significant side effects and requires close serum level monitoring to ensure levels remain within the therapeutic range to minimize the risk of serious adverse effects or toxicity. Lithium levels are also affected by the patient's renal function, any changes is this or their fluid balance and some concomitant medications that affect kidney function and the excretion of lithium (NPSA and NRLS, 2009). Lithium can also cause hypothyroidism, the symptoms of which can overlap with some features of bipolar disorder, particularly in the depressed poles of the illness. Without regular and specific screening tests being carried out small, but potentially incremental, changes in renal function or a new onset of hypothyroidism mimicking symptoms of depression, may remain undiagnosed.

There were no national guidelines for the monitoring of lithium, outside of the recommendations in the BNF, until 2003 with the publication of the British Association for Psychopharmacology (BAP) guidelines and 2006 with the National Institute for Health and Care Excellence (NICE) bipolar guidance (NICE, 2006, BAP, 2009). The BAP guidelines focus on the evidence behind the treatment options for bipolar disorder with no mention to frequency of monitoring,

Lithium therapy is thought to be prone to errors occurring in prescribing and audits have shown that the monitoring of lithium, even after the release of the guidelines above, was

unsatisfactory (NPSA, 2009, Collins et al., 2010). As an aid to help healthcare practitioners comply with the frequency of lithium monitoring recommended by NICE, the National Patient Safety Agency released a patient safety alert on safer lithium therapy. This alert made monitoring and the provision of information to patients prescribed lithium a priority for all healthcare organisations where *'lithium therapy is initiated, prescribed, dispensed or monitored'* (NPSA, 2009).

Within Norfolk a therapeutic drug monitoring database was set up, prior to this NPSA safety alert, to improve the standards of lithium monitoring throughout the region. This occurred following several incidents in primary care within Norfolk involving lithium therapy and inadequate monitoring (Holmes, 2005).This chapter will focus on an evaluation of this actively managed database to determine its impact on the monitoring of lithium treatment within the county. Currently there has not been an analysis of the database and its impact on monitoring of lithium in a way that is comparable to national audits and results.

3.2 Standards of lithium monitoring in the UK

In order to improve standards of care received by patients with mental health or emotional needs the Royal College of Psychiatrists College Centre for Quality Improvement (RCPsychCCQI) exists. The sole aim of this centre is to improve the quality of psychiatric care through the use of audit-based Quality Improvement Programmes (QIPs) (Collins et al., 2010). The Prescribing Observatory for Mental Health UK (POMH-UK) is part of the CCQI and facilitates audit-based QIPs focussing on medications and their use and monitoring within psychiatry. In 2009 all National Health Service (NHS) Trusts within the UK providing specialist mental health services were invited to participate in a baseline audit on the quality of lithium monitoring (Collins et al., 2010). This was the first published audit on national lithium prescribing and monitoring within the UK.

Patient data were submitted from 38 Mental Health Trusts, excluding Norfolk, from 436 clinical teams and included 3373 patients. The number of Mental Health Trusts in the UK at the time is not evident from the report however there are 60 Trusts included in the 2015-16 POMH-UK programme (Royal College of Psychiatrists, 2016). Having a central register of patients prescribed lithium is rare and so Trusts used a variety of methods to identify their sample including a census of prescriptions, clinical team caseloads, pharmacy and pathology records (Collins et al., 2010). The audit standards were derived from the NICE guideline for bipolar disorder published at the time which stated that during maintenance treatment with lithium: *'a serum lithium level should be taken every 3 months, renal and thyroid function tests should be completed every 6 months (more often*

if there is evidence of impaired renal function), and weight, BMI or waist circumference should be done annually' (NICE, 2006).

In addition to NICE recommendations the Quality and Outcomes Framework (QOF) also sets targets for the monitoring of patients receiving lithium in primary care in the UK. The QOF was initiated in 2004, as part of the General Medical Services Contract as a voluntary scheme. Practices in primary care are scored against groups of indicators within this incentive scheme, according to their level of achievement (The Information Centre for Health and Social Care, 2012). Within the QOF section on mental health practices are scored for: *'the percentage of patients on lithium with a record of serum creatinine and thyroid stimulating hormone (TSH) within the preceding 9 months, a record of lithium levels in the therapeutic range within the previous 4 months and a BMI recorded in the past 15 months'* (The Information Centre for Health and Social Care, 2012).

There were two groups of patients within the POMH-UK data: patients who had been prescribed lithium for less than a year; and those patients who were prescribed lithium maintenance treatment and had been on it for over a year. If multiple test results were reported in one month these were treated as one data point as they were unlikely to be due to routine monitoring (Collins et al., 2010).Table 3.1 shows the frequency of tests for patients on maintenance treatment included in this audit.

Number of tests in past year	U&Es with creatinine	Thyroid function tests	Serum lithium
n=2976			
0	553 (19)	524 (18)	273 (9)
1	795 (27)*	976 (33)*	668 (22)
2	592 (20)#	693 (23)#	572 (19)*
3	466 (16)#	453 (15)#	561 (19)*
4	313 (11)#	208 (7)#	503 (17)#
5 or more	257 (9)#	122 (4)#	399 (13)#

* meets QOF targets, # meets NICE standards

Table 3.1: POMH-UK data - Lithium monitoring tests or measures conducted during maintenance treatment, all are number (percentage), adapted from Collins et al., 2010.

This data showed that 19% of patients had no record of renal function tests, including creatinine, 18% had no record of thyroid function tests and 9% had no record of lithium levels in the preceding year. Only 30% of patients who had been prescribed lithium for over a year had received four or more lithium tests in the preceding year and 38% of patients had two or three tests. Data for renal function tests recorded within the past year, including creatinine, showed that 83% of patients had one or more tests, and 56% had two or more tests recorded. For thyroid function tests 82% of patients had one or more tests and 49% had two or more tests recorded (Collins et al., 2010).

3.3 Patient safety alert

In December 2009, the National Patient Safety Agency (NPSA) released a patient safety alert in an attempt to improve the safety of lithium therapy within the UK (NPSA, 2009). The release of this patient safety alert was in part due to the results of the POMH-UK audit as well as concerns about patient safety incident reports. In the five years prior to this NPSA alert, the National Reporting and Learning System (NRLS) received 567 patient safety incidents related to lithium therapy (NPSA and NRLS, 2009). During the same time frame in Norfolk there were there were no reported incidents relating to lithium therapy monitoring (Cree, 2011). The majority of these incidents resulted in no or low harm. However a key theme was inadequate patient monitoring (NPSA, 2009).

A lack of patient monitoring, and the risks it entails, also holds a risk of litigation. In a ten year review the Medical Defence Union found that there were over 100 cases of litigation involving lithium prescribing and monitoring. Out of these poor monitoring was cited in 59 of these cases, 13 of which involved deaths (excluding suicides), and 44 were cases of toxicity with various outcomes (Holmes, 2005). No further details were available on whether this poor monitoring was related to medication or other monitoring of the patient. Between 1995 and 2004 the NHS Litigation Authority dealt with two fatal and 12 severe harm incidents which involved lithium therapy (NPSA, 2009). The NPSA alert highlighted the need for regular monitoring in line with NICE guidance, reliable communication systems for blood test results, the provision of appropriate verbal and written information to patients and that systems are in place to identify and deal with medicines that may adversely interact with lithium therapy (NPSA, 2009).

3.4 Implementation of the Norfolk-wide database

In May 2000, the newly formed clinical liaison prescribing sub-group of the Norfolk Mental Health Care Trust (NMHCT[1]) conceived the idea of a Norfolk wide lithium register and database which came to be known as SystemTDM®. A series of clinical incidents had occurred involving lithium toxicity and this had raised concerns over a lack of a consistent approach in monitoring. Norwich Primary Care Trust (PCT) requested an investigation into the standard of lithium monitoring in GP practices, and found a wide variability in standards (Holmes, 2005). The pathology lab at the Norfolk and Norwich University Hospital (NNUH) also carried out a survey extracting data from their system for any lithium levels recorded between October 1999 and October 2000. There were a total of 1457 lithium patients found on the system and out of these 32.6% had only one test recorded, 54.3% had one or two tests, 45.6% had three or more tests, and 29.4% had four or more tests. It is not known how many patients had no tests during the year as data could only be extracted for those patients who had at least one lithium level recorded on the pathology system at the NNUH (Holmes, 2005).

The main objectives of SystemTDM® are to ensure that all patients prescribed lithium have access to adequate information, education and specialist advice and receive regular blood tests following an agreed protocol (Norwich Clinical Liaison Group, 2010). Once the decision is taken by a prescriber to prescribe a patient lithium, a registration form is

[1] Norfolk Mental Health Care NHS Trust became Norfolk and Waveney Mental Health Partnership NHS Trust in 2004, a Foundation Trust in 2008 and subsequently Norfolk and Suffolk NHS Foundation Trust in 2012.

completed. After registration patients receive an information pack and the blood test reminder system is set in place. Reminders are automatically sent, by letter, 11 weeks after each lithium test, for 12 weekly blood tests, but these can be altered if a different frequency of monitoring is required. Follow-up contact is made with both the patient and prescriber if no test results are subsequently recorded on the database (Holmes, 2005). By May 2012, the database had been in existence for almost ten years across Norfolk allowing the on-going effect of the database on rates of testing for lithium levels and other monitoring parameters to be evaluated.

The database is also considered an 'active management' database in that it not only sends out reminders for blood tests to the relevant people involved in the patients care but it also alerts prescribers to any results that are out of the range specified for that patient. The time taken for the next test to be taken only shows that a re-test has been done but not how long they remain at levels >1.0mmol/L. There is currently no way of predicting which patients are at risk of developing histopathological changes after long-term treatment with lithium and if this is associated with the time spent at different lithium levels. The mechanism(s) behind the histopathological changes are not fully understood, nor is the true long-term risk of lithium treatment (Raedler, 2012, Raedler and Wiedemann, 2007, McKnight et al., 2012, Joint Formulary Committee, 2012).

3.5 Aims and Objectives

3.5.1. Aim

The aim of this service evaluation was to determine the impact of an actively managed database (SystemTDM®) on the services provided to patients by evaluating the rates of testing and responses to lithium levels outside of the recommended ranges from NICE (NICE, 2006).

3.5.2. Objectives

The objectives of this evaluation were to:

- Establish the frequency of lithium, creatinine and thyroid function tests for patients registered on SystemTDM®,
- Evaluate the impact of SystemTDM® on these rates of testing,
- Establish the frequency of lithium levels outside of the recommended ranges and the speed of response to lithium levels outside of the recommended ranges,
- Evaluate the impact of SystemTDM® on the speed of response to these levels.

3.6 Methods

The protocol and supporting documentation for the analyses in chapters three, five and six are included in appendices one, two and three respectively. This research was limited to secondary use of information previously collected in the course of normal care, without an intention to use it for research at the time of collection. It is therefore excluded from Research Ethics Committee (REC) review, provided that the patients or service users are not identifiable to the research team in carrying out the research. Local research governance approval was received from Norfolk and Suffolk NHS Foundation Trust (NSFT) Research Governance Committee prior to commencing data extraction.

3.6.1. Data extraction

The clinical pharmacy team had access to the full data stored on SystemTDM® and passed on the following data to the primary researcher (PhD student) once anonymised: database ID, date of test results and results for: lithium, creatinine, and thyroid function (thyroxine (T4) and thyroid stimulating hormone (TSH)). The data was checked by the clinical team and duplicate entries were removed. For example some patient IDs appeared twice in the original data with differing genders or dates of birth with results recorded for one of these IDs. The clinical team clarified the correct entry and ensured that the correct anonymised entry was passed onto the research team.

From these anonymised results received, test results for 2005, 2009 and the most recent year at the time which was 2012 (Jan 1st –Dec 31st) were used for this evaluation. The year 2005 was taken as the first year of the database for the purposes of this analysis to

allow time for SystemTDM® to become routine across the whole county as it was fully rolled out by mid-2004, and 2009 was used to enable comparisons to the POMH-UK data. Multiple tests conducted within the same calendar month were counted as a single test as these were likely to have been conducted for a purpose other than routine monitoring. If no result was inputted for a recorded test date i.e. a test was logged but had no result recorded, these were excluded, and duplicates in terms of all variables were dropped. Patients whose database IDs were linked to individualised level ranges outside of the nationally recommended range (0.4-1.0mmol/L) were also excluded as it was not known from the data available what the reasons were for these individual level ranges being set, this related to only one patient registered on the database. Once registered patients with individualised level ranges had been excluded there were 1465 patient IDs passed onto the primary researcher for analysis for 2005, 1536 for 2009 and 1381 for 2012.

The number of patients registered and receiving the nationally recommended numbers of blood tests for various monitoring parameters was then analysed. Four groups of ranges of lithium levels were chosen to be analysed: <0.4mmol/L, 0.41-0.8mmol/L. 0.81-1.0mmol/L and >1.0mmol/L as these ranges reflect current UK practice and consensus agreement (NICE, 2006, BAP, 2009). The time taken for the patient to have another blood test after a lithium level result of >1.0mmol/L was calculated. This was done for all results of >1.0mmol/L received in 2005, 2009, and 2012 and gave the number of observations, the mean, and the median time to the next observation. The number and the percentage of recorded tests within seven, 14, 21, 28 and 90 days were calculated. A Kruskal-Wallis test was performed on the data, as it could not be confirmed if repeated tests were conducted on the same participants at all three years from the way that the data was

modelled for the analysis. Therefore the same patients were not necessarily followed through at all three years.

The time to the next lithium level recorded as <1.0mmol/L was then calculated after a level was recorded as >1.0mmol/L for the three date ranges of 2005, 2009, and 2012; this gave the number of observations, the mean, and median time to the next observation. The number and the percentage of recorded tests that were <1.0mmol/L by seven, 14, 21, 28 and 90 days were calculated. A Kruskal-Wallis test was performed on the data, as it could not be confirmed if repeated tests were conducted on the same participants at all three years from the way that the data was modelled for the analysis. Therefore the same patients were not necessarily followed through at all three years.

Including only patients who had tests at all three years would significantly reduce the sample size available due to patients being added or removed from the database over the timeframe from 2005 to 2012.

STATA SE 12.1 was used for all statistical analysis (StataCorp, 2011).

3.7 Service evaluation results

3.7.1. Rates of testing

Table 3.2 shows the number of patients registered on SystemTDM® and the frequency of their lithium level tests between Jan 1st –Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st – Dec 31st 2012, all are number (percentage).

Number of tests in the past year	2005	2009	2012
n=	1465	1536	1381
0	133 (9.1)	0 (0)	15 (1.1)
1	704 (48.1)	61 (4.0)	90 (6.5)
2*	306 (20.9)	105 (6.8)	115 (8.3)
3*	161 (10.9)	307 (15.2)	233 (16.9)
4 or more#	161 (10.9)	1063 (69.2)	928 (67.2)

* meets QOF targets, # meets NICE standards

Table 3.2: Lithium level tests conducted on registered patients between Jan 1st –Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st –Dec 31st 2012

Table 3.2 shows that in 2005 the majority of patients registered on SystemTDM® were receiving fewer than the recommended four serum lithium tests per year (89.0%). A large proportion of these patients had one or two tests recorded (69.0%). At the time of the POMH-UK audit in 2009 this proportion has noticeably increased, with the majority of patients now receiving four or more lithium tests per year (69.2%). By 2012 these figures have not altered, with the majority of patients still receiving four or more tests per year (67.2%).

Table 3.3 shows the number of patients and the frequency of their creatinine tests between Jan 1st –Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st –Dec 31st 2012, all are number (percentage).

Number of tests in the past year	2005	2009	2012
n=	1465	1536	1381
0	1242 (84.8)	176 (11.5)	17 (1.2)
1*	84 (5.7)	116 (7.6)	165 (11.9)
2 or more#	138 (9.4)	1244 (81.0)	1199 (86.9)

* meets QOF targets, # meets NICE standards

Table 3.3: Creatinine tests conducted on all registered patients between Jan 1st –Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st –Dec 31st 2012

This shows that in 2005 the large majority of patients were not receiving two or more creatinine level tests per year as a marker of renal function. By 2009 and again by 2012 there are increases seen in the numbers of patients receiving two or more creatinine level tests over each year analysed.

Table 3.4 shows the number of patients and the frequency of their thyroid function tests between Jan 1st –Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st –Dec 31st 2012, all are number (percentage).

Number of tests in the past year	T4			TSH		
	2005	2009	2012	2005	2009	2012
n=	1465	1536	1381	1465	1536	1381
0	1409 (96.2)	498 (32.4)	330 (23.9)	1228 (83.8)	205 (13.3)	36 (2.6)
1*	28 (1.9)	175 (11.4)	309 (22.4)	117 (8.0)	123 (8.0)	209 (15.1)
2 or more#	28 (1.9)	863 (56.2)	742 (53.7)	120 (8.2)	1208 (78.6)	1136 (82.3)

* meets QOF targets, # meets NICE standards

Table 3.4: Thyroid function tests conducted on all registered patients between Jan 1st – Dec 31st 2005, Jan 1st –Dec 31st 2009 and Jan 1st –Dec 31st 2012

In 2005 a small number of patients had two or more tests for T4 and TSH recorded. By 2009 and again by 2012 there are increases seen in the numbers of patients receiving two or more two or more tests for T4 and TSH over each year analysed.

3.7.2. Speed of response to lithium levels outside of the recommended range

Table 3.5 shows the number of tests recorded as >1.0mmol/L and the times taken for a retest, figures are number (percentage).

Time to next lithium level test	**Year**			
	2005	**2009**	**2012**	
Number of tests recorded as >1.0mmol/L	192	243	222	ANOVA between years
≤7 days	63 (32.8)	107 (44.0)	132 (59.5)	p=<0.05
8-14 days	13 (6.8)	35 (14.4)	23 (10.4)	p=<0.02
15-21 days	7 (3.6)	22 (9.1)	8 (3.6)	p=<0.01
22-28 days	2 (1.0)	12 (4.9)	5 (2.3)	p=<0.01
29-90 days	58 (30.2)	34 (14.0)	36 (16.2)	p=<0.01
>90 days	49 (25.5)	33 (13.6)	18 (8.1)	p=<0.01

Table 3.5: Number of tests recorded as >1.0mmol/L and the times taken for a retest in 2005, 2009, and 2012.

This shows a significant difference between the numbers of patients receiving a retest within seven days (p=<0.05), 14 days (p=<0.02), 21 days (p=<0.01), 28 days (p=<0.01) and 90 days (p=<0.01) in 2005, 2009, and 2012. For the years 2005, 2009, and 2012 after all reports of a level of >1.0mmol/L the time taken (in days) for the level to drop back below 1.0mmol/L was calculated.

Table 3.6 shows the time taken for the lithium levels to return to <1.0mmol/L after a level of >1.0mmol/L was reported, figures are number (percentage).

Time to next lithium level <1.0mmol/L after a level >1.0mmol/L	**Year**			
	2005	**2009**	**2012**	
Number of tests recorded as >1.0mmol/L	192	243	222	ANOVA between years
≤7 days	37 (19.3)	77 (31.7)	101 (45.5)	p=<0.02
8-14 days	14 (7.3)	38 (13.0)	21 (9.5)	p=<0.01
15-21 days	9 (4.7)	23 (9.5)	8 (3.6)	p=<0.01
22-28 days	1 (0.5)	12 (4.9)	7 (3.2)	p=<0.01
29-90 days	36 (18.8)	36 (14.8)	37 (16.7)	p=<0.02
>90 days	94 (49.0)	54 (22.2)	46 (20.7)	p=<0.01
Missing	1 (0.5)	0 (0.0)	0 (0.0)	

Table 3.6: Time to next lithium level <1.0mmol/L after a level >1.0mmol/L has been reported in 2005, 2009, and 2012.

This showed a statistically significant difference in the time for the level to return to <1.0mmol/L within seven days (p=<0.02), 14 days (p=<0.01), 21 days (p=<0.01), 28 days (p=<0.01) and 90 days (p=<0.02) between the years 2005, 2009, and 2012 i.e. random sampling would not result in a sum of ranks as far apart as shown here.

3.8 Discussion

Since the implementation of SystemTDM® throughout Norfolk there has been a steady increase in the number of people receiving lithium, renal and thyroid function tests as recommended by NICE (NICE, 2006). The results from this evaluation were from a year before the NICE guidance was published for lithium monitoring. However, the results for Norfolk from the same year as the POMH-UK audit show that the number of patients having all of the required monitoring tests were much higher. There were 69.2% of patients within Norfolk having the recommended four or more lithium level tests per year compared to 30% nationally (Collins et al., 2010). For the other monitoring parameters the same is seen with 81% of patients within Norfolk having the recommended two or more tests for creatinine compared with 56% nationally and 67.4% of patients within Norfolk having the recommended two or more tests for compared to 49% nationally for thyroid function tests (combined) (Collins et al., 2010). These frequencies have continued to increase by 2012, albeit at a slower rate.

These results show that with the use of SystemTDM® NSFT were able to achieve much better rates of testing for all monitoring parameters, more in line with national guidelines, than other NHS Trusts who took part in the POMH-UK audit. Due to the movement of patients within the country, new starters and people stopping lithium as well as the potential for end of life patients being included in the analysis it would not be expected that 100% of patients would be able to be monitored in line with the guidance.

As discussed in the literature review the risk-benefit of lithium for treating symptoms whilst minimising side effects seems to change at levels above 0.8mmol/L. Levels up to

1.0mmol/L still show some additional benefit albeit with the burden of an increased risk profile for developing side effects. The long-term effect of lithium treatment at different levels on renal function, and the duration of time patients remain at these levels has not been established (McKnight et al., 2012).

3.8.1. Strengths and Limitations

One limitation of this data is that we were not able to control for other external factors that could have impacted on this increase in lithium level monitoring in the years since the database implementation. However from an internal audit conducted in 1999 from one of local pathology labs similar rates of testing to 2005 were seen suggesting that such a noticeable improvement in rates of testing was not just due to the secular trend.

During the timeframe of the data analysed the POMH-UK audit was conducted and reported, additionally the Quality and Outcomes Framework was implemented including markers for lithium monitoring. These two external factors may have had a significant effect on the rates of testing seen in the data analysed.

New initiates and people stopping lithium may also be included in the analysis and may account for the 0 to 1 levels recorded. This could not be determined from the data available to the research team.

The reasons for levels recorded as >1.0mmol/L and the actions taken by the clinical team once these results were reported are also not known from the information on SystemTDM®, only the time taken for retests to occur and the levels recorded from them.

In this analysis patients did not need to have a reading at all three time points to be included in the analysis in a bid to maintain sample size, however if only those patients who did have three tests recorded across the three years analysed may ultimately have greater power with a much smaller sample size and further work could be undertaken with those patients data.

3.9 Conclusion

These results suggest that an actively managed database for lithium aids more effective monitoring of lithium by improving the response times to high levels. This reduces patient exposure to the potentially toxic effects of lithium levels >1.0mmol/L. In addition to the increase in the rates of testing and the speed of response to levels >1.0mmol/L, in the five years prior to the patient safety alert after the POMH-UK audit, there were no reported incidents relating to lithium therapy monitoring within Norfolk compared to the 567 patient safety incidents reported to the NRLS in the same time frame. This suggests that the database has had a direct impact on improving patient safety (NPSA, 2009, Cree, 2011) however the impact of external factors such as an increase in training and awareness of lithium and the introduction of QoF in 2004 cannot be quantified.

■■■ Chapter Four

4: Factors affecting lithium prescribing

4.1 Introduction

As discussed previously the short and long-term effects of lithium on the kidneys are still not fully understood and it is not known whether there is any impact from having a robust monitoring system in place to aid in the therapeutic drug monitoring of lithium on prescribing decisions due to the slight unknown around the long-term effects of lithium. The process for prescribing lithium is slightly different to many other medications, in part due to the level of involvement required for all parties when it is prescribed. Nationally, where lithium prescribing is hospital initiated, there are shared care agreements in place allowing secondary care initiation and prescribing until patients are stabilised and transferred to primary care for continued treatment and monitoring (Collins et al., 2010). These sort of shared care agreements have been in place in both Norfolk and Suffolk since 2002.

Prescribing information suggests that lithium appears to be prescribed more often in Norfolk as in Suffolk per head of population, despite the similarity in their current shared care agreements, population size, and age distribution (Anderson, 2012, ONS, 2011, Powell-Smith and Goldacre, 2015). There is a lack of research on the factors which influence prescribing decisions for established treatments; most focusses on new drugs and comparisons between primary and secondary care or comparisons between different healthcare professionals (Schumock et al., 2004, Ljungberg et al., 2007).

4.2 Current beliefs about decision making in prescribing

There have been several studies in the last two decades researching various aspects of decision making in prescribing, but these have mostly focussed on prescribing in primary care or the prescribing of new drugs (Prosser and Walley, 2006, Cutts and Tett, 2003, Denig et al., 2002b, Jones et al., 2001, Jaye and Tilyard, 2002). Qualitative studies of the influences of prescribing in secondary care are scarce. Those studies that have looked at secondary care prescribing have looked at the differences in factors which influence drug use between doctors, formulary commikttee members and other prescribers, or the schemas that doctors apply to their decision making (Schumock et al., 2004, Higgins and Tully, 2005).

One recent systematic review on non-medical prescribing had also completed a scoping literature search which also showed that most research had been conducted in primary care where the bulk of prescribing occurs. This scoping literature search showed that decisions around prescribing were based on a range of factors both clinical and non-clinical which included:

- Patient expectations
- The doctor-patient relationship
- Doctors previous prescribing behaviour

(McIntosh et al., 2016)

It is difficult to tell if the influences on the prescribing of new drugs are the same as on prescribing in general. Newly marketed drugs are often accompanied by scientific literature alongside an intensive marketing campaign from the relevant manufacturers (Ljungberg et al., 2007). In the first stage of decision-making around new drug prescribing pharmaceutical representatives are thought to be particularly influential as they appear to directly increase awareness of a product, or highlight situations where the new drug has advantages over drugs currently available (Prosser and Walley, 2006, Jones et al., 2001, Ljungberg et al., 2007). This impact of advertising or marketing of medications is not reflected across all studies, with those investigating schemas used for prescribing decisions or the impact of guidelines reporting little to no influence of marketing on the choice of what medicines to prescribe (Perlis, 2007, Schumock et al., 2004, Gill et al., 1999). Although knowledge was needed for the process of prescribing, the source of this information and the doctor's interpretation of this influenced the readiness to prescribe certain drugs. The habits of the prescriber and how drugs can be applied in practice to specific patients can lead to differing decisions for the same clinical cases (Denig et al., 2002b, Ljungberg et al., 2007). Where the information was received through personal communication this appears to have a greater impact on the prescribing decisions than information received through other media (McGettigan et al., 2001).

Monitoring of drugs for doctors working in rural localities has been shown to be a significant factor in the choice of drug to prescribe, so the geographic location of patients and their ability to engage with monitoring from a practical perspective is also important (Cutts and Tett, 2003). Although the concerns raised by participants in the Cutts and Tett study were for general medications this could be an even greater influencing factor for

lithium which is known to have a narrow therapeutic range and require close serum level monitoring.

In the study by Higgins and Tully evaluating whether prescribing is viewed as part of a holistic treatment or as a separate entity, a difference was shown between consultants and junior doctors. Consultants viewed prescribing as part of a more holistic approach to treatment whereas junior doctors did not show this thought process. Each prescribing decision made by consultants also involves a risk-benefit or cost-benefit analysis for each patient and their individual situation (Higgins and Tully, 2005). Jaye and Tilyard looked to see if the length of time doctors had been practising for influenced the relative costs of drugs they prescribed. Doctors who reported more experience were shown to be lower cost prescribers and high cost prescribers reported more concerns about not being able to define a clear diagnosis (Jaye and Tilyard, 2002). If prescribers are more familiar with certain drugs they have been shown to choose these drugs over others with which they are less familiar (Ljungberg et al., 2007).

Lithium is a well-established drug and it is not clear if the factors influencing decisions whether to prescribe it are the same as for newer drugs. It also requires serum level monitoring which has been shown to be a negative factor when prescribing general medications. With the disparity of prescribing between Norfolk and Suffolk where one county has a system designed to aid the engagement and monitoring of lithium it is not clear if this is an influencing factor or if there are other reasons for the variation seen. To determine the potential reasons for the difference in prescribing rates between Norfolk and Suffolk an exploration of the factors which affect the decision to prescribe lithium by

interviewing consultants across Norfolk and Suffolk NHS Foundation Trust (NSFT) was needed. For those consultants based within Suffolk this was done before the lithium monitoring database SystemTDM® becomes normal practice as it currently is within Norfolk.

From these articles found as part of the literature search, covering not only secondary care prescribing but also primary care and in areas other than psychiatry there were two main domains which recurred in the conclusions about factors influencing prescribing:

1. Weighing up clinical factors which could include:

- Patient symptom and severity and diagnosis,
- Patients past experience with medications,
- Medication side effects,
- Concurrent physical health problems,
- Medication interactions,
- Prescribers experience with medications,
- Patient preference and beliefs.

2. Interacting with the patients (and relatives where relevant) along the journey to prescribing in a shared-decision making process.

(Chow et al., 2014, Hajjaj et al., 2010, Rajendran et al., 2012, Shepherd et al., 2014, Denig et al., 2002b, Ljungberg et al., 2007, McGettigan et al., 2001, Tan et al., 2009, Hedenrud et al., 2013).

4.3 Aims and objectives

4.3.1. Aim

The aim of this project is to build on the limited research into established drugs to understand the factors affecting lithium prescribing, by eliciting the views and perceptions of consultants working within NSFT on their current practice through in-depth semi-structured interviews.

4.3.2. Objectives

The objectives of the in-depth semi-structured interviews will be to:

- Explore consultants' views on lithium as a drug,
- Explore what factors consultants consider as influential in decisions to prescribe lithium or another drug in current practice,
- Describe the effect of current guidance on the prescribing of lithium,
- Describe the effect of the current shared care agreement and the procedure for transfer of prescribing to primary care,
- Compare the views and perceptions of Norfolk and Suffolk based consultants on the prescribing of lithium i.e. comparing the views of those experienced with SystemTDM® and those who are not.

4.4 Interview rationale

The focus of this project was on prescribing decisions and the factors influencing these in current practice, with a specific interest on lithium. There was anecdotal evidence that lithium was prescribed about twice as often in Norfolk than in Suffolk despite the relative similarity of the populations of these two counties, supported by prescribing data recently accessible (Anderson, 2012, Powell-Smith and Goldacre, 2015). Lithium is currently classified as an amber drug by local drugs and therapeutics committees under clinical commissioning groups (CCGs). This means that the initiation of lithium is recommended to occur within specialist services, with GPs in primary care being invited to take over the responsibility for prescribing and monitoring once the patient has been stabilised. In Norfolk when a patient is initially prescribed lithium or is transferred into the area they should be registered by their GP or consultant with SystemTDM®(Dye and Barker, 2010, Norwich Clinical Liaison Group, 2010).

A qualitative phenomenological perspective was used exploring how prescribers make sense of prior experiences and their surroundings and translate this into practice. Quantitative research methods would not therefore be appropriate as they would not facilitate the in-depth exploration of the different participants' experiences and how they perceive, describe, feel about, remember and make sense of these experiences in relation to their current prescribing practices (Patton, 2002).

Questionnaires and focus groups were considered for this study as both have their advantages and disadvantages. Although the use of a questionnaire allows greater anonymity for the respondent, there is no control over who actually completes the

questions. The design of the questions must be simple so that they are understood by all respondents; however, there is no way of probing or clarifying answers or resolving any potential misunderstandings. The way the respondents interpret questions cannot be predicted with the use of questionnaires, even with the use of a pilot study, so there is a risk of gathering unreliable information or for the respondents to answer questions in a way that they think the researcher wants (Phellas et al., 2011).

If focus groups had been chosen then this would have allowed for opinions to be gathered from a large number of prescribers and allow for more depth of response than questionnaires but they would also provide an environment where the influences of other prescribers could affect responses (Tonkiss, 2011). Focus groups would explore a range of views expressed within the group and how the participants negotiate these whereas for this study the personal reflections and experiences and decision making factors for each individual consultant on their current practice were wanted. Interviews were therefore chosen because the strengths of this method are well suited to our study. They facilitate a depth of focus and understanding of perspectives and experiences of individual consultants and provide scope for open, and sometimes complex, questions to be asked and explained if needed to the interviewee, as well as allowing the interviewer to pick up on non-verbal cues (Ritchie and Lewis, 2003, Phellas et al., 2011).

4.5 Interviews method

The protocol and supporting documentation for this study are included in appendices four through ten. This study received UK ethics approval from the Faculty of Medicine and Health Sciences Research Ethics Committee and the Norfolk and Suffolk NHS Foundation Trust Research and Development Committee in March 2014.

4.5.1. Participant recruitment

Lithium is recommended to be initiated in secondary care and the initial prescribing decision is likely to be made by a specialist mental health practitioner rather than a GP. If shared care protocols are followed then the initial prescribing decision surrounding lithium should be made by a consultant psychiatrist and any requests for shared care prescribing should then come from them (Dye and Barker, 2010, Norwich Clinical Liaison Group, 2010). Recruitment was therefore targeted through NSFT, the local Mental Health Trust. Whilst house officers and specialist registrars prescribe medication, consultant psychiatrists were purposively recruited as the individuals with ultimate responsibility for patients and prescribing, and should be making the initial prescribing decision.

The work contact details of all consultants working for NSFT were obtained from the Trust Research and Development team in order to contact them for this project. A covering letter was sent to all 110 listed consultants, including locum consultants, inviting them to participate in this study. The letter was accompanied by a participant information sheet, an expression of interest form, a decline to participate postcard and a pre-paid envelope addressed to the primary researcher who was the PhD student. An e-mail was sent out at

the same time as the letter, which had a participant information sheet attached and encouraged respondents to reply via e-mail with the information required for the expression of interest form. Although there were reminder emails and letters prepared the response rate was such that these were not required. In addition, as part of regular research meetings involving NSFT consultants, potential participants were alerted to the project by the Research and Development team at the Trust. As the attendance of consultants in the research meetings varies across localities, contact via letter and email was the main method of recruitment.

To contextualise results, potential participants were asked to detail whether they had worked for Norfolk and Waveney Mental Health Trust, the predecessor organisation to NSFT in Norfolk, in the previous ten years on their expression of interest form along with their age bracket and area of specialism. They were also asked if they had been employed in Norfolk or Suffolk for less than a year. This captured those participants who are likely to be less experienced with SystemTDM®, if based in Norfolk or those working within Suffolk who have had previous interactions with SystemTDM®. The only inclusion criterion for the project was that potential participants were consultants currently employed by NSFT and there were no specific exclusion criteria.

4.5.2. Participant selection

From the consultants who expressed an interest in participating, a purposive sample were recruited covering a range of specialities including older adult, forensics, home treatment team, youth service and general adult with an even spread from Norfolk and Suffolk. Although it was likely that the consultants most likely to encounter lithium in their

practice and prescribe it would be based in general adult teams, no exclusions were placed on the areas of practice for prescribers during our recruitment stage. All consultants would have worked within general adult mental health services as part of their training and would have previous experiences surrounding lithium and its prescribing either as a consultant or a junior doctor. It is also possible that lithium could be prescribed either as a new treatment or for continuation of care in the young, elderly, dual diagnosis and learning difficulties patient groups due to its wide range of therapeutic effects (Sanofi-Aventis, 2012, Norgine, 2011, Rosemont, 2011, Sanofi-Aventis, 2011).

One of the objectives of this study was to see if there was any difference in factors influencing prescribing between Norfolk and Suffolk consultants, i.e. those who had access to a systematic computerised database for lithium and those who did not. We initially recruited five participants from each area, also making sure they had diverse specialities for maximum variation sampling (Patton, 2002). If more participants were required after these initial ten interviews then they would be recruited dependent on which areas or demographics required further investigation.

Once participants agreed to be involved with the research and had suggested times and locations that were suitable for them, they were contacted to confirm a time and date for the interview. Once this had been agreed an email or letter was sent to them with confirmation of the date, time and location of the interview. The remainder of the consultants who expressed interest in participating were sent a regret email once data saturation had been reached. There was no financial incentive offered for participating in this study.

4.5.3. Topic guide

The interviews were conducted over two months in 2014 (May and June). Initially a pilot interview was conducted with a consultant who had been involved with the roll-out of SystemTDM® into Suffolk. Due to her involvement with SystemTDM® she would have added potential bias to the results and so was invited to participate as the pilot interviewee. This pilot interview was conducted to not only test the initial topic guide but the process of the interview itself. Feedback was received on the pilot interview by a supervisor experienced in qualitative research. All consultants interviewed were given information about the general topics to be discussed in the participant information sheet and were each asked to sign a consent form before the interview began. The final topic guide used for the interviews can be found in appendix 11.

4.6 Data analysis

Each interview was audio-recorded, transcribed verbatim by the primary researcher and then checked by a supervisor for accuracy once the transcripts were anonymised. The transcripts were analysed independently, using the principles of thematic analysis, by the primary researcher and a supervisor (Braun and Clarke, 2006). There was continual reference made, at all stages, to the original transcripts to help determine the level of themes and subthemes and confirm that these are relevant to what was said in the transcript and had not been taken out of context during the coding process. Regular meetings took place between the primary researcher and supervisor whilst each transcript was being transcribed and analysed to discuss developing themes, if there were any discrepancies found these were discussed and agreement reached. Once all ten transcripts had been analysed the themes were discussed in a final meeting. At this point it was discussed whether data saturation had been reached and if the objectives of the study had been met. As both of these things had occurred, rejection emails or letters were sent out to the remaining nine consultants who had expressed an interest in being involved in the study.

4.6.1. Thematic analysis

Thematic analysis is often used within the field of psychology and has been described in detail by Braun and Clarke in order to standardise the process for researchers (Braun and Clarke, 2006). It is often utilised by novice researchers as it not only provides core skills for other forms of analysis but is seen as intuitive and straightforward to use (Braun and Clarke, 2006, Riessman, 2008). For this study the inductive approach of thematic analysis,

underpinned by subjectivist ontology, lets the intricacies in the collected data be captured. By letting the themes and assumptions develop from the text, rather than searching for pre-defined themes as would be seen in a deductive approach, an understanding of how and why things happen can be elucidated for each participant (Ryan and Bernard, 2003). The developing themes are inherently linked with the data collected during the study rather than the researchers drive or interest in the study topic. The impact of the researcher themselves on the coding process cannot be removed completely as they are an integral part of the research process (Braun and Clarke, 2006, Coghlan and Brannick, 2014).

The process of thematic analysis as detailed by Braun and Clarke in table 4.1, was followed to produce a rich thematic account of the whole data set in order to get a sense of the predominant or important themes (Braun and Clarke, 2006).

Stage	Description
1. Familiarising yourself with the data	Transcribing the data if required then reading and re-reading the data, noting down initial ideas
2. Generate initial codes	Code features of the data systematically across the whole data set, collate data relevant to each code
3. Search for themes	Collate codes into potential theme, gather all data that is relevant for each theme
4. Review themes	Check if themes make sense in relation to the coded extracts and then the entire data set. This will create a 'thematic map' of the analysis
5. Define and name themes	Refine the specifics of each theme and the overall story of the analysis. Clear definitions and names for each theme are defined
6. Produce the report	Selection of appropriate extracts, final analysis of these extracts relating back to the research questions and the literature and production of a scholarly report

Table 4.1: Stages of thematic analysis adapted from Braun and Clarke, 2006

The scissors and paste technique of 'pawing' was used for the analysis without the aid of a computer program. The advantage of this cutting and sorting technique is that the data can be used to describe how the themes are distributed across the interviews (Ryan and Bernard, 2003). Coding started with the first line of the first transcript and progressed through every line of each transcript in chronological order. Some codes covered more than one line if they were within a long passage of text, and so not each line was individually coded, but an effort was made to code as much as possible. Each transcript was coded by the primary researcher and a supervisor independently. Regular meetings took place to discuss the developing themes and to ensure that all themes had been identified.

The primary researcher was a pharmacist with mental health experience who was funded by the 'Lithium database team', which the participants were aware of at the time of the study. The personal experiences and views of the primary researcher may have impacted on the process of analysis and the findings. To negate this effect however the supervisor involved with analysis and coding was a pharmacist but not a mental health specialist. The primary researcher had also attended a course on interviewing skills and received training on qualitative data analysis.

The coding process returned 135 codes in total. These were collated into a coding table, an example of which can be found in appendix 12, and then printed off and cut into individual strips to be manually arranged to reflect their degree of agreement with others e.g. all codes relating to teaching and learning were grouped together. This initially produced 17 themes which were subsequently further combined where differences did not seem clear or there were aspects which interlinked. The final theme which each code fitted into was decided without reference to the original questions asked within the interviews. There was constant revisiting of the transcripts throughout the coding and analysis to validate these themes. To highlight the similarities and differences between the consultants' views identified in the analysis, selected quotes are presented in the results section.

4.7 Results

From the initial 110 recruitment letters and emails sent out ten consultants replied either by postcard or email declining to participate and nineteen expressions of interest were returned. There were five participants initially recruited from Norfolk (N) and five from Suffolk (S) from the nineteen expressions of interest returned. Table 4.2 details the demographics of the included participants and their reference for the quotes included.

Participant reference	Location	Age/Gender	Type of practice
7	N	51-65/M	Crisis resolution and home treatment team
101	S	36-50/F	Old Age
66	S	51-65/M	Home treatment team Liaison/Private
8	S	36-50/M	Learning Disability
69	N	36-50/F	Old Age
90	N	51-65/F	Forensics
77	S	36-50/F	Adult
106	N	36-50/M	Younger adults
57	S	36-50/M	General Adult
50	N	36-50/M	Adult

Table 4.2: Participant demographics

There were four main themes identified in the analysis:

- Knowledge and experience of prescribers,

- Drug factors,

- Patient factors and patient information,

- The monitoring process and setting for initiation.

However, the themes identified should not to be seen as individual influences; many of them potentially act in combination.

4.7.1. Knowledge and experience of prescribers

There were some differences in opinion over who should initiate and prescribe lithium in terms of the grade of doctor and whether it should be a hospital doctor or a GP. The majority of participants interviewed did not feel that lithium needed to be initiated by a specialist and could be done by any doctor as long as they were deemed competent and if junior doctors were supervised.

> *"I think juniors should be initiating it but in discussion with more senior colleagues so I think they should get the experience of doing it"* **(90)**

However one participant considered the effect that the status of the prescriber may have on the patient and whether this would make a difference to them,

> *"so if a consultant prescribes it I guess it's symbolically going to be more important or more powerful than if someone else does"* **(7)**

Although generally the participants felt that all grades of hospital doctors could, and should, prescribe lithium if supervised and most mentioned that a specialist should be involved at some point in the initiation process.

The past experience of doctors involved in prescribing is taken into consideration when they are choosing which drugs to prescribe and competence can be seen to be obtained from these experiences. Whether they have seen a drug work in the past or not and, based on these experiences, how they think the patient in front of them will respond is a guiding factor in prescribing decisions.

"you've seen a number of people and you've seen that well in this particular situation in this patient this works it might work here" **(69)**

There were various sources of information used by the participants which they felt influenced their prescribing decisions. The impact that colleagues, pharmacy and the scientific literature they had read, and what they understood from this, were the most influential.

"then you also have stuff that your friends say that you meet somewhere you know, (INTERVIEWER: yep) you professional colleagues you know and that influences" **(7)**

The use of other colleagues' experiences in group discussions was apparent for those consultants who worked in a ward based environment. However, for those prescribers who were based in clinics, or saw mainly outpatients, there was less of this discussion with colleagues and one participant even noted that they were not aware of the prescribing practices of their colleagues.

"when it comes to team meetings our team meetings are joint [between consultants covering different specialities on the ward] *so I sit there with two other consultants so there are three consultants sitting there in the same meeting so again if there is a difficult one that comes up there are three heads together plus 20 nurses, so you know there is a lot of erm discussion and toing and froing and well I tried this and have you tried that, that happens so"* **(101)**

Here the collaborative ways of practice seen with an inpatient situation are shown with several doctors and nurses available to discuss patients and possible treatment options, drawing on each other's experiences and knowledge.

A generational difference in prescribing practice was also bought up during the interviews by half of the participants,

> *"from the newer generation the junior doctors who haven't seen it or used it think well there are better drugs so they will say why can't we use the lamotrigine, why can't we use the quetiapine so they will try and sort of tend to erm go to the drugs that have come into the market more recently"* **(101)**

This introduced an idea that the participants interviewed thought that newer doctors were more likely to go for drugs that have been launched onto the market more recently and not prescribe the older drugs such as lithium. This feeling about generational differences, and possibly a lack of knowledge about older drugs, was expanded upon when participants were discussing teaching and learning of junior doctors and around the promotion of drugs.

> *"I just think the drugs that are viewed by our trainees as often being off the ark there's almost a responsibility really amongst the consultant body to just be explicit with their trainees about the drugs that they use any why and keep talking about them"* **(77)**

Older drugs such as lithium are not marketed by anyone so there is no promotional material or other forms of marketing for these drugs. An increased emphasis on older

drugs, which may not be marketed, was mentioned by half of the participants in terms of the training and on-going teaching of junior doctors.

When questions about guidelines were asked, most participants felt that they did not use guidelines as a step-by-step "prescribing manual", but just as a background guide, where the diagnosis was clear and the participants were confident that the diagnosis was correct and reassessed regularly.

> *"at the end of the day it's you know you're fitting the patient to the guidelines as well yeah so depends on who is in front of you"* **(69)**

The impact of the patient and their condition was much more prominent and participants gave more weight to their learnt knowledge and experience rather than using guidelines as a strict prescribing schema. Prescriber's personal preferences and knowledge about medicines they had used, seen used or had experience with were strong influences on prescribing decisions.

4.7.2. Drug factors

The participants all had positive thoughts about lithium as a drug noting its efficacy in a wide range of affective disorders.

> *"entirely positive I often describe it as psychiatric dettol erm because of its utility and incredibly well tolerated by the vast majority of patients"* **(66)**

The term 'psychiatric dettol' could be perceived as a rather negative turn of phrase with its antiseptic associations, this participant uses it to describe how useful he finds lithium

to be in a wide variety of situations. Although the participants note that lithium is a highly efficacious drug, it is by no means 'perfect', but its efficacy and utility was still an underlying element of consideration when consultants thought about which drugs to prescribe. The ease of prescribing a drug was a factor for the majority of the participants interviewed, with them commenting that the complexity of prescribing lithium and the work this entails may influence their decision over which drug to prescribe.

> *"you know it requires a bit more work to give someone lithium*" **(50)**

> *"sometimes that hinders your wanting to prescribe"* **(69)**

As there are several drugs to choose from for the treatment of affective disorders, and the fact that patients respond in varying degrees to each of these options, the fact that lithium requires more effort to initiate and prescribe may result in other, easier drug options being favoured having a negative impact on prescribing practices.

> *"I've started using it [lithium] less and less and it's often for fairly practical reasons"* **(50)**

> *"I think I think it it's an underused drug I'm sure of yeah…erm because of its you know because of the ease of of monitoring it and everything else you know compared to all the other drugs we use it's one of the few drugs we can actually say we know what level is going to help most people"* **(66)**

These participants felt that the prescribing of lithium had reduced and it isn't used as much as it should be in part due to the difficulties surrounding initiation and monitoring

when compared to the newer, and somewhat easier to prescribe drugs for affective disorders.

The generational differences in prescribing as discussed earlier were also mentioned again, with reference to the newer generation(s) of doctors not using it either due to a lack of education, experience or the inherent complexities of prescribing. The fact that lithium needs monitoring may negatively impact on the decision to prescribe it can be countered with the fact that prescribers know what level to aim for to treat a patient and get them well and how to monitor this.

When choosing what drug to prescribe for a patient, all the participants mentioned that they consider the side effect profile of the drugs on offer and the consultant's ability to explain this to patients.

> *"at least you could tell people what the side effects were going to be [with lithium]"* **(66)**

In this case participant 66 felt that he was likely to prescribe older drugs for which the side effect profile was clear and easily explained to patients than newer drugs whose side effects were maybe slightly more unpredictable on a patient by patient basis. If there is some confusion over what is likely to happen to a patient or a lack of complete understanding of the side effect profile from the prescriber's perspective then this will negatively affect their thoughts about prescribing that particular drug. Although all participants had positive comments about lithium as a drug, they commented on its side

effect and toxicity profile negatively whilst also highlighting an area of confusion or lack of complete understanding of these effects of lithium.

> *"actually I think there's some misunderstandings around it as to its what long-term effects it does and doesn't cause to the kidneys I get confused as to what's going on there"* **(106)**

Following on from the prescriber understanding of the side effect profile is the added difficulties and required monitoring which goes alongside drugs with a narrow therapeutic range, such as lithium.

> *"if you've got too little it won't do anything if you've got too much you might kill somebody so you need it in the right sort of range"* **(77)**

> *"the main monitoring is about first of all making sure that it's in the therapeutic range"* **(50)**

As picked up by participant 77 the risks associated with lithium when outside of its therapeutic range can be life threatening and there is a serious overdose risk which needs to be considered.

> *"patients might overdose on it and that's a really messy overdose and I say that not just as a psychiatrist but as someone who used to be a medical registrar erm a lithium overdose is a really difficult thing to sort out, it makes people very ill and is not easily amenable"* **(8)**

The participants are notably considering one major hazard of lithium, which is its impact if taken in an overdose. It is variously described as messy and difficult and the potential for this to be lethal is clearly a factor when deciding what drug to prescribe for their patients.

In addition to the risk-benefit considerations prescribers think about when deciding whether or not to prescribe lithium, there was a clear consideration of particular circumstances when lithium would just not be considered as an option.

> *"people with existing renal damage or thyroid problems, people with perhaps with cardiac problems"* **(7)**

The physical health of the patient and the effect that any drug may have on this is a factor in their decision-making process. There are certain conditions or circumstances under which prescribers would not consider lithium and would choose a drug which would not have an impact on the patient's physical health or interact with any other drugs being taken.

> *"I would look at the interactions, what else they might be on, how it's going to work, erm you know it's not unusual again for my lot to be on diuretic, to be on anti-hypertensive, to be on enalaprils or you name it and it's there, all that other bits come into it as well so erm what else they're taking would sort of make a difference"* **(101)**

This was mainly a consideration for those prescribers dealing with the elderly as the potential for polypharmacy is much greater in this group of patients due to the increase in comorbidities with age.

4.7.3. Patient factors and patient information

The participants commented that the presentation of the patient in front of them was a major factor when choosing what drugs to prescribe, regarding their specific set of symptoms and mental and physical health condition(s). However the previous response of the patient treatments is a factor in the choice of drug to prescribe. If they have had something before that had worked for their illness and symptoms then that drug was more likely to be tried as a first choice.

The majority of participants mentioned the potential for misunderstanding of provided information and finding a way to expand on the provision of written information to more of an education process. However participant seven mentions that this is a difficult process and that there is still the potential for misunderstanding from the patient's perspective.

> *"it's kind of hard really hard to get that right so you give people all the information they want and in a way that they really do understand it"* **(7)**

Although there is an emphasis placed on providing information, this is no guarantee that this information is understood or interpreted by the receiver in the same way as the giver. The provision of information and patient education has another facet to it, which is the protection of the prescriber from legal issues surrounding information and development of side effects or more serious problems from treatment.

"medico-legal because if you prescribe something and you fail to inform the patient of risk X,Y,Z and they then develop a complete heart block or whatever in theory then they can sue you because you didn't give them the information" **(7)**

"I don't want them to come back later to say to me you never told me something" **(101)**

This is something that doctors consider when choosing what to prescribe and there were some thoughts that doctors may choose what they consider to be a 'safer' drug in terms of medico-legal issues.

"people are far more aware of it, patients are rightly erm you know complaining when things go wrong" **(90)**

There is an acknowledgement that patients are much more aware of their rights than previously and are willing to complain if things go wrong in their treatment and have become less passive and more engaged in their treatment and treatment choices.

With more of a focus on the patient side of the prescribing, adherence to drug treatment was discussed. There were two subcategories discussed within this area. The first covering the need for patients to take drugs and the fact that with lithium there is a serious risk of rebound symptoms if the drug is stopped abruptly.

"I would want to prescribe it for someone who I thought would be reasonably likely to take it and umm you know do the tests and and stuff and if I thought someone was unreliable and they wouldn't do it then I probably wouldn't prescribe it because that's not going to help anyone" **(7)**

"the discontinuation, the rebound mania that occurs with discontinuation is a big concern" **(50)**

There are risks involved with patients not taking lithium as prescribed, not only that they will not be effectively treated, so it is in effect prescribing a drug that is not going to be taken, but lithium comes with a risk of rebound mania if abruptly stopped. The second subtheme bought in concerns about insight and the capacity to consent to treatment. There is a need for patients to understand their treatment and have the insight to agree to a drug such as lithium which requires a long-term commitment to blood tests for monitoring.

"I've got a clear view as to whether the person has got capacity to make the decision erm and also how how committed they are to that form of treatment" **(66)**

For those patients who do not have the insight and capacity to agree to a form of treatment there are processes in place recognised by the participants of either a "best interest decision" or treating immediately with the constant reassessment for capacity.

"there have been occasions where I've given people, inpatients, antipsychotics and given them the information leaflet quite a lot later" **(90)**

"of course I'm assessing capacity all the time" **(66)**

This assessment of capacity is an ongoing process with some patients being given information about their drugs at a later date when they are able to take this information

on board and make decisions for themselves when perhaps a “best interest decision” had been made at the initial time of prescribing.

Over half the participants also raised the involvement of the patient in the choice of drug to prescribe. The participants acknowledged that it was not them who would be taking the drug and so the thoughts and feelings of the patient on their options of drugs were strongly considered.

> *“at the end of the day it’s their care and they’re going to be taking the tablets and you know having the side effects not you”* **(69)**

> *“or if there’s huge patient preference I try go down that line first”* **(90)**

However they also acknowledged that if drug treatment was necessary there is still a limited amount of choice available and although they may be giving the patient a choice, it is a shortlist choice of drugs from which the patient can express a preference.

> *“what I tend to say is you’re taking one of these but you can choose which one”* **(90)**

> *“I’d offer a choice of the options I wouldn’t just say I’d tell them what the options were”* **(106)**

The second aspect of this category was what the patient was expecting to achieve from their treatment and what they are able or willing to accept in terms of side effects.

> *“what the person want to get out of it i.e. if somebody’s saying I just want to feel better, enough to you know live around my own house or I’m going fully back to*

work and you know I want my whole life, active life back so what what do they really want what are they trying to achieve" **(101)**

What each patient is willing to tolerate in terms of side effects is influenced by what they expect to gain from their treatment and the relative effects of untreated illness or side effects on their life.

All participants acknowledged that patients need time to make an informed decision about their treatment options. For some the provision of written information is assumed enough to allow this process to happen, but other participants felt that this process was more about educating the patient with more than just the provision of written information about the treatment so that they are more able to come to an informed decision.

4.7.4. Setting for initiation and the monitoring process

This was the only area in the analysis where there was a difference seen in the responses from participants based in Norfolk and those based within Suffolk.

One area which had a negative impact on the prescribing of drugs, such as lithium, was the duration of contact with inpatient services. The participants felt that there was a push to get patients out of hospital quickly, with the long-term care moving to an outpatient setting and then primary care. Without a lengthy contact period some participants felt that lithium was not an ideal drug in these situations, and did not want to initiate it as they would not be taking on the long-term management of those patients, their colleagues would.

"this is part of the problem with the model, that you're committing your colleagues to a course of action that they might not well not proceed on erm …so I think it does it does make a difference and that and that's probably the reason why because my contact with patients is anything from two days to six weeks I wouldn't make the decision about lithium because I think it should be the treating consultant who has longer term responsibility" **(66)**

Only the presenting symptoms were dealt with by the inpatient consultant in the short term for the patient to then be discharged for the outpatient consultant for a long term treatment plan to be formulated with the patient for the continued management of their symptoms.

"they've been manic three times which surprises me they get the symptoms squashed with valproate and olanzapine and sent back out again" **(106)**

Leading on from this, however, there were differences in opinion on where lithium should be initiated with several participants having had experience of starting lithium in both outpatients and inpatients and not feeling that the setting of the patient should make any difference to the choice of drug to prescribe. Other participants felt that lithium may be easier to start in inpatients, due to the ease of access to patients and results, but others commented that patients are generally more unwell as inpatients and starting lithium in the community may be easier.

However there were concerns raised by participants about the robustness of processes outside of secondary care, for monitoring patients and the ease of access to blood tests.

This highlighted some concerns that patients should not necessarily be discharged from secondary care services unless these processes were strong and secure. In some cases participants would check their patients' blood tests if they had access to a pathology lab system because they did not feel confident that these checks were going to be performed if they did not do this personally.

> *"I think there are sometimes difficulties in in getting the results but we, most people in Suffolk, the bloods at the moment are done at the -------- so we can find someone who can access their computer system"* **(66)**

> *"It felt quite ad hoc and you sort of set things up and you write please can this person do, I do the bloods and who looks at them and it was all it wasn't it seemed it was easier to do it yourself often"* **(106)**

For those participants who did not have access to a computerised system which collated all blood results for patients and sent reminders and alerts to prescribers, there was repeated mention of creating their own version of this system on a smaller scale for each patient. The idea that it is negligent on the part of the prescriber to not do these tests and know what is happening with their patients was also discussed and has links to the medico-legal issues raised earlier.

> *"if you don't do that regularly you would be negligent, not doing your job"* **(77)**

> *"it's irresponsible as well it's actually irresponsible not to know when you are prescribing something"* **(69)**

However, this role of monitoring the patient varied between participants with several feeling, as described above, that it was the prescriber's role to ensure that all monitoring was being performed and to know what was happening with the test results, but the practicalities of this raised other concerns and thoughts discussed later.

Several participants, who had experience of using SystemTDM®, raised the idea that such systems were an aid to practice, and had the ability to improve the quality of care and reduce the numbers of incidents due to adverse effects.

> *"So I think the lithium database has been a fantastic thing to have happened and I think it's hugely improved the quality of care and I suspect that's measurable and demonstrable possibly even including the number of side effects and so on that we have seen I would expect has probably reduced as a result of the database"* **(7)**

> *"at Norfolk I loved the lithium database it made the whole thing feel so much safer and er coming back to Suffolk felt like a return to the dark ages"* **(8)**

They also highlighted that computerised systems gave prescribers the ability to oversee a large cohort of patients, and see any trends emerging in the data recorded for groups or individual patients over time.

> *"with the lithium database you're still having a system that is overseeing"* **(50)**

> *"also the trends for the individual patient…cause you can see if something's slowly slipping even though it's in the normal range"* **(90)**

The computerised system as described here allows for slow changes in individual patient's blood test results to be picked up and show any trends occurring in the wider lithium-treated population. Those participants who used a computerised system felt that more than one person, the prescriber, getting the blood results was a good system, allowing for a second person for whom that is a particular part of their job to get notified of test results.

> *"I think it's fantastic that someone else looks at them for whom that is their job or at least is a par.., sort of their day"* **(8)**

> *"think actually it's quite a good system that it goes to the prescriber and the person who keeps the database"* **(90)**

This was discussed alongside the idea that sometimes front line staff and prescribers are not always best placed to receive such results as they often have their attention or time pulled in multiple directions.

> *"someone else needs to be a step back from that taking the longer-term view and I think that all of those roles are important in the NHS, front line staff are often battered around too much"* **(8)**

The participants also raised the question of whether GPs or primary care, who are conducting the ongoing monitoring, are the most appropriate people to receive test results and act upon them. The participants commented that if they had their attention or time diverted, within a specialist area, then a GP is likely to suffer this effect even more.

Although the need for strict monitoring systems was important, the participants also highlighted the need for someone to look at and respond to the results.

> *"I think there's been a focus on doing the bloods rather than looking at the bloods"* **(8)**

> *"I mean there is no point taking you know looking, having blood results around if you're not going to look at them and act on them you might as well not of bothered"* **(90)**

Without the results of the blood tests being looked at, the responsible clinician for those patients will not be able to act on them. Changes in patients' physical health may not be picked up on and the slower, creeping changes may not be seen.

Some participants suggested that the long-term monitoring and prescribing of lithium would be suited to an outpatient clinic, in particular for patients who were mentally stable and may not have much other contact with specialist services. In current practice once patients are stable, prescribing responsibility for lithium passes to primary care under a shared care agreement. If their treatment maintains their mental stability they could be discharged from mental health services completely.

> *"When perhaps the psychiatric spotlight has come off that patient because they're not unwell, which is of course another consequence of lithium treatment"* **(8)**

> *"so I don't know that erm gap can be breached or instead have a lithium monitoring clinic, like you know like clozapine monitoring clinic"* **(69)**

The consequence of patients being well treated and maintaining mental stability is that they do not have such a high intensity of psychiatric help readily available and this could be an area where the use of a specialist clinic could allow for ongoing monitoring as well as links to secondary care for easy access back into specialist services if required. With a good link between primary and secondary care, or the use of a lithium database, participants commented that they were happy discharging patients back to primary care and for GPs to continue with lithium monitoring.

> *"in terms of monitoring if they have been stable for a long and because we have the lithium database so we're actually quite happy to have that monitored by the GPs"* **(50)**

> *"combination of a lithium database plus link, good solid link workers could mean that you could discharge people from secondary care"* **(8)**

However, in some cases this did still rely on primary care being open to discussing the patient with secondary care if needed. There were some cases where communication between primary and secondary care, particularly surrounding the reporting of ongoing monitoring results, was not as robust as the participants felt it could be with a knock-on negative impact on clinic times and resources.

> *"and not only does it [lithium monitoring] not always happen and we don't always know if it's happened or not I also think it also leads to so many wasted clinics"* **(8)**

> *"when it's done [lithium monitoring] they don't let you know they don't tell you anything so you know communication can be a bit of a problem"* **(69)**

Some areas of practice required the patient to have links with both primary and secondary care with one doing the monitoring and prescribing, and the other providing ongoing advice on treatment, communication between the two is needed for this process to work. Any lack of communication about what is happening with patients can lead to clinics which cannot perform as needed due to incomplete knowledge surrounding the monitoring and results or the fact that no monitoring had occurred. Those consultants who had a good relationship and communication between primary and secondary care or were used to using a lithium database were comfortable discharging patients back to primary care and for GPs to continue with lithium monitoring. This suggests that the need for an outpatient clinic or the patient remaining under secondary care services is negated by the use of robust monitoring systems. This allows for patients to be discharged from secondary care services and managed within primary care with the consultant and other selected healthcare professionals retaining oversight to monitor levels.

4.8 Interviews discussion

This is the first study eliciting the views and perceptions of consultants working within a Mental Health Trust on the factors affecting their prescribing decisions with a particular focus on lithium. Although this has had many other types of research conducted around it, is still an old drug and there has not been a focus on whether the same factors as for other drugs are influential when it comes prescribing decisions.

The two main domains and factors influencing prescribing decisions pulled out from the literature review for this chapter were all reiterated in our results along with some other factors such as the setting for initiation and the monitoring process which is more specific to drugs such as lithium which require therapeutic drug monitoring.

Although the scientific literature is important in providing further knowledge about medications and clinical cases, the application of this knowledge and discussions with colleagues or pharmacy are much more influential when choosing which drugs to prescribe. This echoes the findings from previous studies (Perlis, 2007, Schumock et al., 2004, Gill et al., 1999, McGettigan et al., 2001, Ljungberg et al., 2007, Prosser and Walley, 2006, Denig et al., 2002b). It has been shown previously that habitual prescribing practices are relatively common, particularly in primary care (Denig et al., 2002b). Denig et al., noted that general practitioners, who were the focus of their study, did not have a wide range of decision behaviours with almost 40% of the transcripts showing habitual behaviour when prescribing. This is reflected by the multiple papers referenced in the literature review for this chapter expanding on the familiarity with certain drugs and previous practical experience with them being influential factors in decisions to prescribe

these drugs (Chow et al., 2014, Hajjaj et al., 2010, Rajendran et al., 2012, Shepherd et al., 2014, Denig et al., 2002b, Ljungberg et al., 2007, McGettigan et al., 2001, Tan et al., 2009, Hedenrud et al., 2013, McIntosh et al., 2016). This was also reflected in our research with a familiarity with particular drugs and whether they had been seen to work before in similar situations leading our participants to be more likely to choose those drugs before. These experiences also influenced prescribing decisions in another way, with the competence of the prescriber being raised, and with the thought that there should not necessarily be any restrictions on the grade or type of doctor who could prescribe complex drugs such as lithium, as long as a specialist is involved and the initial prescriber is deemed competent. Where collaboration with other colleagues is available such as in ward-based environments discussions were considered influential for making prescribing decisions where there are perhaps slightly more complex cases. This expands from previous research which has not picked up on this facet before, with most focussing on primary care where this sort of knowledge exchange is not as readily available.

The fact that the older drugs are not marketed or 'pushed' to prescribers in the same way as the newer drugs, was considered detrimental to drugs such as lithium. The influence of pharmaceutical representatives and their marketing material has been shown to have an impact on the first stages of decision making around new drug prescribing or for the use of specific drugs in situations where an advantage may be perceived over others (Prosser and Walley, 2006, Jones et al., 2001, Ljungberg et al., 2007). The consultants interviewed felt that this impact of marketing, or a lack thereof, was apparent in a generational difference in prescribing practices. They felt that newer doctors were more likely to prescribe newer drugs that had come onto the market more recently, with older drugs

being somewhat underused. It was felt that there needed to be an increased emphasis on these drugs which are not actively marketed, such as lithium, to ensure that they are not underused due to a lack of knowledge. However, the lack of influence of guidelines on prescribing decisions was echoed in this study as had been picked up previously in studies investigating prescribing schema. Guidelines are used as just that, a base to be used initially to guide treatment choices, but other factors are more influential in making prescribing decisions (Perlis, 2007, Schumock et al., 2004, Gill et al., 1999). As guidelines are not really used by this group of specialists in their day-to-day practice this may mean that juniors, who do not have the older drugs marketed to them, may be unaware of their place in treatment.

There was also no mention of costs raised by the consultants in this study which has been previously seen as an influencing factor in previous studies, with prescribers conducting cost-benefit analysis (Higgins and Tully, 2005). However the costs of a service such as SystemTDM® has been raised as an issue by funding bodies who feel that if monitoring is done in line with the Quality and Outcomes Framework, see chapter three, this is sufficient and the finances required to implement SystemTDM® are not in line with any additional advantages it would add to practice (Anderson, 2015).

Where drugs need therapeutic monitoring the ability of the patient to engage with this has previously been a concern and a key factor in deciding what drugs to prescribe, particularly for rural communities (Cutts and Tett, 2003). This is also reflected in several ways when the decision to prescribe lithium or another drug is made. The risks associated with prescribing lithium, which has a narrow therapeutic range and the potential for

toxicity, were raised and linked to the needs for rigorous monitoring processes. There were variations in confidence that these monitoring processes could be done in primary care, without any link to secondary care specialist services. In cases where the robustness of this service was not clear, other drugs were more likely to be chosen which did not require this level of monitoring. This complex process was also a negative factor on the prescribing of lithium with decisions being made sometimes to prescribe 'easier' drugs. Computerised systems were seen as a positive factor and if these were in place alongside good communication between sectors of practice, the negative factors on decisions to prescribe complex drugs or drugs which require monitoring were negated.

Computerised systems can allow changes in individual patients monitoring results to be seen, as well as any trends in the data for the whole treated population which may require further investigation. These individual changes could be large or small creeping changes that may be important in terms of ongoing side effects and potential toxicity for drugs such as lithium. The fact that more than one person gets to see the results for all patients is thought to help in the long-term monitoring of patients as prescribers and front line staff have their attention drawn in multiple directions over the course of a working day and following up on monitoring on their own may be an area of practice that gets missed. This sort of centralised results and reporting system for blood test monitoring has been in place for other complex drugs such as clozapine and warfarin in order to improve the quality and outcomes of the drug monitoring conducted (Steinman et al., 2011, Hickey et al., 2014, Luchins et al., 1998). The dynamic process of actively monitoring the benefits and harms of the prescribed drugs over time, not only focussing on the initial prescribing decision is essential and this process comes across in the

concerns about the ownership of the prescribing decision and the long-term follow-up of patients raised by our participants.

Appropriate prescribing requires some form of risk-benefit analysis encompassing the effects of any untreated illness and the side effect profile of the drug for each particular patient and their lifestyle, as well as risks posed by drugs with a narrow therapeutic range as mentioned above. This was discussed by Higgins and Tully who commented that consultants in previous studies have shown a more holistic view of appropriate prescribing with this encompassing the need for some form of risk-benefit analysis taking into account the patient as an individual (Higgins and Tully, 2005), supported by the results from this study.

This is a complex process and Zetin coined the phrase psychopharmacohazardology in an attempt to encompass this all (Zetin, 2004). The prescribing of multiple drugs, known as polypharmacy, is becoming more of an issue, not only with an aging population but the increasing prevalence of chronic diseases (Linjakumpu et al., 2002, Wise, 2013). Mental health patients will not only present with their psychiatric condition which needs treating but may also have chronic physical health conditions for which they are required to take drug treatment. Interactions of the drug to be prescribed with not only other conditions but any drugs being used to treat these conditions was considered when choosing a treatment option. Adherence, consent and the ability to make an informed decision were new factors in the prescribing decisions raised in this study, particularly in relation to lithium itself due to the long-term monitoring and severe rebound effects if abruptly stopped (NICE, 2014a, Moncrieff, 1995).

Several participants expressed frustration around the service configuration where they are treating patients without being able to see them through to successful treatment conclusions, merely getting them well enough to be managed in the community. Nationally within mental health services there is an inpatient/outpatient functional split model of consultant psychiatrist care. This represents a change over the past decade from the sectorised model in which a single consultant was responsible for the patient's whole journey of care (Begum et al., 2013). In the current model of care a patient will see patients may well see four or five different consultants throughout one episode of illness and they may even be in separate geographical locations (Tyrer, 2013). This goes some way to explain the reluctance by the inpatient consultant to make a long-term treatment choice as they will not be looking after the patient in the longer-term. They are therefore less likely to initiate the drugs used for long-term treatments as the initiating doctor will not be the one who continues to see the patient. This had an impact on the prescribing of lithium in that, once again, the consultants interviewed were not likely to initiate it as often as they maybe would have liked if they were based in acute or inpatient services.

4.8.1. Strengths and Limitations

This study focusses on the views and perceptions of ten consultants working within NSFT on factors that influence their prescribing. The response rate for the study allowed for a sample size to reach data saturation, with more consultants expressing an interest to participate than was needed for the interviews to reach data saturation with consultants working within a wide variety of areas of specialism replying. The option of a 'decline to participate postcard' may have increased nonresponse by making prominent the option

to refuse (Abi-Habib et al., 2004, VanGeest et al., 2007). From the 110 consultants invited to participate in the research only 19 replied with an expression of interest, a response rate of only 17%.

The consultants who responded expressing an interest in being involved in the study may have been those who had stronger opinions on either lithium or prescribing practices and may not reflect the views of those consultants who maybe do not have such strong views. Although not specified during recruitment, only prescribers of lithium ended up being interviewed and all had very positive comments on lithium as a drug. Gaining the views of consultants who actively did not prescribe lithium or did not feel positively about it may have added further to the analysis, gaining additional insight into reasons why they did not prescribe it and the impact of negative feelings about the drug on their practice. However, the objectives of this study were achieved.

The interviews were conducted by a pharmacist and the participants were aware of this from the outset. This may have influenced the way that they felt they could talk about prescribing decisions for their patients. It was made clear in the participant information sheet and at the start of the interview that they were free to say anything and decline to answer questions if they wished, and that nothing would leave the room afterwards unless an issue raising a concern of professional misconduct or negligence was disclosed.

4.9 Conclusion

This study supports some current beliefs about prescribing decisions surrounding the familiarity of prescribers with certain drugs, the implications of the practicalities of therapeutic drug monitoring (TDM) monitoring when required and the impact of promotion and marketing. This study also adds detail to prescribing decisions for older drugs and those within a specialist area, with some restrictions on their prescribing.

There is a continual process of reassessment and confirming a diagnosis for the types of patients seen by our participants, which may not be seen in other areas of practice, leading to less of a reliance on guidelines for treatment choices. The idea of an outpatient clinic for the ongoing prescribing and monitoring of lithium was raised and would seem to alleviate some concerns as well as aiding the monitoring process. The link with specialist services, if needed for reassessment and a continual risk-benefit analysis of the current treatment, could be achieved in an outpatient clinic setting.

Although there are current shared care guidelines for the prescribing and monitoring of lithium, the participants interviewed did not convey complete confidence in the processes in place once patients were discharged from hospital to community services. Within Norfolk, where SystemTDM® is in operation, these concerns were allayed as the participants commented that they knew that all of the relevant people involved in that patients care, as well as someone managing the database, would be kept informed of blood test results.

The prescribers within our study were very focussed on patient information and education and their involvement with treatment than has been highlighted in previous studies. Concerns were raised about the way that older drugs are treated within the training program for doctors and psychiatrists and this is something that will need addressing. Due to this a lack of knowledge surrounding drugs negatively affects the prescribing of these drugs due to prescribers' tendencies to primarily select drugs with which they are more familiar.

■■■ Chapter Five

5: An analysis of a management database for the relationship between lithium levels and monitoring parameters.

5.1 Background

Lithium has been proven to have efficacy against both the manic and depressed poles of the illness (Malhi et al., 2011). Despite its effectiveness there are disadvantages to its use including its narrow therapeutic range (NTR) and its potential detrimental effects on the kidneys and thyroid. Lithium is mainly excreted unchanged by the kidneys and any decline in renal filtration rates can lead to an accumulation of lithium, which will subsequently increase serum levels. This is of particular concern if lithium is taken by older people who have a general age-related decline in renal filtration rates (NICE, 2014b, Zhang and Rothenbacher, 2008). Until the fourth decade of life, glomerular function remains well maintained, but after this, it is expected to decline by about 8ml/min/1.73m^2 body surface area per decade. However, using glomerular filtration rate (GFR) estimates some population-based studies suggest that this decline may begin after the second decade of life (Weinstein and Anderson, 2010).

Potential renal adverse effects of lithium include a decline in urinary concentrating ability, diabetes insipidus, chronic kidney disease (including renal failure), nephrotic syndrome, hypercalcaemia, hyperparathyroidism and distal tubular acidosis. In a small proportion of patients GFR gradually declines, with some subsequently developing chronic renal insufficiency or renal failure, 0.2-0.5% of the populations studied (Gitlin, 1999, McKnight

et al., 2012). Abnormal renal function or structure is included under the umbrella term Chronic Kidney Disease (CKD) and commonly occurs alongside other conditions such as diabetes mellitus and cardiovascular conditions, although it is frequently unrecognised. The cost of CKD has an impact on the NHS spend within England with this estimated to be £1.44-£1.45 billion in 2009-10, which was approximately 1.3% of all NHS spend in that year (NICE, 2014b). Previous studies on the renal adverse effects of lithium have not included patients with a history of lithium toxicity or included details about the number of episodes of lithium toxicity, or out-of-range levels (Zhang and Rothenbacher, 2008). This study was an aim to use data already collected in routine care patients prescribed lithium to see real life effects on calculated eGFR of levels used for treatment.

5.2 Aims and Objectives

5.2.1. Aim

The aim of this analysis was to determine if there is an association between lithium levels and renal function.

5.2.2. Objective

The objective was to:

- Establish the relationship between estimated glomerular filtration rate (eGFR) after ≤3months and 6 months (±3 months) and one year (±3 months) after exposure to one lithium level within specified ranges.

5.3 Methods

This study was limited to secondary use of information previously collected in the course of normal care, without an intention to use it for research at the time of collection. It is therefore excluded from Research Ethics Committee (REC) review, provided that the patients or service users are not identifiable to the research team in carrying out the research. Local research governance approval was received from Norfolk and Suffolk NHS Foundation Trust Research Governance Committee prior to commencing data extraction. The protocol and supporting documentation is included in appendix one.

SystemTDM® currently holds the following information about the patients registered with the service:

- Database ID, NHS number, alternative ID, full name, address and registered GP practice of each patient,
- Date of registration,
- Date of and test results: lithium, urea, creatinine, eGFR (2006 onwards), TSH, T4,
- Risk factors: Age >70, Impaired renal function, taking a non-steroidal anti-inflammatory drug (NSAID), angiotensin-converting-enzyme (ACE) inhibitor or Diuretic [2]
- Patient's date of birth,

[2] Tick box system reliant on primary care to initially provide the data upon patient registration and update for any change in or new diagnoses

- Gender,
- Psychiatric diagnosis/diagnoses,
- Current and past addresses,
- Copies of SystemTDM® letters sent,
- Any notes relating to the patient,
- Uploaded documents,
- Any alerts relating to the patient such as reduced renal function/co-morbidities/prescribed interacting medications.

The clinical pharmacy team had access to the full data stored on SystemTDM® and passed on the following data to the primary researcher once anonymised: database ID, date of registration, date of test results, and results for: lithium and creatinine, patient's year of birth and gender. Any duplicate entries were removed by the clinical team.

5.3.1. Data modelling

Data modelling was done by a statistician used to working with STATA, with clinical input on the required model from the primary researcher. Statistical analysis was then performed by the primary researcher.

Three ranges of lithium levels were chosen to be analysed to reflect current practice and consensus agreement: patients who had all lithium levels ≤0.8mmol/L (reference group) and a single exposure to lithium levels between 0.81-1.0mmol/L (group two), 1.01-1.2mmol/L (group three) or 1.21-2.0mmol/L (group four). Patients with multiple

exposures to the levels for groups two, three and four were excluded for the purpose of this analysis.

The term exposure is used to indicate that at the time the blood test was taken for the lithium level the body of the patient had for that moment been exposed to that level of lithium. The timings of lithium level testing is recommended to be 12 hours post dose for routine monitoring, if however a patient had taken their dose of lithium less than the recommended 12 hours before the blood test the lithium level reading recorded would show a slightly high level for that patient. It is not possible to tell from the data received by the research team if any of the high readings were due to dose timing issues.

The reference group (≤0.8mmol/L) reflects recommendations from the National Institute for Health and Care Excellence Guidelines (NICE) for patients prescribed lithium for the first time and the level to aim for in prophylaxis of bipolar disorder (0.6-0.8mmol/L). NICE guidelines also recognise that the elderly, and any patients with reduced renal function, are more susceptible to the adverse effects of lithium and may respond to lower levels, hence the lower part of this range reaching below 0.6mmol/L (NICE, 2006, BAP, 2009). Groups two and three acknowledge the differing levels from the British Association for Psychopharmacology Guidelines (BAP) and the NICE guidelines. Levels up to 1.0mmol/L are recommended by BAP for all patients requiring prophylaxis if needed and in NICE this is reserved for *'people who have relapsed previously while taking lithium or who still have sub-threshold symptoms with functional impairment while receiving lithium'* or those who present with acute mania (NICE, 2006). The BAP guidelines acknowledge that higher levels may be used in acute mania, from 1.0-1.2mmol/L, covering group three (BAP,

2009). Group four was chosen as this is a range of lithium levels not routinely used for the longer term treatment of bipolar disorder within the UK and would be generally considered to be an out-of-range or 'high' level.

Estimated glomerular filtration rate (eGFR) was manually calculated using the creatinine levels recorded on SystemTDM® and the simplified Modification of Diet in Renal Disease (MDRD) equation. The MDRD Study equation is the most thoroughly validated equation for approximating GFR (Myers et al., 2006). Race was not recorded on the database so no corrections could be applied for African-American patients. However within Norfolk there is a predominantly Caucasian population (ONS, 2011 (b)) and so not making this correction is unlikely to have any significant influence.

5.3.2. Statistical analysis

The start of the follow-up for patients in the reference group was determined by creating a pseudo-exposure date. This was done by adding the median duration that exposed patients had been registered on the database prior to their exposure event to the registration date for patients in the reference group. The median duration that patients had been registered on the database was calculated by working out the time between teach patients registration and the first exposure event (a lithium level >1.0mmol/L). The average time of being registered on the database before an exposure event took place was then calculated and this figure was then used as the time to use from database registration to the pseudo-exposure event for the control group patient i.e. when to 'start the clock' for the follow up period. This process is detailed in table 5.1.

Control group*		**Follow up period**	
	Baseline	**3 months**	**6 months (±3 months)**
Database registration	Same length of time as the mean time of registration as exposure groups e.g. registered in 2007 pseudo exposure in 2009 - Li - Renal	2nd result - Li	Follow up test - Renal (Li data not extracted for this model)
Exposure groups			
Database registration	1st high (H) since database registration - Li - Renal	2nd result - Li	Follow up test - Renal (Li data not extracted for this model)

*Control group never has a high reading

Table 5.1: Detail of control and exposure groups used in this analysis.

The follow-up periods of ≤3 and six months (±3 months) are in line with the UK guidance from 2006 for three monthly monitoring (NICE, 2006). By one year (±3 months) follow-up post-exposure all results had returned to within range and so this was used as the reference group for time.

A random effects repeated measures mixed model with an interaction with time was run using STATA SE 12.1 to ascertain the significance of the exposure groups and time-periods, adjusting for baseline eGFR (StataCorp, 2011). Initially time-series analysis was considered for this analysis but due to the naturalistic data, the time points for blood tests were not as regimented as are needed for this approach so the repeated measures model was chosen. There are several commands in STATA to build a random effects

model including xtreg, anova and xtmixed. The reference and treatment groups in this analysis are made up of different patients. However, by using a repeat-measures design for the analysis each subject serves as their own control. This means that the variability between subjects is isolated and the analysis can focus on treatment or intervention effects which may otherwise have been masked by subject variability. As eGFR was normally distributed there was no need to perform any transformations on the data. Using the simplified MDRD equation gender and age are taken into consideration when calculating eGFR so no further adjustments were required.

The Wald Chi^2statistic is used to test the hypothesis that at least one of the predictors' regression coefficients is not equal to zero. The number in the brackets indicates the degrees of freedom of the Chi^2 distribution used to test the Wald Chi^2 statistic and is defined by the number of predictors in the model (12).

5.4 Results

5.4.1. Inclusion and exclusion criteria

Patients were included for analysis if they were registered on SystemTDM® between 2002 and the end of January 2013 and had had at least one lithium and one creatinine reading recorded. The reference group was made up from patients whose lithium levels never exceeded 0.8mmol/L in the time they were registered on the database. Lithium levels remaining in the same range for the three months after the initial test result were classed as the same exposure. The first instance of a level within the highest group recorded was classed as the point of exposure and the start of the follow-up period. After any of the exposure events patients remained prescribed lithium for the duration of the follow-up period in which they were included. If lithium levels over the follow-up period were recorded as >0.8mmol/L, only eGFR levels up to the last known lithium reading of ≤0.8mmol/L were used and after that the patient was not included in the analysis.

Levels above 5.0mmol/L were not included for analysis as these were likely to have been erroneous levels, either from mistimed sample collection, overdose or collection of blood samples in lithium-heparin containers (Wills et al., 2006). Patients who had creatinine levels outside of the range 30-1500µmol/L not included for analysis as the MDRD equation used was not validated for levels outside of this range (St George's University of London). Figure 5.1 shows the process of sample selection.

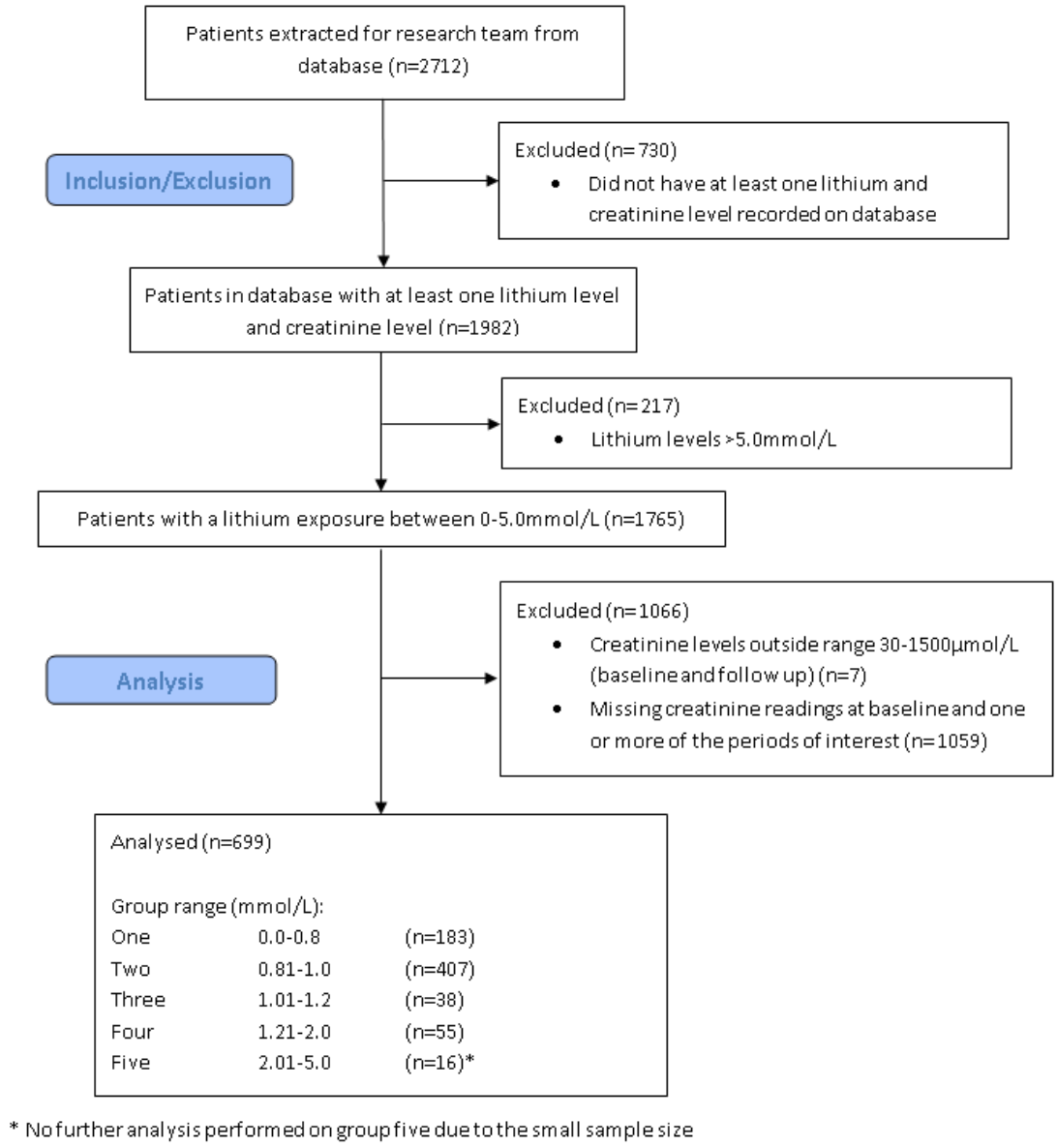

Figure 5.1: Process of sample selection for eGFR analysis

Once patients who did not have the required data recorded to enable analysis had been excluded, there were 699 patients left for inclusion. There were only 16 patient records with levels recorded 2.01-5.0mmol/L so no further analysis was performed on this group as the small sample size is associated with a lack of statistical reliability leaving 683 patients for the analysis. Tables 5.1 and 5.2 detail the baseline demographics of the patients who were included for analysis in total and split by exposure group.

	Gender	Age					
n=	**Female**	**<20**	**20-29**	**30-39**	**40-49**	**50-59**	**>60**
683	407	1 (0.1)	28 (4.1)	67 (9.8)	115 (16.8)	136 (19.9)	336 (49.2)

Table 5.2: Single exposure baseline demographics (all figures are number, (%))

There was a higher percentage of females than males in this sample, with nearly half of the sample ages >60. The following table details the demographics of the sample patients after being separated by exposure groups.

		Gender	Age					
Exposure group	**n=**	**Female**	**<20**	**20-29**	**30-39**	**40-49**	**50-59**	**>60**
<0.8mmol/L (group 1)	183	101 (55.2)	0 (0)	9 (4.9)	26 (14.2)	41 (22.4)	36 (19.7)	71 (38.8)
0.81-1.0mmol/L (group 2)	407	251 (61.7)	0 (0)	16 (3.9)	34 (8.4)	62 (15.2)	79 (19.4)	216 (53.1)
1.01-1.2mmol/L (group 3)	38	24 (63.2)	0 (0)	1 (2.6)	4 (10.5)	3 (7.9)	9 (23.7)	21 (55.3)
1.21-2.0mmol/L (group 4)	55	31 (56.4)	1 (1.8)	2 (3.6)	3 (5.5)	9 (16.4)	12 (21.8)	28 (50.9)

Table 5.3: Single exposure baseline demographics by exposure group (all figures are number, (%))

In all exposure groups there were a similar number of males and females and variation across age groups. Those patients included aged >60 have a more uniform distribution across all exposure groups, whereas for those aged <60 there is more weighting towards the patients being in exposure groups 1 and 2.

Using the xtmixed command which performs a multilevel mixed-effects linear regression, being in exposure groups three or four leads to a significant decrease in eGFR at ≤3 months follow-up (interaction p=0.047 and p=0.040 respectively). No other main effects

or interactions were significant, suggesting that eGFR levels seem to recover over time.

Table 5.4 shows the results of this analysis.

Independent variable		Coefficient (95% CI)*	p
Exposure			
0.81-1.0mmol/L	(Group 2)	0.23 (-1.75 to 2.24)	0.814
1.01-1.2mmol/L	(Group 3)	2.78 (-2.11 to 7.68)	0.266
1.21-2.0mmol/L	(Group 4)	0.43 (-3.48 to 4.44)	0.834
Time			
≤3 months	(Time 1)	-0.35 (-2.17 to 1.47)	0.705
6 months (±3 months)	(Time 2)	0.83 (-0.82 to 2.50)	0.322
Exposure X Time interactions			
Group 2 X Time 1		-1.16 (-3.42 to 1.10)	0.314
Group 2 X Time 2		-0.57 (-2.72 to 1.58)	0.603
Group 3 X Time 1		-5.18 (-10.3 to -0.08)	0.047
Group 3 X Time 2		-1.91 (-7.13 to 3.31)	0.473
Group 4 X Time 1		-4.45 (-8.70 to -0.19)	0.040
Group 4 X Time 2		-2.29 (-6.61 to 2.02)	0.298

Wald $chi^2(12) = 2947.86$, $Prob>chi^2 = < 0.001$

Table 5.4: Random effects repeated measures mixed model (using xtmixed) to predict eGFR, adjusting for baseline eGFR.

In this analysis the Wald chi^2 value has a significance of < 0.001, so we can conclude that the parameters associated with these variables are not zero and so should be included in the model.

5.5 Discussion

The results from this analysis show that a single exposure to a lithium level >1.0mmol/L is associated with an increased risk of renal impairment in the first three months after exposure. However, by six months (±3 months) there is no detectable difference from the mean baseline eGFR. The decline in eGFR seen in the three months after the exposure is not likely to be clinically relevant unless this decline in eGFR is sustained.

The results of a retrospective cohort study conducted recently showed that any exposure to lithium is associated with an increased risk of renal failure (Close et al., 2014). The Close study was a retrospective cohort study using a database examining the tsk to renal health for patients who had been prescribed lithium in primary care compared to non-users of lithium. The comparison between users and non-users of lithium was not something that was able to be done as part of this thesis due to the nature of the data used for the analysis. Due to the design of the Close et al., study the role of duration of treatment with lithium and any variation in this risk to renal function for different serum levels could not be determined however they did determine that the ever use of lithium was associated with an increased hazard ration for renal failure when compared to non-users of lithium with an absolute risk which was age dependent (Close et al., 2014). In this thesis, the comparison of different lithium level ranges compared to a reference group meant that any variations in the risk from single exposures in these ranges could be determined. Clinically being able to determine if the number of exposures the kidney has from different lithium levels and the duration of these exposures is relevant for continued

monitoring or if it is the degree of the lithium level that determines the impact on renal function.

Variability in the measurement of plasma creatinine could lead to changes in GFR of up to 5ml/min in individual patients. This is unlikely to require any action to be taken unless this change is sustained or there is further deterioration picked up by regular monitoring.

The mean age of the population studied was 60, which is slightly higher than the means seen in previous audits or studies of 48-55 (Collins et al., 2010, Close et al., 2014). Compared to the rest of the UK, Norfolk has a higher percentage of the population over the age of 65, so this higher mean age was expected for the sample. This sample is representative of a group of patients at higher risk for the renal effects of lithium but one confounding factor is that an age-related decline in renal function may be overshadowing any effects of lithium. According to a review performed on previous studies by Rej et al., examining chronic kidney disease in lithium-treated older adults, in mixed-aged community samples of long-term lithium users the prevalence and incidence of severe renal disease varying from stage IV-V CKD, end stage renal disease or renal replacement therapy is 0.5–2 % and in patients aged >55 prescribed lithium the prevalence of renal replacement therapy is estimated to be 1.5%. These estimates suggest that results from previous studies in the elderly population echo findings from mixed age samples so this thesis data can be considered representative for UK practice populations even with the slightly older population that other studies (Rej et al., 2015).

5.5.1. Strengths and limitations

Estimated GFR was used for this second analysis, but due to laboratory reporting standards this is only available routinely for patients from 2006 onwards. The eGFR was therefore calculated for all patients using the simplified MDRD equation. As eGFR is affected by age, fractional age (age in decimal years) was used in the analysis to minimise this impact. Well known risk factors for declines in renal function due to chronic kidney disease (CKD) include diabetes mellitus, hypertension and cardiac disease (NICE, 2014b). Data about any of these conditions and other risk factors for CKD were not reliably recorded on the database and could not be adjusted for in the analysis. In this analysis only one year post-exposure was used as a follow up period, although in on-going work expanding on this research a longer follow-up period will be used. Without a longer follow up period and the full analysis of single and multiple exposures of various lithium levels it is not clear whether the kidneys can fully recover from the impact of the different lithium level exposures.

5.6 Conclusion

These analyses only looked at the impact of single exposures to a range of lithium levels on creatinine and then on eGFR. The short follow-up periods, further broken down in the eGFR analysis shows that the kidneys may be able to recover the decline in renal function. It is still not known, however if the associated decline in renal function is additive if there are multiple exposures. Determining if the number of exposures the kidney has from different lithium levels and the duration of these exposures or if it is the degree of the lithium level that determines the impact on renal function is clinically relevant for continued monitoring. Currently this analysis suggests that even short term exposure to elevated lithium levels is associated with a significant impact on glomerular renal function and regular monitoring of lithium levels and timely responses to these levels is important.

Chapter Six

6: A longitudinal analysis of a monitoring database for the relationship of multiple lithium levels on estimated glomerular filtration rate.

6.1 Background

Lithium is an important treatment option for the prophylactic management of bipolar disorder but the effects on renal function are poorly understood. It has not as yet been confirmed whether the kidneys can recover from the decline in renal function shown after single exposures to elevated lithium levels or if the negative relationship of multiple or longer-term exposures on renal function are additive.

During the course of this research national guidance has changed on the frequency of monitoring required for lithium. NICE now recommends six monthly lithium levels as the routine after the first year of treatment rather than the previously recommended three monthly monitoring (NICE, 2014a). This change was due to non-adherence to the three monthly recommendations and the cost of unnecessary investigations (Bazire, 2014, Rej et al., 2015). The results in the previous chapter led to a change in the new guidelines which recommended more frequent monitoring in certain groups of patients but now includes the addition of the last bullet point regarding previous lithium levels recorded:

- older people,
- people taking drugs that interact with lithium,
- people who are at risk of impaired renal or thyroid function, raised calcium levels or other complications,

- people who have poor symptom control,
- people with poor adherence,
- people whose last plasma lithium level was 0.8 mmol/litre or higher.

(Bazire, 2014, NICE, 2014a)

It has been repeatedly noted in local and national audits that the recommended rates for serum lithium levels and eGFR monitoring are not being met which potentially puts patients at risk for renal adverse effects (Rej et al., 2015). At the moment patients need to have blood tests multiple times per year for the duration of their treatment. If knowledge can be solidified surrounding the relationship between lithium serum levels and kidney function this recommendation might be able to change for clinical reasons, and not cost reasons or a lack of adherence to guidelines.

6.2 Aims and Objectives

6.2.1. Aim

The aim of this analysis was to determine the relationship of double exposures of various lithium levels on renal function measured by eGFR.

6.2.2. Objectives

The objective of this analysis was to:

- Establish the relationship on eGFR after ≤3months, six months (±3 months) and one year (±3 months) after exposure to two lithium levels within specified ranges.

6.3 Methods

This study was limited to secondary use of information previously collected in the course of normal care, without an intention to use it for research at the time of collection. It is therefore excluded from Research Ethics Committee (REC) review, provided that the patients or service users are not identifiable to the research team in carrying out the research. Local research governance approval was received from Norfolk and Suffolk NHS Foundation Trust Research Governance Committee prior to commencing data collection. This is an extension of the initial research detailed in chapter five and so follows the same protocol in appendix one. The information held by SystemTDM® is detailed in the previous chapter.

6.3.1. Data modelling

The ranges of lithium levels used in this analysis were the same as those described in the previous chapter following the same reasoning: 0.0-0.8mmol/L (reference group), 0.81-1.0mmol/L (group two), 1.1-1.2mmol/L (group three), 1.21-2mmol/L (group four) and 2.01-5mmol/L (group five). The objective of this analysis was to establish the relationship of double exposures of different lithium levels on renal function. Lithium levels recorded at routine intervals and those taken immediately after an anomalous or unexpected result were used for the data modelling.

From the previous analysis the level at which a significant negative association was seen on renal function after a single exposure was >1.0mmol/L. Due to this groups three, four and five were combined for this analysis. Each group was then coded with a single letter

or symbol: missing value = ".", 0-0.8mmol/L = "L", 0.81-1.0mmol/L = "S", 1.01-5.0mmol/L = "H" for simplicity.

The start of follow-up for patients in the reference group was determined by creating a pseudo-exposure date. This was done by adding the median duration that exposed patients had been registered on the database prior to their exposure event to the registration date for patients in the reference group. The follow-up periods of ≤3 and six months (±3 months) are in line with the UK guidance from 2006 for three monthly monitoring. As most effects occurred by six months (±3 months) this time-period was used as the reference group for time.

Once patients who did not have the required data recorded to enable analysis and those remaining were classified by pattern of exposure there were five groups included in the analysis. The other pattern groups that were possible either did not occur in the sample at all or they had too small numbers to consider including for statistical analysis.

6.3.2. Inclusion and exclusion criteria

Patients were included for analysis if they were registered on SystemTDM® between 2002 and the end of January 2013 and had at least one lithium and one creatinine reading recorded. The reference group was made up from patients whose lithium levels never exceeded 0.8mmol/L in the time they were registered on the database. Lithium levels remaining in the same range for the three months after the initial test result were classed as the same exposure. The first instance of a level within the highest group recorded was

classed as the point of exposure, as the previous analysis looked at single exposures the start of the follow-up period for this analysis starts at the second exposure.

Readings were included following a level >1.0mmol/L up to the point at which another level in this range occurred. A further 12 months with all results being in the range 0.0-0.8mmol/L was used as the time period before the recorded results for that patient could be used again. This was the length of time suggested as the earliest point for renal recovery to be consistently seen after an acute kidney injury episode (Macedo et al., 2012). Levels above 5.0mmol/L were not included for analysis as these were likely to have been erroneous levels, either from mistimed sample collection, overdose or collection of blood samples in lithium-heparin containers (Wills et al., 2006). Patients who had creatinine levels outside of the range 30-1500µmol/L not included for analysis as the MDRD equation used was not validated for levels outside of this range (St George's University of London)

6.3.3. Statistical analysis

Estimated glomerular filtration rate (eGFR) was manually calculated using the creatinine levels recorded on SystemTDM® and the simplified Modification of Diet in Renal Disease (MDRD) equation as in the previous chapter.

A random effects repeated measures mixed model with an interaction with time was run using STATA SE 12.1 to ascertain the significance of the patterns of lithium exposure and time-periods (StataCorp, 2011). The reference and treatment groups in this analysis are made up of different patients. However by using a repeated measures design for the

analysis each subject serves as their own control. This means that the variability between subjects is isolated and the analysis can focus on treatment or intervention effects which may otherwise have been masked by subject variability. Using the simplified MDRD equation gender and age are taken into consideration when calculating eGFR so no further adjustments were required. The data for both MDRD and residuals were normally distributed and were checked for outliers and heteroscedasticity. As eGFR was normally distributed there was no need to perform any transformations on the data. The LL exposure pattern (group 5) and the 1 year (±3 months) time period were used in this model as the reference groups.

6.4 Results

Estimated glomerular filtration rate (eGFR) was manually calculated using the creatinine levels recorded on SystemTDM® and the simplified Modification of Diet in Renal Disease (MDRD) equation as detailed in the previous chapter. Tables 6.1 and 6.2 detail the baseline demographics of the patients who were included in the analysis and then further by pattern group. There are a larger number of patients included in this analysis than the single exposure analysis due to the fact that in the previous analysis only eGFR levels up to the last known lithium reading of 0.8mmol/L were included and after that the patient was not included in the analysis whereas those patients are able to be included in the different pattern groups for this analysis, including pattern groups HH and HS.

	Gender	**Age**					
n=	**Female**	**<20**	**20-29**	**30-39**	**40-49**	**50-59**	**>60**
777	461 (59.3)	1 (0.1)	29 (3.7)	72 (9.3)	122 (15.7)	166 (21.4)	387 (49.8)

Table 6.1: Double exposure baseline demographics (all figures are number, (%))

There was a slightly higher percentage of females than males in this sample, and nearly half of the sample ages >60. The following table (6.2) details the demographics of the sample patients after being separated by exposure groups. It would have been expected that the database would have reduced the number of patients with repeated exposures to levels >0.8mmol/L, however due to the lack of clinical information able to be provided to the researchers for this analysis clinical decisions and reasons for any high levels cannot be explained so it is not possible to know if these repeated exposures are intentional for example, for use in manic episodes.

		Gender	Age					
Pattern group	**n=**	**Female**	**<20**	**20-29**	**30-39**	**40-49**	**50-59**	**>60**
H.	40	20 (50)	0 (0.0)	0 (0.0)	4 (10.0)	5 (12.5)	13 (32.5)	18 (45)
HH	31	22 (71)	0 (0.0)	0 (0.0)	3 (9.7)	1 (3.2)	3 (9.7)	24 (77.4)
HL	178	116 (65)	0 (0.0)	3 (1.7)	11 (6.2)	21 (11.8)	36 (20.2)	108 (60.7)
HS	38	25 (66)	0 (0.0)	2 (5.3)	4 (10.5)	3 (7.9)	8 (21.1)	21 (55.2)
LL	490	278 (57)	1 (0.2)	24 (4.9)	50 (10.2)	92 (18.8)	106 (21.6)	216 (44.1)

Table 6.2: Double exposure baseline demographics (all figures are number, (%))

The pattern group refers to the following exposures:
H. = 1.01-5.0mmol/L then missing value
HH= 1.01-5.0 then 1.01-5.0mmol/L
HL= 1.01-5.0 then 0-0.8mmol/L
HS= 1.01-5.0 then 0.81-1.0mmol/L
LL= 0-0.80 then 0-0.80mmol/L

There was more of a difference in the percentage of males and females in this analysis at baseline. Three groups had a larger percentage of females than at baseline (HH, HL and HS) and there was also a greater variation in the ages seen in each of the pattern groups at baseline. However, all showed a similar trend towards the majority of patients being in the oldest age bracket.

A non-significant, increase in eGFR is seen for pattern groups H., HH and HL at time period on and a non-significant increase in eGFR is seen for pattern groups H. and HS for time period two. A non-significant decrease in eGFR is seen for pattern groups HH at time period two and HS at time period one. The interaction of pattern and time is significant only for pattern three (HL) showing a significant increase in eGFR at ≤3 months follow-up after the second exposure event (p=<0.001). Table 6.3 shows the results of this analysis.

Independent variable	Coefficient (95% CI)*	p
Pattern		
1 = H.	-5.11 (-8.94 to -1.28)	0.009
2 = HH	-4.93 (-10.6 to 0.72)	0.087
3 = HL	-2.66 (-4.62 to -0.71)	0.008
4 = HS	-4.22 (-8.36 to -0.09)	0.045
Time		
≤3 months (Time 1)	-1.89 (-2.73 to -1.05)	<0.001
6 months (±3 months)(Time 2)	0.39 (-0.46 to 1.23)	0.368
Pattern X Time interactions		
Pattern 1 X Time 1	1.28 (-2.34 to 4.89)	0.489
Pattern 1 X Time 2	2.22 (-1.14 to 5.57)	0.195
Pattern 2 X Time 1	3.56 (-1.75 to 8.87)	0.189
Pattern 2 X Time 2	-3.54 (-9.07 to 1.99)	0.210
Pattern 3 X Time 1	3.30 (1.63 to 4.98)	<0.001
Pattern 3 X Time 2	-1.56 (-3.21 to 0.08)	0.062
Pattern 4 X Time 1	-0.01 (-3.60 to 3.59)	0.998
Pattern 4 X Time 2	0.02 (-3.60 to 3.65)	0.989

Wald $chi^2(15) = 3536.14$, $Prob>chi^2 = < 0.001$

Table 6.3: Random effects repeated measures mixed model to predict eGFR, adjusting for baseline eGFR.

In this analysis the Wald chi^2 value has a significance of < 0.001, so we can conclude that the parameters associated with these variables are not zero and so should be included in the model.

6.4.1. Findings from individual cases

To see what was happening for individual cases, where significant changes may have been hidden by the amalgamation into the large data set a selection of cases were pulled

from the raw data (5 patients, as an arbitrary figure, from each pattern group). Table 6.4 shows the data for these patients.

Patient I.D	Pattern group	Patient Age at exposure	Gender	Lithium level for 'H' value	eGFR baseline	eGFR time 1	eGFR Time 2
126	H.	61	M	1.02	90.6	113.0	102.1
452	H.	47	F	2.56	45.7	38.3	46.4
1057	H.	49	M	1.4	103.9	94.6	84.7
2886	H.	79	F	1.09	56.6	67.5	79.3
3163	H.	63	F	1.09	59.9	74.1	77.7
308	HH	70	F	1.09	50.9	51.8	55.8
492	HH	59	M	1.2	70.5	76.6	71.8
1562	HH	55	F	2.67	69.3	69.6	63.9
2542	HH	68	M	1.3	90.3	100.5	96.8
3374	HH	65	F	1.15	76.1	82.7	84.0
18	HL	62	F	1.18	76.3	71.9	67.7
48	HL	84	F	1.35	27.1	20.1	20.1
1482	HL	61	M	1.12	79.9	65.3	61.8
2800	HL	41	M	1.4	122.4	122.7	126.9
3418	HL	37	M	2.89	89.8	110.9	112.5
109	HS	95	F	1.13	38.3	33.8	37.6
458	HS	62	M	1.02	27.9	30.0	30.9
1547	HS	48	F	1.48	65.1	73.6	69.3
2989	HS	55	F	1.02	88.3	91.9	88.5
3370	HS	73	F	1.2	64.9	66.2	61.1

Table 6.4: Individual case data for selection of patients in each pattern group

The average effect seen for the pattern group H., HH and HL from the statistical analysis was a non-significant increase in eGFR at time period one a non-significant increase in eGFR at time period two for pattern groups H. and HS. For the five cases for each pattern group pulled out to look at individually a variation in increases and decrease in eGFR was seen which would explain why there was not a statistically significant effect as there was variability in the effect for individual cases. This effect was not explained by gender, age at exposure or lithium level at exposure.

The interaction of pattern and time is significant only for pattern three (HL) showing a significant increase in eGFR at time period one. For the five cases for this pattern group pulled out to look at individually a variation in increases and decrease in eGFR was seen however the increase was only seen in the younger group of patients with a decrease seen in all three patients aged over 60 looked at individually.

6.5 Discussion

For patients within this sample, having the lithium level pattern of 1.01-5.0 then 0-0.8mmol/L (HL), there appears to be a short term positive association on renal function ≤3 months follow-up after the second exposure event (L) and a borderline decline at 6 months (±3 months). All groups except 1.01-5.0 then 0.81-1.0mmol/L (HS) showed an increase in eGFR after exposure at time one with two levels between 1.01-5.0mml/L (HH) and 1.01-5.0 then 0-0.8mmol/L (HL) showing a decrease in eGFR at time two. However the interaction between pattern and time was only significant for 1.01-5.0 then 0-0.8mmol/L (HL) at the first time period. This correlates with recent research from Clos et al who concluded that long-term lithium therapy is not associated with changes in renal function, demonstrated by changes in eGFR, in the absence of episodes of acute toxicity (Clos et al., 2015). Our results also seem to suggest that there may be more to investigate surrounding changes in lithium levels, as well as cumulative doses or just exposures to levels thought to be out of the therapeutic range.

As detailed in chapter five, variability in the measurement of plasma creatinine could lead to changes in GFR of up to 5ml/min in individual patients. This is unlikely to require any action to be taken unless this change is sustained or there is further deterioration picked up by regular monitoring variability in plasma creatinine.

No additive effects were shown in this analysis although one major limitation was the sample size of the relevant groups. Currently this suggests that close monitoring is needed for lithium levels to prevent them from, as much as is practically and clinically

possible, from reaching a level of 1.01-5.0mml/L (H), as this single exposure still shows an association as was initially reported in the previous analysis of single exposures.

6.5.1. Strengths and limitations

Estimated GFR was used for this analysis but as in the previous chapter, this is only available routinely for patients from 2006 onwards. The eGFR was therefore calculated for all patients using the simplified MDRD equation using calculated creatinine levels recorded on SystemTDM®. As eGFR is affected by age, fractional age was used in the analysis to minimise this impact.

Well known risk factors for declining renal function include diabetes mellitus, hypertension and cardiac disease. Data about any of these conditions was not reliably recorded on the database and could not be adjusted for in the analysis. Due to the way the data was recorded on the database there was no reliable information about other medications the registered patients were taking which may have included nephrotoxic drugs, these could have caused an impact on renal function separate to any relationship to lithium exposure which could not be accounted for in our analysis.

The mean age of the population studied was 60, which is slightly higher than the means seen in previous audits or studies of 48-55 (Collins et al., 2010, Close et al., 2014). Compared to the rest of the UK, Norfolk has a higher percentage of the population over the age of 65, so this higher mean age was expected for the sample. The relationship between age and lithium level was not analysed in this thesis and with the age groups of

the sample having a significant proportion of patients aged >60 this could be considered a limitation of the analysis.

The sample sizes for all groups apart from 1.01-5.0 then 0-0.8mmol/L (HL) were relatively small and would benefit from a collaborative research project to expand on these results and this analysis. It is therefore still unclear from this analysis if two levels between 1.01-5.0mml/L (HH) have an additive negative relationship on renal function.

In this analysis two exposures were analysed due to the complexities of the data. Clinically this allows a determination of the relationship of two different lithium levels on renal function over time. One main limitation of this analysis is the small sample size of most of the exposure groups, with only group three having a large sample size.

6.6 Conclusion

The results from this analysis still suggest that close monitoring of lithium levels still needs to occur to prevent a single level between 1.01-5.0mmol/L (H) exposure as previously discussed in chapter five. These results raise the discussion point that it could possibly be changes in lithium levels which lead to the longer-term association with a decline in renal function with the results not clearly showing a difference between high and lower levels of exposure. With only small sample sizes this is not a definitive conclusion from this work but something to be considered in future, larger, analyses. Currently, although there are still unanswered questions about multiple exposures to lithium levels which have not been answered from this analysis, recommendations would be to continue monitoring lithium levels more frequently, not less frequently as has recently been recommended until the additional question of whether changes in the level also have an association with renal function, not just the level itself (NICE, 2014a).

There is a need for collaborative research to expand the sample sizes of pattern groups either not seen in this sample or those that were too small. All pattern groups apart from 1.01-5.0 then 0-0.8mmol/L (HL) have less than 40 patients in them. This means that statistically they are viable for analysis but may not be large enough to infer suggested changes in current practice.

Chapter Seven

7: Discussion and Conclusion.

7.1 Overall discussion

The original aim for this PhD was to determine the relationship between various lithium levels on renal function, however, as the research has progressed this expanded into a more comprehensive research question. The eventual focus of the PhD encompasses not only work to quantify the association of lithium levels with declines in renal function at different lithium serum levels and multiple exposures, but also whether the use of the systematic aid to help with the monitoring of lithium has any impact on prescribing decisions or if there are other factors at play as shown in prescribing research focussed on newer drugs (Ljungberg et al., 2007, Schumock et al., 2004, Prosser and Walley, 2006, Perlis, 2007). There has been a surge in research in lithium over the past couple of years alongside the work conducted for this thesis, suggesting that there are still numerous unanswered questions about lithium prescribing, monitoring and long-term effects.

From the literature review conducted the current guidelines for the frequency of lithium level monitoring have not veered far from original customs, which were based on common practice, so this was clearly an area where the work from this thesis would add to the evidence-base for practice recommendations in the UK. This is reflected in the change in NICE guidelines on lithium monitoring that occurred part way through this thesis, a change apparently based on what is, or is not, performed in practice rather than what may be needed for patient safety (Bazire, 2014). Concerns have been raised prior to this work about the consistency of lithium monitoring across the UK, with the results of the POMH-UK audit leading to a NPSA patient safety alert (Collins et al., 2010, NPSA,

2009).The first part of this thesis was to establish the impact of the local computerised monitoring system on lithium monitoring to see if there was a difference seen from the poor compliance reported in the national POMH-UK audit (Collins et al., 2010). The results suggest that an actively managed database such as SystemTDM®, which was the system evaluated within Norfolk, aids more effective monitoring of lithium by not only ensuring that the majority of patients receive the recommended number of monitoring tests per annum but also appears to be associated with improved response rates to out-of-range results received. One major limitation of this data is that we were not able to control for other external factors that could have impacted on this increase in lithium level monitoring in the years since the database implementation such as an increase in training and awareness of lithium and the introduction of QoF in 2004. The reasons for the high lithium levels and any actions taken by the clinical team are also not known from the information on the database.

The qualitative work in this thesis evolved from the results in the service evaluation and prescribing information (Anderson, 2012, Powell-Smith and Goldacre, 2015). Consideration was being made at the time of the work for SystemTDM® to be rolled out to Suffolk from the neighbouring county of Norfolk particularly as the two counties are covered by the same Mental Health Trust. There was a disparity in prescribing of lithium seen between the two counties and so it was felt that by interviewing prescribers, in this case consultants who hold overall responsibility for patients, before SystemTDM® was rolled out it, what the influential factors were on prescribing decisions could be investigated. Work in this area had previously been conducted on newer drugs or comparing different areas of practice and not on older drugs such as lithium or comparing

two areas that shouldn't display such disparity in prescribing (Schumock et al., 2004, Ljungberg et al., 2007). This study adds to the current evidence in these areas by supporting that the application of knowledge and discussions with colleagues, patient symptom and severity and diagnosis, patients past experience with medications, medication side effects, concurrent physical health problems, medication interactions, patient preferences and beliefs and the prescriber's familiarity with certain drugs and practical experiences with drugs are all influential factors for prescribing of drugs such as lithium as well as drugs studied previously (Chow et al., 2014, Hajjaj et al., 2010, Rajendran et al., 2012, Shepherd et al., 2014, Denig et al., 2002b, Ljungberg et al., 2007, McGettigan et al., 2001, Tan et al., 2009, Hedenrud et al., 2013).

However, the idea of prescribing based on the competence of the doctor rather than based on their grade was discussed, which ties in with issues of the knowledge and experience of prescribers. The idea that there needs to be more of an emphasis on teaching of older drugs such as lithium to ensure that generational differences are not seen in prescribing practices for newer doctors was also raised from this study. The emphasis on competence, education and training is not only relevant for lithium but for any drugs requiring therapeutic drug monitoring (TDM). With computerised systems in place any negative factors from the added complexities of prescribing drugs requiring TDM is partially negated alongside good communication between areas of practice.

Unlike other studies the cost of drugs themselves was not raised as an issue, more so the cost of wasted services or clinics with a lack of robust communication or electronic systems to aid communication between areas of practice (Higgins and Tully, 2005,

Anderson, 2015). There are issues surrounding this raised in this study due to the recent changes in service configuration for mental health services whereby the consultant responsible for the long-term care of the patient is no longer likely to be the consultant who sees the patient as an inpatient, and may even be in a different geographical area (Begum et al., 2013). This leads to issues around initiating complex and long-term medications as the person who would be initiating the drugs, such as lithium, is not able to have a full discussion around the considerations needed from the patient's perspective about their long-term treatment. This correlates with the previously raised factor that interacting with the patients (and relatives where relevant) along the journey to prescribing in a shared-decision making process is important in the prescribing decision. If the prescriber is not able to be involved after the initiation of a drug this process cannot be followed. At some points the idea of a lithium clinic was raised as a way to aid in the long-term care of patients prescribed lithium, and to bridge any issues from the change in structure of mental health services where the initial consultant initiating a treatment option is not the consultant following the patient up in the long-term. However where there was a computerised system in place to aid the prescribing and monitoring of patients prescribed lithium, concerns raised about its prescribing were negated along with the cost implication of missed or repeated clinic visits and blood tests.

As early on in the thesis work the effectiveness of a computerised system has been evaluated, a logical next step was to further investigate the relationship of lithium levels on renal function using the data collected by this robust system. This had been an area where there was inconsistent research conducted previously and an area where there

were still uncertainties about the definite effects of lithium on long-term renal function (McKnight et al., 2012).

As part of a systematic approach to analyse the patient data collected by SystemTDM® since its inception, the impact of one lithium level, of varying degrees, was explored initially. Serum creatinine was used as the initial marker for renal function as this was recorded on the system. However, although this is an endogenous marker of kidney disease, it has its limitations as a marker of renal function (NICE, 2008). Estimated GFR was therefore used for the final analysis as reported in the thesis. There are also still limitations to using this marker of renal function as not all factors that can affect the calculated eGFR were recorded on the database. These factors include race, other current medications, or diseases (NICE, 2014b).

This showed that exposure to one lithium level >1.0mmol/L had a statistically significant negative association on renal function in the first three months after exposure but with no other high levels the kidneys appeared to be able to recover this function. In practice however, lithium is a long-term treatment and it is therefore likely that lithium levels will change over time for patients potentially leading to multiple or further exposures to levels >1.0mmol/L. This data adds to previous research which was not able to determine variations in this risk to renal function for different serum levels, due to the comparison of different lithium level ranges compared to a reference group (Close et al., 2014).

The next step for the progression of the thesis was to look at multiple exposures to various lithium levels. The NICE guidance on lithium monitoring changed since the first analysis was run on single lithium levels, and was amended in part due to the results

presented. The guidance at the time of this analysis therefore only recommended six monthly lithium level testing for patients after their first year, except for certain groups. Patterns including missing values at the second exposure point (three months) were of interest as well as those with a level recorded then as this would reflect a change to the six monthly testing. However, due to the impact of SystemTDM® on ensuring that patients received lithium levels and other testing parameters in line with the previous national guidance of three monthly testing, we found that there were very few patients in our sample with missing values.

With the results from the double exposure analysis showing mainly non-significant increases in eGFR apart in all pattern groups apart from HH which showed a non-significant decrease in eGFR at time period two i.e. six months after the second exposure and HS at time period one i.e. three months after the second exposure. This correlates with recent research from Clos et al who concluded that long-term lithium therapy is not associated with changes in renal function, demonstrated by changes in eGFR, in the absence of episodes of acute toxicity (Clos et al., 2015).

When evaluating these results it started to be considered whether in fact the change in the lithium levels was a factor to be considered on the impact on renal function not just the level itself due to the variation in increases and decreases in eGFR and the fact that the interaction of pattern and time was significant only for pattern three (HL) showing a significant increase in eGFR at ≤3 months follow-up after the second exposure event. This was evidenced in the variation in the effects shown in the individual results for various patients pulled out as examples, when looking at these examples there was no correlation

between lithium level at exposure, age or gender that could explain the variation apart from the three patients aged >60 in the HL pattern group who all showed a decline in eGFR. The sample sizes of the pattern groups in this analysis were too small to be statistically reliable for most of the groups apart from 1.01-5.0 then 0-0.8mmol/L (HL) so not much reliance should be placed on these results. There were also multiple tests run for the analysis on the data on single and multiple exposures to lithium which does limit the robustness of the results presented. However this was thought to be an appropriate limitation to the analysis due to the way the data was presented for analysis.

7.2 Conclusions

Mental health disorders for which treatment with lithium is appropriate are long-term, chronic conditions and require a long-term treatment. Therapeutic ranges of lithium for the treatment of the various disorders for which it is licensed to treat have been well established. Evidence, however, to support recommended monitoring frequencies is lacking. The use of a computerised, actively managed database for the monitoring of lithium has, within Norfolk, been associated with a steady increase in the numbers of patients receiving tests at the recommended frequencies, and a quicker response to levels outside of the recommended range reducing patient exposure to the potentially toxic effects of lithium. However this increase could also be partly explained by an increase in education about lithium levels and the implementation of QoF.

The evidence contained within this thesis provides a backbone on which to conduct further research for multiple exposures to various lithium levels on a larger scale with the potential for collaborative research across the UK. So far the evidence is suggestive of a short-term negative association on renal function after exposures to single, high lithium levels but due to the small patient groups in the multiple exposures analysis the results from this are not statistically reliable so we cannot draw robust conclusions from them. These results did, however, raise the considerations that changes in lithium levels, not just the level itself, may impact on renal function. This lends itself to further research in order to investigate further to see if this hypothesis is correct or if the level of lithium is the principal factor contributing to the statistical increase in renal function seen for some

groups at follow-up after multiple exposures and the non-significant decrease seen for other groups.

In terms of the factors affecting prescribing decisions many factors mentioned correlate with previous studies researching newer medications and other healthcare settings. However, the new themes bought up added to the idea of knowledge, learning and competence of prescribers with concerns around a lack of knowledge of older drugs seen in newer doctors. There needs to be focus maintained on older drugs so that knowledge about their use and how to prescribe them is not lost with newer generations of prescribers.

Although the idea of a lithium clinic was raised as an option for the ongoing prescribing of lithium, the feasibility of this was outside of the remit of this thesis. However the prescribers who used a computerised system such as SystemTDM® for the monitoring of their lithium patients were less concerned about setting up a specific clinic as they were confident in the long-term monitoring process. The initial prescribing of lithium and other drugs for the longer term treatment of patients was still an area of debate with prescribers not wanting to commit their colleagues to a specific course of action, and all prescribers had a reluctance to completely 'let go' of patients, wanting to still oversee their lithium treatment.

This suggests that a clearer, structured way of lithium being prescribed, with guidance surrounding at what points during the patient's journey the initial prescribing choice should be discussed and a decision made is needed. This would help overcome the barrier of split services within mental health and give clearer roles to the various consultants

involved in a patient's care. In addition the wider roll out of a system which could act as a centralised lithium monitoring system with access for all those involved in the patients care along their journey should be considered to aid in the long-term monitoring of lithium. This would help to maintain levels within acceptable ranges consistently and avoid any exposures to levels outside of these ranges, or multiple changes in lithium levels to minimise the potential detrimental effects on renal function. This sort of system would also allow for all those involved being able to retain some sort of oversight over patients whether or not they are still directly under their care. It would also allow for greater research to be conducted to address the additional research questions raised by this thesis.

7.3 Publications and conferenced proceedings arising from the thesis

Peer-reviewed Journals

Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA; One lithium level >1.0mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. (*BMJ Open 2014;4:11 e006020 doi:10.1136/bmjopen-2014-006020*)

Kirkham E, Bazire S, Anderson T, Wood J, Grassby P and Desborough JA; Impact of active monitoring on lithium management in Norfolk; Therapeutic Advances in Psychopharmacology; 2013;(5):260-265

Published Conference Abstracts and presentations

Kirkham E, Desborough JA, Skinner J, Bazire S, Anderson T, Wood J, Grassby P (2013) The effects of computerised standardisation on lithium monitoring (Oral Presentation at College of Mental Health Pharmacy Conference 2013)

Kirkham E, Desborough JA, Skinner J, Bazire S, Anderson T (2013) What happens if you go 'high' on lithium. (Poster at College of Mental Health Pharmacy Conference 2013)

Kirkham E, Desborough JA, Skinner J, Bazire S, Anderson T (2013) Does the 'active' part of an actively managed database for lithium have an effect? International Journal of Pharmacy Practice 21 (Suppl. 2) 30-137 (Poster at Royal Pharmaceutical Society Conference 2013)

Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. 'What does lithium do to your creatinine?' European Neuropsychopharmacology. 2014;24(Supplement 2):S410 (Poster at European Congress of Neuropsychopharmacology 2014)

Kirkham E, Bazire S, Twigg MJ, Anderson T, Desborough JA (2015) Factors which influence prescribing of lithium: views and perceptions of consultant psychiatrists (Poster at Health Services Research and Pharmacy Practice Conference 2015)

Kirkham E, Bazire S, Twigg MJ, Anderson T, Desborough JA (2015) Robustness of monitoring systems influential in decisions to prescribe lithium. (Poster at British Association of Psychopharmacology Summer meeting 2015)

Planned publications

Final PhD Project: Factors affecting lithium prescribing: views and perceptions of consultants on current practice.

7.4 Recommendations for future work

- Collaborative work with other areas of the UK, and possibly internationally, where lithium is prescribed and initiated to expand on the statistical analysis of multiple exposures of various lithium levels. By collaborating with other areas which have similar data to that recorded on the SystemTDM® may mean a more reliable interpretation could be gained from the results. Specific patterns of exposure which were not present in the Norfolk cohort may also be available to be analysed. This work could also be expanded to look at three, four, five and so on different lithium level exposures and expand on the pattern groups evidenced in the Norfolk data where significant conclusions could not be drawn from the results. The population in Norfolk is also not the most diverse and so additional collaborations would enable any demographics which may have an additional impact on renal function.
- The relationship between age and lithium level was not fully explored in this thesis, this is an area where there is scope for future work focussing on the >60 age group of patients which are prevalent within Norfolk.
- Further interviews could also be conducted across the UK within different Trusts to see if there are other factors at play in other areas of the UK where per head of population there are disparately different rates of lithium prescribing as recorded from Openprescribing.net (Powell-Smith and Goldacre, 2015).

Chapter Eight

8: References

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Appendices

Appendix One

Norfolk and Suffolk NHS
NHS Foundation Trust

University of East Anglia

Protocol: What is the role of lithium monitoring? A retrospective analysis of a lithium monitoring database

Primary Researcher

Emma Kirkham

PhD Student, School of Pharmacy, University of East Anglia

Research Supervisors

Dr James Desborough

Lecturer in Pharmacy Practice, School of Pharmacy, University of East Anglia

Dr Jane Skinner

Lecturer in Medical Statistics, School of Medicine, University of East Anglia

Professor Stephen Bazire

Consultant Pharmacist, Norfolk and Suffolk NHS Foundation Trust, Hellesdon Hospital, Norwich

Timothy Anderson

Lead Clinical Pharmacist, Norfolk and Suffolk NHS Foundation Trust, Hellesdon Hospital, Norwich

1. Introduction

Since the early 1970s lithium carbonate has been approved in the US for long-term prophylactic use in bipolar disorder with approval in the UK occurring by 1985 (Sanofi-Aventis, 2011, FDA, 2012 (a)). Lithium has since been licensed for the treatment and prophylaxis of mania and hypomania, prophylactic treatment of recurrent affective disorders, treatment of recurrent bipolar depression where the use of alternative antidepressants has been ineffective and the treatment of aggressive or self-mutilating behaviour (Sanofi-Aventis, 2012, Norgine, 2011, Rosemont, 2011). During the 1950s the narrow therapeutic range of lithium was determined and ad-hoc monitoring for signs of toxicity including gastric disturbances, motor disturbances such as muscular weakness and ataxia and slurred speech occurred (Ashburner, 1950, Noack and Trautner, 1951).

Until 2003, with the publication of the British Association for Psychopharmacology (BAP) guidelines and later in 2006 with the National Institute for Health and Clinical Excellence (NICE) bipolar guidance, there were no nationally recognised guidelines in the UK for lithium monitoring outside of the recommendations in the British National Formulary (BNF) (NICE, 2006, BAP, 2009). By the 1980s these BNF recommendations were limited to adjusting the dose to achieve plasma concentrations between 0.6 and 1.2mmol/L (Joint Formulary Committee, 1988). However renal toxicity and side effects had been associated with higher levels (>0.8mmol/L) suggesting that tolerability may be problematic with the higher levels recommended even if further benefits are gained in symptom control (Gelenberg et al., 1989, Severus et al., 2008). Long-term use of lithium has been associated with thyroid disorders and effects on renal function. Lithium has been associated with a nephrogenic diabetes insipidus and a speculative description of specific lithium nephropathy (McKnight et al., 2012, Joint Formulary Committee, 2012).

NICE guidelines on the management of bipolar disorder developed in 2006 state that during maintenance treatment with lithium, a serum lithium level should be taken every 3 months, renal and thyroid function tests should be completed every 6 months (more often if there is evidence of impaired renal function), and weight, BMI or waist

circumference should be done annually (NICE, 2006). The BAP guideline recommends that kidney and thyroid function are tested every 12 months, with lithium levels checked every 3-6 months in people on a stable dose (BAP, 2009).

In December 2009 the National Patient Safety Agency (NPSA) released an alert to improve the safety of lithium therapy due in part to concerns that guidelines were not being followed (NPSA, 2009). This focussed on regular monitoring in line with NICE guidance, reliable communication systems for blood test results, appropriate verbal and written information provided to patients and systems are in place to identify and deal with potential interactions with lithium therapy (NPSA, 2009). Seven years before this alert a lithium database and register (System TDM®) had been implemented across Norfolk following a clinical incident in primary care. The main objectives of this database were to ensure that all patients on lithium have access to adequate information, education and specialist advice and receive regular blood tests following an agreed protocol (Holmes, 2005).

In a recent meta-analysis and systematic review the toxicity profile of lithium was investigated showing little evidence for a clinically significant reduction in renal function in most patients and an association with an increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain. The quality and quantity of the primary evidence available was a main limitation of this study. High quality data from long-term randomised or controlled cohort studies were sparse and the sample size of most included observational studies was quite small (McKnight et al., 2012).

The Norfolk based database (System TDM®) now has ten years' worth of data collected during routine clinical practice allowing a retrospective single cohort study to be performed with a large sample size. Both renal function (from urea, creatinine and eGFR) and thyroid function (from TSH and T4) are recorded for all patients along with lithium levels, and other risk factors.

2. Aims

- To investigate the importance of lithium monitoring

3. Objectives

- To determine the impact of an active management system on lithium monitoring
- To determine the effects of lithium control on renal function
- To determine the effects of lithium control on thyroid function
- To determine the relationship between lithium control and other significant variables

4. Method

Data analysis will not commence until all relevant approvals are in place. As the research is limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) it is excluded from REC review, provided that the patients or service users are not identifiable to the research team in carrying out the research as in this case, therefore only requiring NHS R&D approval.

The database currently holds the following information about those patients registered on it:

Database ID, NHS number, alternative ID, full name, address and registered GP practice of each patient
Date of registration
Date of test results and results for: lithium, urea, creatinine, eGFR, TSH, T4
Risk factor: ACE inhibitor, Age >70, Diuretic, Impaired renal function, NSAID
Patient DoB
Gender
Diagnosis
Past and future addresses

Letters sent

Notes relating to patient

Uploaded documents

Any alerts relating to patient

The clinical pharmacy team will then anonymise this data removing NHS number, alternative ID, full name, address and registered GP practice of each patient, past and future addresses, letters sent, notes relating to patient, uploaded documents, any alerts relating to patient.

4.1 Participant Identification

All patients registered on the data base have data collected in routine clinical care which will be accessed for analysis. The patients will be identified by the clinical team who have access to the full data stored on the database.

4.1.1. Inclusion Criteria

- Patients who have been prescribed lithium for any indication and whose results were collected in routine clinical care and entered onto the database.
- Patients over the age of 18 years.

4.1.2. Exclusion Criteria

- Nil specific exclusion criteria due to the data being collected in routine clinical practice

4.2 Sample size

At the time of writing the clinical pharmacy team have informed the researchers that there are 1730 patients on the database (active, inactive, suspended or deceased). All patients who meet the inclusion criteria are expected to be included for analysis.

4.3 Data collection

The anonymised data from the clinical team will be locally encrypted using AES-256 encryption and then saved to cloud based storage for backup prior to analysis. This analysis will be performed at the University of East Anglia using computers which require a password log-in. All anonymised, locally encrypted data on the database from the sql server management studio will be stored electronically with direct access only for the principal researcher.

Data extraction and analysis will be repeated six monthly to ensure that the most comprehensive and current data is being used for analysis.

4.4 Data analysis

Data gained from the study will be analysed using STATA. The tests to be used will be determined by the distribution of the data and the different relationships between the monitoring parameters and lithium levels to be analysed. Assuming that the test results or a transformation of them (e.g. log) are approximately normally distributed, regression methods will be used to model each of the results and the risk factors above, together with age, sex and diagnosis. Otherwise, non-parametric methods (Mann-Whitney, Kruskal–Wallis) will be used to examine the effect of the risk factors.

Only anonymised data will be analysed by the researcher and their supervisors using password protected computers. All anonymised data will be destroyed five years after completion of the study.

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Appendix Two

Norfolk and Suffolk NHS
NHS Foundation Trust

Research and Development Dept
Hellesdon Hospital
Drayton High Road
Norwich, NR6 5BE
Telephone 01603 421255
E mail: RDOfficemailbox@nsft.nhs.uk

Miss Emma Kirkham
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

1st February 2013

Dear Miss Kirkham,

Re: 2013MH02: Retrospective analysis of a lithium monitoring database

Thank you for submitting the above project for local research governance approval. The Committee reviewed the application on the meeting of the 31st January 2013, and has made the following comments:

- The committee complimented the proposal for being well-written and clear, and a low risk to the Trust from a governance perspective.
- The committee noted that according to GAfREC regulations, "Research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) is generally excluded from REC review, provided that the patients or service users are not identifiable to the research team in carrying out the research" http://www.nres.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=134016. It was confirmed that for this study, this statement would be applicable and NHS REC review was not required.
- The committee asked why the date of birth would be needed as this is identifiable data. Miss Kirkham confirmed that it is only the year of birth that will be provided in the information.
- The committee asked for clarification if deceased patients will be included in the study. Miss Kirkham confirmed that the only exclusion criterion is if the patient is under 18 otherwise even deceased patients will be included in the data. It would not be possible to know from the database the cause of death of the patients.
- The committee asked that once the data is collected every six months, would the researcher be using new patients in the data? Miss Kirkham confirmed that data will be collected every six months so the latest information could be used for the study (such as updated blood test results)
- The committee asked Miss Kirkham to see a copy of any publication material.

If you have any queries regarding this or any other project, please contact, Bonnie Teague, Research Manager, at the above address.

The reference number for this study is: **2013MH02,** and this should be quoted on all correspondence.

Yours sincerely,

Dr Jon Wilson
Deputy Medical Director (Research) and NSFT Research Governance Chair.

Appendix Three

Norfolk and Suffolk NHS
NHS Foundation Trust

Research and Development
The Knowledge Centre
Hellesdon Hospital
Drayton High Road,
Norwich, NR65BE
Telephone 01603 421255
E mail: RDofficemailbox@nsft.nhs.uk

Miss Emma Kirkham
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

27th February 2013

Dear Miss Kirkham,

Re: 2013MH02: Retrospective analysis of a lithium monitoring database

Thank you for submitting the above project for local research governance approval. I am pleased to inform you that your project has been given full approval and you may begin your research at the following site:

- Norfolk & Suffolk NHS Foundation Trust

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies returning one copy to the Research and Development office, at the above address, and keeping the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval. **Under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.**

Any researcher(s) whose substantive employer is not the Norfolk & Suffolk NHS Foundation Trust must have a Letter of Access or Honorary Research contract and evidence of Good Clinical Practice (GCP) training before coming on site to conduct their research in this project. Please note that you cannot take part in this study until you have this documentation. If a Letter of Access / Honorary Research Contract has not been issued – please contact us immediately.

If you have any queries regarding this or any other project, please contact, Tom Rhodes, Research Governance Administrator, at the above address.

The reference number for this study is: **2013MH02,** and this should be quoted on all correspondence.

Yours sincerely,

Dr Jon Wilson
Deputy Medical Director (Research)

Your research governance approval is valid providing you comply with the conditions set out below:

1. You commence your research within one year of the date of this letter. If you do not begin your work within this time, you will be required to resubmit your application.
2. You notify the Research and Development Office should you deviate or make changes to the approved documents.
3. You alert the Research and Development Office by contacting the address above, if significant developments occur as the study progresses, whether in relations to the safety of individuals or to scientific direction.
4. You complete and return the standard annual self-report study monitoring form when requested to do so at the end of each financial year. Failure to do this will result in the suspension of research governance approval.
5. You comply fully with the Department of Health Research Governance Framework and Trust Research Policies, and in particular that you ensure that you are aware of and fully discharge your responsibilities in respect to Data Protection, Health and Safety, financial probity, ethics and scientific quality. You should refer in particular to Sections 3.5 and 3.6 of the Research Governance Framework.
6. You ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice, Data Protection Act and Human Rights Act. Unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.
7. **UKCRN Portfolio Studies only**: You will make local Trust research team members aware that it is expected that the "first participant, first visit" date should be within 70 days of the full submission for Trust Research Governance Approval, and this date must be reported to the Research and Development office using the email address above. Delay to recruitment due to study-wide developments must be reported to the Trust as soon as possible.
8. **UKCRN Portfolio Studies only**: You will report and upload Trust recruitment to the UKCRN portfolio accurately and in a timely manner, and will provide recruitment figures to the Trust upon request.

List of Approved Documents:

Documents Received	Version	Date
Protocol	2	Nov-12

Appendix Four

University of East Anglia

Norfolk and Suffolk NHS
NHS Foundation Trust

Protocol: Factors affecting lithium prescribing: views and perceptions of consultants on current practice

Primary Researcher

Emma Kirkham

PhD Student, School of Pharmacy, University of East Anglia

Research Supervisors

Dr James Desborough

Lecturer in Pharmacy Practice, School of Pharmacy, University of East Anglia

Dr Jane Skinner

Lecturer in Medical Statistics, School of Medicine, University of East Anglia

Professor Stephen Bazire

Consultant Pharmacist, Norfolk and Suffolk NHS Foundation Trust, Hellesdon Hospital, Norwich

Timothy Anderson

Lead Clinical Pharmacist, Norfolk and Suffolk NHS Foundation Trust, Hellesdon Hospital, Norwich

1 Introduction

Lithium is licensed in the UK for the treatment and prophylaxis of mania and hypomania, prophylactic treatment of recurrent affective disorders, treatment of recurrent bipolar depression where the use of alternative antidepressants has been ineffective and the treatment of aggressive or self-mutilating behaviour (Sanofi-Aventis, 2012, Norgine, 2011, Rosemont, 2011). Lithium is considered to be effective when its serum level is maintained between 0.6 and 0.8mmol/L in newly initiated patients. Few patients will benefit from higher serum levels above 1.0mol/L as these are associated with an increase in signs and symptoms of lithium toxicity. Since lithium has a narrow therapeutic window the National Institute for Health and Clinical Excellence (NICE) guidance currently recommends that the serum lithium level is checked every 3 months whilst the British Association for Psychopharmacology (BAP) guidelines recommend every 3-6 months. Renal and thyroid function tests are also recommended at baseline and routinely throughout treatment. These additional monitoring requirements are because lithium is almost entirely renally excreted, so any change in renal function or fluid balance can potentially lead to lithium accumulation. Treatment with lithium has also been associated with an increased risk of clinical hypothyroidism (BAP, 2009, NICE, 2006).

Despite these guidelines there remain a number of concerns regarding adherence to monitoring recommendations which is a cause for concern in relation to patient safety (Collins et al., 2010, Eagles, 2000). Between the years 2005-2009 there were 567 patient safety incidents reported to the National Reporting and Learning System (NRLS) relating to lithium therapy. A key theme in these incident reports was lack of patient monitoring which holds a risk of litigation (NPSA, 2009). In a ten year review the Medical Defence Union found that there were 102 cases of litigation involving lithium prescribing and monitoring. Out of these, poor monitoring was cited in 59 cases, 13 of which involved deaths (excluding suicides) and 44 cases of toxicity (Holmes, 2005). In 2009 the Prescribing Observatory for Mental Health UK (POMH-UK) audit of lithium prescribing identified that only 30%, 55% and 50% of patients met monitoring standards for serum lithium, renal and thyroid function respectively (Collins et al., 2010). In December 2009 the National Patient Safety Agency (NPSA) released a patient safety alert partially due to the results of the POMH-UK audit as well as concerns about patient safety incident reports (NPSA, 2009). The alert focussed on regular monitoring in line with NICE guidance, reliable communication systems for blood test results, appropriate verbal and written information provided to patients and systems to be developed to identify and deal with potential interactions with lithium therapy (NPSA, 2009).

Although the NPSA alert was released in 2009 a unique Norfolk-wide lithium register and database (SystemTDM®) has been in operation since 2002. This database was developed by a local prescribing group and is currently only used in Norfolk. Recently, there has been interest in providing this service to other Mental Health Trusts across the country. The main objectives of this database are to ensure that all those on lithium have access to adequate information, education and specialist advice and receive regular blood tests following an agreed protocol. The database incorporates a reminder service for blood tests to patients together with alerts to prescribers of lithium results that are out of the specified range or overdue blood tests, both of which require action. In January 2012 individual Norfolk and Suffolk Mental Health Trusts merged to form Norfolk and Suffolk NHS Foundation Trust (NSFT). The intention of NSFT is to roll out SystemTDM® to Suffolk, however, to date only one area in Suffolk has been approached and registered patients on the database.

Nationally (where lithium prescribing is hospital initiated), there are shared care agreements in place allowing secondary care initiation and prescribing until the patient is stabilised and then transferred to primary care for continued treatment. These shared care agreements have been in place in both Norfolk and Suffolk for some years. However, anecdotal prescribing information suggests that lithium appears to be prescribed twice as often in Norfolk as in Suffolk, despite the similarity in their current shared care agreements, population size and age distribution (Anderson, 2012, ONS, 2011). Therefore, we want to explore the factors which affect the decision to prescribe lithium by interviewing consultants within NSFT to determine potential reasons why this difference is observed. For those consultants based within Suffolk this will be done before the database becomes normal practice as it currently is within Norfolk.

There is a dearth of research on the factors which influence prescribing decisions for established treatments, most focusses on new drugs and comparisons between primary and secondary care or different healthcare professionals within secondary care (Ljungberg et al., 2007, Schumock et al., 2004). The aim of this project is to build on this limited research to ascertain the key factors which influence consultants prescribing choices relating specifically to lithium. Semi-structured interviews will be used to ascertain the views and perceptions of consultants currently working across NSFT.

2. Aims and Objectives

2.1 Aim

The aim of this project is to understand the factors affecting lithium prescribing by eliciting the views and perceptions of consultants on current practice through semi-structured interviews.

2.2 Objectives

The objectives of the semi-structured interviews will be to:

- Explore consultants' views on lithium as a medicine.
- Explore what factors consultants consider as influential in decisions to prescribe lithium or another medicine in current practice
- Describe the effect of current guidance on the prescribing of lithium.
- Describe the effect of current shared care agreement and the procedure for transfer of prescribing to primary care
- Compare the views and perceptions of Norfolk and Suffolk based consultants on the prescribing of lithium i.e. comparing the views of those experienced with the database and those who are not

3. Methodology, Procedure and Analysis

3.1 Method

This has been reviewed and approved by the Faculty of Medicine and Health Sciences Research Ethics Committee and the relevant NHS research governance committee. Semi-structured interviews will be undertaken with mental health consultants within NSFT. Interviews were chosen because the strengths of this method are well suited to our study in that they will facilitate a depth of focus and understanding of perspectives and experiences. The aim of this study is to capture the current practices of consultants within the trust; therefore interviews provide the opportunity for them to describe these without external influences as would be present in a focus group situation. In addition, semi-structured interviews should be more accessible to the population studied, which is made up of busy professionals, compared to focus groups (Ritchie and Lewis, 2003).

3.2 Participant Recruitment

As part of regular research meetings (involving NSFT consultants) potential participants will be alerted to the project. This is routine practice within these meetings and will be conducted by the NSFT Research and Development (R&D) lead in conjunction with the primary researcher (EK). The R&D lead will ask attendees if they are happy for the primary researcher to be present for the appropriate portion of the meeting. If consultants express an interest at any of these meetings they will be given a covering letter (Appendix 1) inviting them to participate in this study on behalf of the researchers. The letter will be accompanied by a participant information sheet (Appendix 2), expression of interest form (Appendix 3) and a pre-paid envelope addressed to the primary researcher. Potential participants will be able to complete the appropriate documentation at the meeting and return directly to the researcher or take it away to allow them time to think about their participation. As the attendance of consultants in the research forums varies across localities contact via letter and email will however be the main method of recruitment as described below.

The work contact details of all consultants working within Suffolk will be obtained by the primary researcher from research and development or the Trust e-mail group 'consultants' in order to contact them for this project. The primary researcher will then send out a covering letter (Appendix 1) inviting them to participate in this study. The letter will be accompanied by a participant information sheet (Appendix 2), expression of interest form (Appendix 3), decline to participate postcard (Appendix 4) and a pre-paid envelope addressed to the primary researcher. The e-mail (Appendix 5) will have attached a participant information sheet (Appendix 2) and will

encourage respondents to reply via e-mail with the information required on the expression of interest (Appendix 3). After two weeks, consultants that have not responded will be sent a second letter (Appendix 6) and email (Appendix 7).

During the process of recruitment an encryption form (Appendix 12) will be kept allowing for each potential participant to be allocated a study reference number. When either an expression of interest form decline to participate postcard is returned these will be recorded to keep track of who has replied and the dates on which reminders are due to be sent out.

Once participants have agreed to be involved with the research and have suggested times and locations that are suitable for them they will be contacted to confirm a time and date for the interview. Once this has been agreed an email or letter will be sent to them with confirmation of the date, time and location of the interview (Appendix 8). A reminder will be sent one week before the interview date. If more consultants are willing to be interviewed than it is feasible to conduct then the demographic data collected will be used to ensure that the two groups of interviewees from Norfolk and Suffolk are as similar as possible. The remainder of the consultants who expressed interest in participating will be send a regret email/letter (Appendix 9)

To contextualise results, potential participants will be asked to detail whether they have worked for Norfolk and Waveney Mental Health Trust (the predecessor organisation to NSFT in Norfolk) in the previous ten years. They will also be asked if they have been employed in Norfolk or Suffolk for less than a year. This will capture those participants who are likely to be less experienced with the database (if based in Norfolk), and is due to the need to understand whether they have worked with SystemTDM® in the past. The only inclusion criteria for the project are that potential participants all consultants currently employed by NSFT, there are no specific exclusion criteria.

3.3 Data Collection

The interviews will take place at a venue and time that is suitable for the interviewees and will be conducted by the primary researcher. As a risk reduction measure these details will be shared with the supervisory team, and telephone contact made at the end of each interview. All participants will need to sign a consent form (Appendix 10) on the day of the interview in order to participate and a copy will be given to participants for their records. Refreshments will be provided for all participants by the researcher.

A pilot interview will be conducted by the primary researcher with a second researcher (MT) present for quality and assurance purposes of the primary researcher, not for interaction with the participant. This pilot interview will be transcribed by the primary researcher and will be reviewed by the supervisory team. Data collected during this interview will not be included in analysis and amendments will be made to the interview topic guide if required.

The interviews are expected to last up to one hour and the participant will be free to leave at any point. If they choose to leave due to time constraints then the data up to the point of them leaving will be used in the analysis, if they choose to leave for other reasons then the participant will be asked if they consent to their data up to that point being included in the analysis or if they want it to be removed. The topics expected to be covered in the interviews are:

- Introduction and background to the project
- What are your views on lithium as a medicine?
- When and for what type of patients would you consider prescribing lithium?
- What influences your choice to prescribe lithium rather than other medicines?
- Do you routinely use any treatment guidelines to influence choice of medicine?
- Do you think it matters who prescribes/initiates lithium?
- Conclusion

The interviews will be audio recorded using two voice recording devices. The interviews will be transcribed confidentially by the primary researcher and checked for accuracy by another member of the research team. Alternatively, depending on finances, an option would be to outsource the transcribing to a reputable company such as Clayton Research Support, 54 Chapmans Drive, Old Stratford, Northamptonshire, MK19 6NT, who have been used for such projects previously and then the verbatim transcripts will be checked for accuracy by the researcher. If transcribing is outsourced a confidentiality agreement will be signed before they undertake any transcribing (Appendix 11).

In order to encourage the participants to be open and honest the interview recordings will only be accessed by the principal researcher and the member of the research team checking accuracy. Once transcribed and checked for accuracy the interview recordings will be deleted. The consent, and expression of interest forms and the decline to participate postcards in hard copy will be

stored in lockable storage at the University of East Anglia and will all be destroyed within five years of completion of the study. An encrypted memory stick will be used to hold the data and analysis after completion of the study and this will stored in a locked environment for five years and then destroyed. The encryption form will be destroyed within six months of completion of the study.

3.4 Data Analysis

A thematic analysis will be undertaken of the anonymous transcripts which will be performed at the University of East Anglia using computers which require a password log-in. These transcripts will be analysed by two researchers independently and consensus reached if disagreements occur. Manual coding, using a 'scissors and paste' technique, will be undertaken by the primary researcher who has attended a course in interviewing skills and received training on qualitative data analysis. The supervisory team will be involved in the coding process and advise as required. Thematic analysis will be used allowing for identification and analysis of themes or patterns that that are elicited from the data. Due to the nature of this research we will aim to produce a rich thematic account of the whole data set in order to get a sense of the predominant or important themes (Braun and Clarke, 2006). The process of thematic analysis as described by Braun and Clarke:

1. Familiarise yourself with your data e.g. transcription and reading
2. Generating initial codes
3. Searching for themes e.g. organising codes into groups, starting to identify themes
4. Reviewing themes e.g. checking themes match with the originally generated codes
5. Defining and naming themes
6. Producing the report

There will be constant reference at all stages to the original transcript as this will help the researcher determine the level of themes and subthemes and confirm that these are relevant to what was said in the transcript and have not been taken out of context during the coding process.

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Appendix 1

Covering Letter

School of Pharmacy

University of East Anglia

Norwich

NR4 7TJ

Tel. 01603 591973

Pharmacy Department

Hellesdon Hospital

Norwich

NR6 5BE

Tel. 01603 421480

Dear [Name]

Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

The pharmacy department at Hellesdon Hospital is currently working with the University of East Anglia on a project to evaluate the role of lithium monitoring. As part of this project we would like to learn about factors which affect lithium prescribing, focussing on the views and perceptions of consultants on their current practice. To facilitate this we would like to invite you to be a part of the project and arrange an interview with Emma Kirkham (the primary researcher), of approximately 1 hour with you as a consultant currently working within NSFT. You will also receive this invitation via email.

This work is being conducted as part of a research project and therefore we intend to publish the results in a peer-reviewed journal, albeit in an anonymised format. The data collected will be kept in an anonymised format within the School of Pharmacy and all raw data from the project will be destroyed within one year of the study's completion. Relevant approvals have been obtained for the project.

Please read the enclosed participant information sheet and if you are happy to participate please return the expression of interest form using the pre-paid envelope or reply via email to Emma Kirkham on e.kirkham@uea.ac.uk or emma.kirkham@nsft.nhs.uk with the following information:

- Year of qualification
- Gender
- Age group: 20-35, 36-50, 51-65, 66+
- Whether you have worked within mental health in Norfolk or Suffolk for less than one year.
- In the last 10 years have you ever worked for Norfolk and Waveney Mental Health Trust?
- Your speciality e.g. Adult Services, Forensics, Older Age, CAMHS
- Preferred contact details

- If possible suitable times/locations for interviews or details for best person to contact for this

If after two weeks no response has been received we will contact you again to confirm whether you wish to participate in this project. If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and I will endeavour to answer them for you.

Thank you in anticipation of your help.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich, NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich, NR6 5BE

Enclosures (3)

Appendix 2

Participant Information Sheet

University of East Anglia

Norfolk and Suffolk NHS Foundation Trust

Factors affecting lithium prescribing: views and perceptions of consultants on current practice

Research funded by the Pharmacy department at Hellesdon Hospital

Participant Information Sheet

This information sheet is designed to be read by you, the potential participant, to help you understand this project and what it will involve. It is set out as a series of questions and answers. If any question that you would like to ask is not provided for then please feel free to contact the primary researcher via telephone or email.

What is the project about?

The aim of this project is to better understand the views and perceptions of consultants who prescribe lithium on factors which influence their prescribing decisions.

What are the benefits of becoming involved in this project?

The results of this project will be used to evaluate and influence the way in which lithium is monitored within Norfolk and Suffolk NHS Foundation Trust. Additionally, the preliminary findings from this project will be shared with you, verbatim quotes from the interviews may be published but personally identifiable information will be removed. Participants will only be identifiable by their study numbers in written documentation and any quotes will be attributed to the study number allocated to that participant.

What does the project involve?

The project will involve a face to face interview of approximately 1 hour with the primary researcher (EK), refreshments will be provided for you. You will be free to leave at any point with no ill effects. If you choose to leave due to time constraints then the data up to the point of leaving will be used in the analysis, if you choose to leave for other reasons then you will be asked if you consent to your data up to that point being included in the analysis or if you want it to be removed. You will be asked questions on the following topics:

What are your views on lithium as a medicine?

When and for what type of patients would you consider prescribing lithium?

What influences your choice to prescribe lithium rather than other medicines?

Do you routinely use any treatment guidelines to influence choice of medicine?

Do you think it matters who prescribes/initiates lithium?

Do I have to take part?

Participation is entirely voluntary. If we do not hear from your two weeks after sending out this invitation pack (via email and letter) we will send out a second pack to you. If you do not wish to participate please return the decline to participate postcard and you will received no further correspondence from us.

Will information need to be provided on individual patients under my care?

No, the interviewer will not ask for any data which identifies individual patients. Additionally, you will be able to decline to answer questions if you wish. However, if an issue raising a concern of professional misconduct or negligence is disclosed as part of the research study then this will be passed onto the Research Integrity Officer as per Trust policy.

What happens next?

If you would like to participate then please contact the primary researcher Emma Kirkham on e.kirkham@uea.ac.uk or emma.kirkham@nsft.nhs.uk or return the expression of interest form in the pre-paid envelope provided to confirm your participation. You will then be contacted to arrange a time and location for the interview to take place convenient for you.

Complaints

If you have a complaint about how you were approached or how the interviews were conducted please contact the Research and Development office at Hellesdon Hospital on 01603 421340 or RDofficemailbox@nsft.nhs.uk . They will be able to answer any concerns you may have.

For further information please contact:

Primary Researcher:
Miss Emma Kirkham
School of Pharmacy,
University of East Anglia,
Norwich, NR4 7TJ
Tel: 01603 591973

Research Supervisor:
Dr. James Desborough
School of Pharmacy,
University of East Anglia,
Norwich, NR4 7TJ
Tel: 01603 593413

Thank you for taking the time to read this information sheet

Appendix 3

Expression of Interest Form

Expression of Interest form

Name:	
Year of qualification	
Gender	
Age group (please circle)	20-35 36-50 51-65 66+
Speciality e.g. Adult Mental Health, CAMHS, Older adult	
In the last 10 years have you ever worked for Norfolk and Waveney Mental Health Trust?	
Have you been employed within mental health in Norfolk or Suffolk for less than a year?	
Preferred contact number:	
Email address:	
If possible please suggest suitable times/locations for interview:	

Please return this form to the research team in the pre-paid envelope supplied. No stamp is required

Appendix 4

Decline to Participate Postcard

Decline to Participate Postcard

If you do not want wish to participate in this research, please return this postcard (no stamp needed) and you will not be contacted again. If you do not return this postcard or

I do not wish to take part in this research ☐ (Please tick)

Thank you for your time

Appendix 5

Covering email

Subject: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

---

Dear [Name]

The pharmacy department at Hellesdon Hospital is currently working with the University of East Anglia on a project to evaluate the role of lithium monitoring. As part of this project we would like to learn about factors which affect lithium prescribing, focussing on the views and perceptions of consultants on their current practice. To facilitate this we would like to invite you to be a part of the project and arrange an interview with Emma Kirkham (the primary researcher), of approximately 1 hour with you as a consultant currently working within NSFT. You will also receive this invitation via letter.

This work is being conducted as part of a research project and therefore we intend to publish the results, albeit in an anonymised format, in a peer-reviewed journal. The data collected will be kept in an anonymised format within the School of Pharmacy and all raw data from the project will be destroyed within one year of the study's completion. Relevant approvals have been obtained for the project.

Please read the attached participant information sheet and if you are happy to participate please reply via email to Emma Kirkham on e.kirkham@uea.ac.uk or emma.kirkham@nsft.nhs.uk with the following information:

- Year of qualification
- Gender
- Age group: 20-35, 36-50, 51-65, 66+
- Whether you have worked within mental health in Norfolk or Suffolk for less than one year.
- In the last 10 years have you ever worked for Norfolk and Waveney Mental Health Trust?
- Your speciality e.g. Adult Services, Forensics, Older Age, CAMHS
- Preferred contact details
- If possible suitable times/locations for interviews or details for best person to contact for this

If after two weeks no response has been received we will contact you to confirm whether you wish to participate in this project. If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and I will endeavour to answer them for you.

Thank you in anticipation of your help with the project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich,
NR6 5BE

Attachments (1)

REF NO: _____

==========

Miss Emma Kirkham MRPharmS
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ, UK

Tel: 01603 591973
Mob: 07841702776
E-mail: e.kirkham@uea.ac.uk
emma.kirkham@nsft.nhs.uk

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Appendix 6

Second letter

University of East Anglia

Norfolk and Suffolk NHS
NHS Foundation Trust

School of Pharmacy

University of East Anglia

Norwich

NR4 7TJ

Tel. 01603 591973

Pharmacy Department

Hellesdon Hospital

Norwich

NR6 5BE

Tel. 01603 421480

Dear [Name]

Re: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

You were recently contacted to see if you would like to be involved in the above research project being run by the Pharmacy Department in conjunction with the University of East Anglia. As yet we have not received any response to our invite and would like to see if you are interested in participating. If you have already responded then please ignore this letter.

Please read the enclosed participant information sheet and if you are happy to participate please return the expression of interest form using the pre-paid envelope or reply via email to Emma Kirkham on e.kirkham@uea.ac.uk or emma.kirkham@nsft.nhs.uk with the following information:

- Year of qualification

- Gender
- Age group: 20-35, 36-50, 51-65, 66+
- Whether you have worked within mental health in Norfolk or Suffolk for less than one year.
- In the last 10 years have you ever worked for Norfolk and Waveney Mental Health Trust?
- Your speciality e.g. Adult Services, Forensics, Older Age, CAMHS
- Preferred contact details
- If possible suitable times/locations for interviews or details for best person to contact for this

If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and I will endeavour to answer them for you.

Thank you in anticipation of your help with the project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich,
NR6 5BE

Enclosures (2)

Appendix 7

Second email

Subject: Re: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

---

Dear [Name]

You were recently contacted to see if you would like to be involved in the above research project being run by the Pharmacy Department in conjunction with the University of East Anglia. As yet we have not received any response to our invite and would like to see if you are interested in participating. If you have already responded then please ignore this email.

Please read the attached participant information sheet and if you are happy to participate please reply via email to Emma Kirkham on e.kirkham@uea.ac.uk or emma.kirkham@nsft.nhs.uk with the following information:

- Year of qualification
- Gender
- Age group: 20-35, 36-50, 51-65, 66+
- Whether you have worked within mental health in Norfolk or Suffolk for less than one year.
- In the last 10 years have you ever worked for Norfolk and Waveney Mental Health Trust?
- Your speciality e.g. Adult Services, Forensics, Older Age, CAMHS
- Preferred contact details
- If possible suitable times/locations for interviews or details for best person to contact for this

If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and she will endeavour to answer them for you.

Thank you in anticipation of your help with the project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich,
NR6 5BE

Attachments (1)

REF NO: _____

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Miss Emma Kirkham MRPharmS
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ, UK

Tel: 01603 591973
Mob: 07841702776
E-mail: e.kirkham@uea.ac.uk
emma.kirkham@nsft.nhs.uk

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Appendix 8

Confirmation letter/email

University of East Anglia

Norfolk and Suffolk NHS
NHS Foundation Trust

School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ
Tel. 01603 591973

Pharmacy Department
Hellesdon Hospital
Norwich
NR6 5BE
Tel. 01603 421480

Dear [Name]

Confirmation of participation in research: local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

This letter confirms our arrangements for your involvement in the above project. As previously noted your involvement will consist of an interview of approximately one hour in length. Refreshments will be provided.

Time:

Location:

If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and I will endeavour to answer them for you.

Thank you in anticipation of your help with the project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich,
NR6 5BE

Subject: Re: Confirmation of participation in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

---

Dear [Name]

This email confirms our arrangements for your involvement in the above project. As previously noted your involvement will consist of an interview of approximately one hour in length. Refreshments will be provided.

Time:

Location:

If at any point you have any questions about the project please feel free to contact Emma Kirkham by email or on 01603 591973 and I will endeavour to answer them for you.

Thank you in anticipation of your help with the project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich,
NR6 5BE

==========

Miss Emma Kirkham MRPharmS
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ, UK

Tel: 01603 591973
Mob: 07841702776
E-mail: e.kirkham@uea.ac.uk
emma.kirkham@nsft.nhs.uk

==========

Appendix 9

Regret letter/email

University of East Anglia
Norfolk and Suffolk NHS
NHS Foundation Trust

School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ
Tel. 01603 591973

Pharmacy Department
Hellesdon Hospital
Norwich
NR6 5BE
Tel. 01603 421480

Dear [Name]

Re: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

Thank you for your response agreeing to participate in the above research project. Unfortunately at this time we have more participants than needed so we will not need to arrange an interview with you at this time.

Once again many thanks for your willingness to participate in this research project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich, NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospuital
Norwich, NR6 5BE

Subject: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

---

Dear [Name]

Re: Invite to participate in research - local interviews with consultants to get their views and perceptions on the factors affecting lithium prescribing in current practice

Thank you for your response agreeing to participate in the above research project. Unfortunately at this time we have more participants than needed so we will not need to arrange an interview with you at this time.

Once again many thanks for your willingness to participate in this research project.

Yours sincerely,

Emma Kirkham
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

and

Tim Anderson
Lead Clinical Pharmacist
Hellesdon Hospital
Norwich
NR6 5BE

==========

Miss Emma Kirkham MRPharmS
Research Pharmacist
School of Pharmacy
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ, UK

Tel: 01603 591973
Mob: 07841702776
E-mail: e.kirkham@uea.ac.uk
emma.kirkham@nsft.nhs.uk

==========

Appendix 10

Consent Form

University of East Anglia

Norfolk and Suffolk NHS
NHS Foundation Trust

Factors affecting lithium prescribing: views and perceptions of consultants on current practice

Interview consent form

If you wish to take part, please initial each box and complete the details at the bottom of the form.

1. I agree to participate in the above study to investigate my views and perceptions of factors affecting lithium prescribing in current practice. ☐

2. I confirm that I have read and understood the participant information sheet dated 12/13, version 3 for the above interview and have had the opportunity to ask questions. ☐

3. I am willing to allow the interview to be audio-recorded for the purposes of analysis and possible publication. ☐

4. I understand that everything I say will be anonymised and will be kept securely at the UEA. ☐

5. I agree to be interviewed and understand that my consent to participate can be withdrawn up until the point when the interviews are transcribed and analysed. ☐

Name of participant	Date	Signature
Name of person taking consent	Date	Signature

Address of participant:

_____

_____

When completed: 1 copy for participant
1 copy for research team

Appendix 11

Confidentiality Agreement

Confidentiality Form between University of East Anglia, Norfolk and Suffolk NHS Foundation Trust and [name of transcribing company]

Project title: Factors affecting lithium prescribing: views and perceptions of consultants on current practice

Name of researcher: Emma Kirkham

The digital recordings you are transcribing have been collected as part of a research project. Digital recordings may contain information of a very personal nature, which should be kept confidential and not disclosed to others. Maintaining this confidentiality is of utmost importance.

We would like you to agree:

- Not to disclose any information you may hear on the digital recording to others
- When using the digital recording to ensure it cannot be heard by other people
- To show your transcription only to the relevant individual (named above) who is involved in the research project.

If you find that anyone speaking on a digital recording is known to you, we would like you to stop transcription work on that digital recording immediately and inform the person who has commissioned the work (Emma Kirkham).

Declaration

I have read the above information and I understand that:

1. I will discuss the content of the digital recording only with the individual(s) involved in the research project.

2. I will keep the digital recording in a secure place where it cannot be heard by others.

3. I will treat the transcription of the digital recording as confidential information.

4. If the person being interviewed on the digital recordings is known to me I will undertake no further transcription work on the digital recording.

I (and my team) agree to act according to the above constraints

Your name _____ on behalf of [name of transcribing company]

Signature _____ Date _____

Appendix 12

Encryption Form

Norfolk and Suffolk NHS
NHS Foundation Trust

Factors affecting lithium prescribing: views and perceptions of consultants on current practice
Encryption Form

Study Number	Participant Name	Date invitation sent	Date to resend	Expression of interest form returned	Withdrawn	Date interview reminder to be sent	Interview date

Appendix Five

Norfolk and Suffolk NHS
NHS Foundation Trust

Research and Development
The Knowledge Centre
Hellesdon Hospital
Drayton High Road,
Norwich, NR6 5BE
Telephone 01603 421255
E mail: RDofficemailbox@nsft.nhs.uk

Miss Emma Kirkham
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

1st August 2013

Dear Miss Kirkham,

Re: 2013MH19: Views and perceptions of consultants on lithium prescribing

Thank you for submitting the above project for local research governance approval. The Committee reviewed the application on the meeting of the 25th July 2013, and has made the following comments:

- The committee complimented the proposal for being well-written. This was felt to be low-risk to the Trust from a governance perspective.
- The committee queried in the protocol the statement that the data will be checked with another researcher. The committee asked who the other researcher is as this is not stated.
- The committee felt that as the attendance of consultants in the research forums varies across localities, it was suggested the mail shot would be the preferred way of recruiting participants.
- The committee raised concern about the lack of information regarding sampling methods for identifying and recruiting participants. If one intention of the study is to compare consultants in Norfolk and Suffolk, what procedures are in place to ensure that a representative sample from each area, and, potentially different services/condition areas, is consented into the study?
- The Committee wished to see more justification for the sample size of 20 consultants, and how this related to 10-15 interviews. Additionally, it was felt that the transcribing work-load for 15-20 hours of interviews would be extremely time-intensive. The committee asked what support was in place for the researcher to undertake this role.
- Within the scientific justification there is a statement "Is there something within Norfolk that has an impact on the prescribers' decisions to use lithium?" This was felt to be lacking detail and did not give a clear justification for the rationale of the study.
- The committee also asked what procedures were planned if more than 20 consultants wished to take part in the study.
- The committee queried how the researcher would know who has returned the withdrawal postcard as there are no linked participant codes on the consent/acceptance form. The specific need for the postcard was also felt to be unclear.

- The committee suggested that that although patient information should clearly not be discussed, there should be a line in the participant information sheet that if professional misconduct or negligence arises then this will be passed on.

- The committee asked if the participant will have the chance to review transcripts of their interviews as this is not stated in any documentation.

- The committee queried if the participant does need to leave the meeting due to their clinical commitments, will they get the chance to complete the interview at another time? Additionally, it is stated that refreshments were to be provided. If the interviews are within the Consultants offices, how will this be arranged?

- The committee raised the issue of when the participant is able to withdraw consent for use of their data from the study. The committee asked that this is stated in the consent/information sheets that they are able to withdraw up until the point when the interviews are transcribed and analysed.

- The committee asked to see the results of the study before publication.

The Committee are happy to receive a response to these queries by email at the address above, and the final approval decision will be delegated to the Chair of the committee.

If you have any queries regarding this or any other project, please contact, Bonnie Teague, Research Manager, at the above address.

The reference number for this study is: **2013MH19,** and this should be quoted on all correspondence.

Yours sincerely,

Dr Jon Wilson
Deputy Medical Director (Research) and NSFT Research Governance Chair

Appendix Six

Norfolk and Suffolk NHS
NHS Foundation Trust

Research and Development
The Knowledge Centre
Hellesdon Hospital
Drayton High Road
Norwich
NR6 5BE

Telephone 01603 421255
E mail: RDofficemailbox@nsft.nhs.uk

Miss Emma Kirkham
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

6th September 2013

Dear Miss Kirkham,

Re: 2013MH19: Views and perceptions of consultants on lithium prescribing

Thank you for submitting the above project for local research governance approval. I am pleased to inform you that your project has been given full approval and you may begin your research at the following site:

- Norfolk & Suffolk NHS Foundation Trust

I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign both copies returning one copy to the Research and Development office, at the above address, and keeping the other in your study file. Failure to return the standard terms and conditions may affect the conditions of approval. **Under the agreed Standard Terms and Conditions of Approval you must inform the R&D department of any proposed changes to this study and submit annual progress reports to the R&D department.**

Any researcher(s) whose substantive employer is not the Norfolk & Suffolk NHS Foundation Trust must have a Letter of Access or Honorary Research contract and evidence of Good Clinical Practice (GCP) training before coming on site to conduct their research in this project. Please note that you cannot take part in this study until you have this documentation. If a Letter of Access / Honorary Research Contract has not been issued – please contact us immediately.

If you have any queries regarding this or any other project, please contact, Tom Rhodes, Research Governance Administrator, at the above address.

The reference number for this study is: **2013MH19,** and this should be quoted on all correspondence.

Yours sincerely,

Dr Jon Wilson
Deputy Medical Director (Research)

Your research governance approval is valid providing you comply with the conditions set out below:

1. You commence your research within one year of the date of this letter. If you do not begin your work within this time, you will be required to resubmit your application.
2. You notify the Research and Development Office should you deviate or make changes to the approved documents.
3. You alert the Research and Development Office by contacting the address above, if significant developments occur as the study progresses, whether in relations to the safety of individuals or to scientific direction.
4. You complete and return the standard annual self-report study monitoring form when requested to do so at the end of each financial year. Failure to do this will result in the suspension of research governance approval.
5. You comply fully with the Department of Health Research Governance Framework and Trust Research Policies, and in particular that you ensure that you are aware of and fully discharge your responsibilities in respect to Data Protection, Health and Safety, financial probity, ethics and scientific quality. You should refer in particular to Sections 3.5 and 3.6 of the Research Governance Framework.
6. You ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice, Data Protection Act and Human Rights Act. Unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.
7. **UKCRN Portfolio Studies only**: You will make local Trust research team members aware that it is expected that the "first participant, first visit" date should be within 70 days of the full submission for Trust Research Governance Approval, and this date must be reported to the Research and Development office using the email address above. Delay to recruitment due to study-wide developments must be reported to the Trust as soon as possible.
8. **UKCRN Portfolio Studies only**: You will report and upload Trust recruitment to the UKCRN portfolio accurately and in a timely manner, and will provide recruitment figures to the Trust upon request.

List of Approved Documents:

Documents		
Protocol	2	
Acceptance Form	1	June-13
Confirmation Email	1	June-13
Confirmation Letter	1	June-13
Consent Form	1	June-13
First Email	2	Aug-13
First Letter	2	Aug-13
Participant Information Sheet	1	June-13
Regret Letter	1	Aug-13
Regret Email	1	Aug-13
Second Email	2	Aug-13
Second Letter	2	Aug-13
Withdrawal Postcard	1	June-13

Appendix Seven

National Research Ethics Service

NHS Health Research Authority

NOTICE OF SUBSTANTIAL AMENDMENT (non-CTIMP)

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) available in the Integrated Research Application System (IRAS) at http://www.myresearchproject.org.uk or on the EudraCT website at https://eudract.ema.europa.eu/document.html.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.nhs.uk/applications/after-ethical-review/notification-of-amendments/.

Details of Chief Investigator:

Name:	Emma Kirkham
Address:	School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich
Postcode:	NR4 7TJ
Telephone:	01603 591973
Email:	e.kirkham@uea.ac.uk

Full title of study:	Factors affecting lithium prescribing: views and perceptions of consultants on current practice.
Lead sponsor:	University of East Anglia Yvonne Kirkham – Project Officer
Name of REC:	No NHS REC review required
REC reference number:	N/A
Name of lead R&D office:	Norfolk & Suffolk NHS Foundation Trust
Date study commenced:	Not yet commenced – expected start date March 2014

Protocol reference *(if applicable)*, current version and date:	2013MH19 Version 5, February 2014
Amendment number and date:	Amendment 1, 10th February 2014

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC Application Form

Yes ~~*No*~~

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes ~~*No*~~

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

~~*Yes*~~ ***No***

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

~~*Yes*~~ ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study.

If this is a modified amendment, please explain how the modifications address concerns raised previously by the ethics committee.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

Due to delays in the roll-out of the lithium register and database to Suffolk one method of recruitment has now been altered.

Initially consultants were to be contacted as part of the roll out by the SystemTDM® administrator and all relevant documents required by consultants would be sent out through them. However now the work contact details of all consultants working within Suffolk will be obtained by the principal investigator from Research and Development or the Trust e-mail group 'consultants' in order to contact them for this project. The principal investigator will then send out all relevant documentation to the consultants directly.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	*Version*	*Date*
Protocol	5	February 2014
Covering letter	3	November 2013
Participant Information Sheet	3	December 2013
Expression of Interest form	1	November 2013
Decline to Participate postcard	2	November 2013
Consent form	3	November 2013
Confidentiality agreement	1	August 2013
Encryption form	1	November 2013

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator:

Print name: EMMA KIRKHAM

Date of submission: 10/2/14

Declaration by the sponsor's representative

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules about delegated authority should be adhered to.

- I confirm the sponsor's support for this substantial amendment.

Signature of sponsor's representative: .....

Print name: ***Yvonne Kirkham*** .....

Post: ***Project Officer*** .....

Organisation: ***UEA*** .....

Date: 26/02/2014

Appendix Eight

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Emma Kirkham
School of Pharmacy
UEA
NR4 7TJ

Research & Enterprise Services
REN West (SCI)
University of East Anglia
Norwich
NR4 7TJ

Email: fmh.ethics@uea.ac.uk
Direct Dial: +44 (0) 1603 59 1720

Web: http://www.uea.ac.uk

3rd February 2014

Dear Emma,

Project Title: Factors affecting lithium prescribing: views and perceptions of consultants on current practice. Reference: 2013/2014 – 13

The submission of your research proposal was discussed at the Faculty Research Ethics Committee meeting on Thursday 30th January 2014.

The Committee were happy to approve your application in principle but have the following concerns which they would like you to address and amend accordingly:

1. Page 14, second paragraph, please revise the following sentence to include: "However, if **an issue raising a concern of** professional misconduct or negligence..."
2. You need to include a sentence to say that this has been reviewed and approved by the Faculty of Medicine and Health Sciences Research Ethics Committee.
3. Appendix 4, please rename this to "Decline to Participate Postcard".

Please write to me once you have resolved/clarified the above issues. I require documentation confirming that you have complied with the Committee's suggestions. The Committee have requested that you detail the changes below the relevant point on the text in this letter and also include your amendments as a tracked change within your application/proposal. The revisions to your application can be considered by Chair's action rather than go to a committee meeting, which means that the above documentation can be resubmitted at any time. Please could you send your revisions to me as an attachment in an email as this will speed up the decision making process.

As your project does not have ethics approval until the above issues have been resolved, I want to remind you that you should not be undertaking your research project until you have ethical approval by the Faculty Research Ethics Committee. Planning on the project or literature based elements can still take place but not the research involving the above ethical issues. This is to ensure that you and your research are insured by the University and that your research is undertaken within the University's 'Guidelines on Good Practice in Research' approved by Senate in February 2012.

Yours sincerely

Yvonne Kirkham
Project Officer

cc Dr James Desborough by email

Appendix Nine

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Emma Kirkham
School of Pharmacy
UEA
NR4 7TJ

Research & Enterprise Services
West Office (Science Building)
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Telephone: +44 (0) 1603 591720
Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

13th February 2014

Dear Emma,

Project Title: Factors affecting lithium prescribing: views and perceptions of consultants on current practice. Reference: 2013/2014 – 13

The amendments to your above proposal have been considered by the Chair of the Faculty Research Ethics Committee and we can confirm that your proposal has been approved.

Please could you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee. Please could you also arrange to send us a report once your project is completed.

The Committee would like to wish you good luck with your project.

Yours sincerely,

Yvonne Kirkham
Project Officer

cc Dr James Desborough by email

Appendix Ten

Norfolk and Suffolk NHS
NHS Foundation Trust

Research and Development
The Knowledge Centre
Hellesdon Hospital
Drayton High Road,
Norwich, NR65BE
Telephone 01603 421255
E mail: RDofficemailbox@nsft.nhs.uk

Miss Emma Kirkham
School of Pharmacy
University of East Anglia
Norwich
NR4 7TJ

Dear Miss Kirkham,

21st March 2014

Re: 2013MH19: Views and perceptions of consultants on lithium prescribing

Further to the initial study approval letter, dated 6th September 2013, an amendment has been received for research governance review and approval.

I am pleased to inform you that the amendment has been approved, and so may proceed. This approval is valid in the following organisation:

- **Norfolk and Suffolk NHS Foundation Trust**

The final list of amendment documents reviewed and approved are as follows:

Documents	Version	Date
Protocol	5	Feb-14
Covering Letter	3	Nov-13
Participant Information Sheet	3	Dec-13
Expression of Interest form	1	Nov-13
Decline to Participate postcard	2	Nov-13
Consent Form	3	Nov-13
Confidentiality agreement	1	Aug-13
Encryption Form	1	Nov-13

Your research governance approval is valid providing you comply with the conditions set out below:

1. You notify the Research and Development Office should you deviate or make changes to the approved documents.
2. You alert the Research and Development Office by contacting me, if significant developments occur as the study progresses, whether in relations to the safety of individuals or to scientific direction.
3. You complete and return the standard annual self-report study monitoring form when requested to do so at the end of each financial year. Failure to do this will result in the suspension of research governance approval.

4. You comply fully with the Department of Health Research Governance Framework, and in particular that you ensure that you are aware of and fully discharge your responsibilities in respect to Data Protection, Health and Safety, financial probity, ethics and scientific quality. You should refer in particular to Sections 3.5 and 3.6 of the Research Governance Framework.
5. You ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice, Data Protection Act and Human Rights Act. Unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

If you require any further confirmation, please contact me at the above address.

Yours sincerely,

Dr Jon Wilson
Deputy Medical Director (Research)

Appendix Eleven

Interview Topic Guide (summary version)

- **Introduction and background**
    - Aims and objectives of project
    - Area of speciality of participant
    - Provide assurances about confidentiality and timing, and confirm consent

- **What are you views on lithium as a drug?**

- **When and for what type of patients would you consider prescribing lithium for?**
    - Prompts:
        - Process of prescribing
        - Where initiated – outpatient or inpatient

- **What influences your choice to prescribe lithium rather than other drugs?**
    - Prompts:
        - Compliance of patient – **patient information**
        - Medical history
        - Social history
        - Blood results – what happens if patients go toxic/actions taken
        - Monitoring – why important or that looked at
    - …and reasons for not prescribing lithium? – what are the alternatives

- **Do you routinely use any treatment guidelines to influence your choice of drug?**

- **Do you think it matters who prescribes/initiates lithium?**
    - Prompts:
        - What influences this?

- Experience of doctor
- Experience with lithium

- **Conclusion**
  - Is there anything you would like to add?

Appendix Twelve

Participant: 7, Location: N, Age/Gender: 51-65/M, Type of practice: CRHTT

Line numbers	Raw text	Initial code
10	it's a challenging drug	Challenging drug
11	it is both quite effective and quite flawed at the same time	Effective and flawed
12	serious side effects	Serious side effects
12-13	if you use lithium continuously you **will** get renal failure	Inevitable renal failure
22	monitor for routinely	Routine monitoring
23	my understanding of what I have read	Read about S/E
23	that's what happens if you use it long enough	Duration of tx
24-25	severe enough to mean you have to stop taking it	Severity of side effects and stop tx
26	if I needed lithium would I use it myself? Well I'm not sure actually	Not use on self
27-28	if I had an acute condition and use it as a short term medication	Use on self as acute/short term
28	tends to be used longer term	Long-term tx
29	I'd also inject personal experience into this because this is how prescribing works	Personal experience
30	what you learn and get taught	Teaching and learning
30	and what you read in scientific literature	Read in literature
31-32	then you also have stuff that your friends say that you meet somewhere you know, you professional colleagues you know and that influences	Friends/colleagues and prescribing
32-33	if they've had really good results or whatever	Good experiences
33-35	the first patient I ever prescribed lithium for, who I still remember, developed a complete heart block within a couple of days of starting it which is an irreversible side effect of lithium	Bad 1st experience
37-38	So after that I didn't prescribe lithium for another couple of years	Stopped prescribing lithium
38-39	the second patient I prescribed for it then took an overdose of lithium	Bad second experience
41	took quite a large overdose	Overdose

42-43	it took the ---------- 32 hours to measure their lithium level after being admitted for a lithium overdose	Long time to measure level after overdose
44-45	so these things colour one's use so I am not a high prescriber of lithium	Experiences affect Rxing
45-47	I do prescribe it sometimes erm it's most often in the context of continuing someone else's prescription and less often in terms of me initiating it myself	Continues prescriptions not initiate
48	big advantages are its cheap	Cheap = advantage
48-49	because its subject to monitoring process I suspect that erm the reliability of someone taking it as prescribed is probably slightly better	Monitoring process increases reliability of taking
50-51	because at least psychologically if you know you have blood tests and so on it means you're more likely to do the thing you're supposed to be doing	Monitoring process increases reliability of taking
56-57	people with a bipolar disorder and people with severe depression	Use for bipolar and severe depression
61-62	people with existing renal damage or thyroid problems, people with perhaps with cardiac problems	Factors - not prescribe for
62-65	I would want to prescribe it for someone who I thought would be reasonably likely to take it and umm you know do the tests and and stuff and if I thought someone was unreliable and they wouldn't do it then I probably wouldn't prescribe it because that's not going to help anyone	Reliability of patient taking it
66-68	Interviewer: so the monitoring and getting those blood tests done (PARTICIPANT 7: Yeah) is something that quite important PARTICIPANT 7: yeah sure (INTERVIEWER: you) I mean you don't want to waste everyone's time	Monitoring important
69-70	it's more damaging almost as far as I know with almost any psychotropic medication to chop and change from medication to medication than it is to you know stick on one medication	More damaging to chop and change
70-72	so someone who that you know is not going to use it properly because of whatever factors then that would be less likely	Reliability of patient taking it
72	but then I think other factors I don't know err you know polypharmacy or something	Factors - not prescribe for
73	if there was an increased risk of renal damage or drugs that would interact in some way	Factors - not prescribe for
76-79	Do you think the speed at which people respond to maybe a lithium level or getting that test done is something that's important?	Speed of response to levels

	PARTICIPANT 7: umm well in that patients case it is important because the person's taken an potentially lethal overdose of lithium	
79-80	in order to treat it they need to have some idea of what the toxicity level	Toxicity levels and overdose
80-82	so if the level's normal despite them having allegedly taken 35 tablets or something you're going to treat it very differently to if you do the level and its 25 point something you know	Treat overdose on levels
83-84	how closely you support and scrutinise to monitor the patient will be very influenced by what the result is	Treat overdose on levels
88	lithium's got a relatively narrow therapeutic window	Narrow therapeutic range
89-90	I was at a conference recently where people were talking about information on lithium	People talking – conferences
91-92	he was talking about the results from the lithium database	Results from database
93-96	having a level over around point eight was about right and that more than that was more toxic which is interesting because for instance in America its accepted therapeutic level might even be 1 or 1.2	Intercontinental differences in practice
97	it's within the realm of acceptable practice	Acceptable practice
99-102	you want to start the person on it and then because individuals metabolise it differently you want to stabilise them and to do that you need to do a series of tests and then at some point they'll get to kind of equilibrium state and then you'll do tests from time to time just to check that nothing's changed	Stabilise patient, reduce monitoring
107-109	I work in the acute service which is defined as people who would normally be admitted to hospital but they are treated either in hospital or in a home treatment service	Acute service
111-113	technically I'm supposed to see people out of hospital but because I'm part of the acute service in fact I see both because I cover for colleagues who work on the wards	See I/P and O/P
119	in hospital everything that happens is usually more symbolically important	In hospital – more important
120-121	because you're in hospital and its more dramatic and you know psychologically you know it is just more important	In hospital – more important
123-125	INTERVIEWER: so it wouldn't influence your choice to choose to prescribe lithium or another drug if they were an inpatient compared to if they were an outpatients or under the home treatment team PARTICIPANT 7: not hugely, not by itself no	I/P or O/P alone not influence choice
125-127	I mean you can get someone who's an inpatient who's completely unreliable and someone who's at home who is completely reliable	Reliability of patient taking it
128-129	INTERVIEWER: so it's much more based on each patient individually?	Based on individual patients

	PARTICIPANT 7: yeah	
132-135	there's a symbolism you know err, consultants…errr……, consultants are perceived as having a certain status now that might be a rubbish status for some people and a high status for others but erm they're perceived in that way and essentially patients view consultants as the person who will have the answer you know	Symbolism of consultants
135-137	so if a consultant prescribes it I guess its symbolically going to be more important or more powerful than if someone else does	More important if consultant prescribes
139-140	you just have to think of one's own experience or one's families experience if my mother in law's unwell then I'd like her to see the consultant...it's just how people…	Personal experience
145-147	I think patients generally speaking, not always, but generally speaking want to have information about the treatments	Patients want information
147-148	erm I think that's perfectly appropriate a lot of them research it themselves now	Patients self-research
148-149	some will use the doctors or nurses or pharmacists or whatever it is to to get information	Sources of information
149-151	I think you know it's it's it should be a kind of human right in a sense that you should have as much information as you want about it	As much information as want
152-153	how much the information do patients actually understand is a completely different question and people tend to get what they want from the information	Understanding and interpreting information
155-156	you know, people see what they want to see erm and that happens to everybody cause we're all coloured by our life experience	Understanding and interpreting information
158-160	how they've perceived it is that it is a completely hit and miss things you know errrrr what they will take from the information is not necessarily what I would take from it	Understanding and interpreting information
160-161	yes it's a really good thing to give information and at the same time yes the information's frequently misunderstood	Understanding and interpreting information
161-163	it's kind of hard really hard to get that right so you give people all the information they want and in a way that they really do understand it	Understanding and interpreting information
163-164	so I think what happens at the moment is people effectively have the ability to get information overload	Information overload
164-165	they can use the internet and so on even if the doctor doesn't want to talk to them they can just look it up on google	Sources of information
166-167	that they have information overload and they don't necessarily have the skills or the training to interpret all information	Information overload Understanding and

		interpreting information
170-173	medico-legal because if you prescribe something and you fail to inform the patient of risk X,Y,Z and they then develop a complete heart block or whatever in theory then they can sue you because you didn't give them the information	Medico-legal issues – protecting self
173	informed consent	Informed consent
173-174	so it's very hard and it's even more hard when you know that they don't understand the information necessarily	Understanding and interpreting information
177	I think people understand more than they used to	Increased understanding
178	because they can look it up at their leisure on google	Sources of information
179-180	I think it's really positive that people have the information can use it	Provision of information
182-184	I just think we need to acknowledge that having all the information doesn't necessarily mean the patient becomes an expert on it and has a balanced view on it	Understanding and interpreting information
188-189	you can read about lithium from someone else and have a different view and it's all in the scientific literature	Differing views in literature
193-194	do I practice broadly in accordance with treatment guidelines I think yes, erm but do I consciously try and do it as in step one, step two…probably not erm	Broadly follow guidelines
194-196	but that's not because I'm opposed to the guidelines it's because I'm hopefully good at what I do so I do that automatically without having to check it	Experience
196-198	when I'm not following the guideline it would be because there are particular circumstances for that patient that justify a deviation from the guideline cause the guideline is a guideline it's not you know …	Justify deviation
201-208	the guidelines I'd use myself would be NICE guidelines erm …errr in terms of prescribing I would look at ---- ---'s book [PDD], I would look at the Maudsley book erm …every now and then I've actually got err have I got it here yes I have I've got a Martindale[…]other guidelines I'd look at less often so for instance in Scotland they have the SIGN, S.I.G.N a whole variety of international ones erm but I would tend to look at more guidelines if there was a particular problem I wasn't sure about	Guidelines
210-211	there are loads of guidelines so it's not possible to practice in accordance with the guidance because they all say slightly different things so	Difference in guidelines
216	I think it should be according to the competence of the person doing it	Initiation on competence
219-223	so if someone works in primary care but they are competent to do it because they have had the relevant training and	Competence and experience

	experience then that's great and if it's in secondary care and you walk in here as a patient and the first person you see is my junior doctor who started yesterday and has never seen a psychiatric patient then you know so the setting isn't as important as the competence	- initiation
229-230	in the crisis team we often work quite closely with GPs so they might prescribe while we're managing the patient	Primary care prescribe, secondary care manage
230-231	for example sometimes we do the prescribing sometimes they do it just depends	Setting for prescribing varies
232-234	there are other instances that I'm aware of where we might prescribe a certain drug and GPs wont prescribe it erm or even where we're told its double red whatever that means as though its illegal	Conflict over certain drugs
236-237	there are case where GPs will refuse to continue medication because they claim they haven't had the training or something like that	Training issue in primary care
241-243	but I think that if you're a GP you should give yourself the training, get the training, you know if you're your patients need a certain drug you should make yourself aware of what you need to be aware of	Doctors take responsibility for relevant training
248-250	lithium because of the toxicity issue and the narrow therapeutic index and so on that's window it's erm really useful to have a system in place that helps make managing all of that easier	Systems to manage monitoring
251-252	and I'm very keen on, in medicine, using systems to improve safety rather than relying on the individual person being able to remember something	Systems to improve safety
253-256	I so I think the lithium database has been a fantastic thing to have happened and I think its hugely improved the quality of care and I suspect that's measurable and demonstrable possibly even including the number of side effects and so on that we have seen I would expect has probably reduced as a result of the database.	Database improved quality of care
258-259	INTERVIEWER: So systems like that you think help improve quality and... PARTICIPANT 7: Yep sure they make it easier for me to do my job properly	Systems help do job properly
261-262	I think that erm it's an interesting observation about whether medications are promoted or not and how that affects their use and so on	Promotion or lack of meds
265-268	I think that's an interesting question because what should society do about the drugs that are not marketed but that should be used, should the government have a responsibility to promote them you know and if so how?	Responsibility to promote all drugs