QUANTITATIVE ASSESSMENT OF THE PHARMACOTHERAPY OF BIPOLAR DISORDER AND SCHIZOPHRENIA

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The work present in this thesis was aimed at assessing the efficacy of lithium in the acute treatment of mania and for the prophylaxis of bipolar disorder, and investigating the value of plasma haloperidol concentration for predicting response to treatment in schizophrenia. The pharmacogenetics of psychotropic drugs is critically appraised to provide insights into interindividual variability in response to pharmacotherapy.

In clinical trials of acute mania, a number of measures have been used to assess the severity of illness and its response to treatment. Rating instruments need to be validated in order for a clinical study to provide reliable and meaningful estimates of treatment effects. Eight symptom-rating scales were identified and critically assessed. The Mania Rating Scale (MRS) was the most commonly used for assessing treatment response. The advantage of the MRS is that there is a relatively extensive database of studies based on it and this will no doubt ensure that it remains a gold standard for the foreseeable future. Other useful rating scales are available for measuring mania but further cross-validation and validation against clinically meaningful global changes are required.

A total of 658 patients from 12 trials were included in an evaluation of the efficacy of lithium in the treatment of acute mania. Treatment periods ranged from 3 to 4 weeks. Efficacy was estimated using (i) the differences in the reduction in mania severity scores, and (ii) the ratio and difference in improvement response rates. The response rate ratio for lithium against placebo was 1.95 (95% CI 1.17 to 3.23). The mean number needed to treat was 5 (95% CI 3 to 20). Patients were twice as likely to obtain remission with lithium than with chlorpromazine (rate ratio = 1.96, 95% CI 1.02 to 3.77). The mean number needed to treat (NNT) was 4 (95% CI 3 to 9). Neither carbamazepine nor valproate was more effective than lithium. The response rate ratios were 1.01 (95% CI 0.54 to 1.88) for lithium compared to carbamazepine and 1.22 (95% CI 0.91 to 1.64) for lithium against valproate. Haloperidol was no better than lithium on the basis of improvement based on assessment of global severity. The differences in effects between lithium and risperidone were -2.79 (95% CI -4.22 to -1.36) in favour of risperidone with respect to symptom severity improvement and -0.76 (95% CI -1.11 to -0.41) on the basis of reduction in global severity of disease. Symptom and global severity was at least as well controlled with lithium as with verapamil. Lithium caused more side-effects than placebo and verapamil, but no more than carbamazepine or valproate.

A total of 554 patients from 13 trials were included in the statistical analysis of lithium's efficacy in the prophylaxis of bipolar disorder. The mean follow-up period was 5-34 months. The relapse risk ratio for lithium versus placebo was 0.47 (95% CI 0.26 to 0.86) and the NNT was 3 (95% CI 2 to 7). The relapse risk ratio for lithium versus imipramine was 0.62 (95% CI 0.46 to 0.84) and the NNT was 4 (95% CI 3 to 7). The combination of lithium and imipramine was no more effective than lithium

alone. The risk of relapse was greater with lithium alone than with the lithium-divalproate combination. A risk difference of 0.60 (95% CI 0.21 to 0.99) and an NNT of 2 (95% CI 1 to 5) were obtained. Lithium was as effective as carbamazepine.

Based on individual data concerning plasma haloperidol concentration and percent improvement in psychotic symptoms, our results suggest an acceptable concentration range of 11.20-30.30 ng/ml. A minimum of 2 weeks should be allowed before evaluating therapeutic response. Monitoring of drug plasma levels seems not to be necessary unless behavioural toxicity or noncompliance is suspected.

Pharmacokinetics and pharmacodynamics, which are mainly determined by genetic factors, contribute to interindividual and interethnic variations in clinical response to drugs. These variations are primarily due to differences in drug metabolism. Variability in pharmacokinetics of a number of drugs is associated with oxidation polymorphism. Debrisoquine/sparteine hydroxylase (CYP2D6) and the S-mephenytoin hydroxylase (CYP2C19) are polymorphic P450 enzymes with particular importance in psychopharmacotherapy. The enzymes are responsible for the metabolism of many commonly used antipsychotic and antidepressant drugs. The incidence of poor metabolisers of debrisoquine and S-mephenytoin varies widely among populations. Ethnic variations in polymorphic isoenzymes may, at least in part, explain ethnic differences in response to pharmacotherapy of antipsychotics and antidepressant drugs.

Key words: lithium, haloperidol, rating scales, evidence-based pharmacotherapy, pharmacogenetics

To my parents, brother and sister

for their love, support and encouragement

In memory of my grandmother

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Abbreviations

AUC	Area under the plasma concentration-time curve
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
CV	Coefficient of variation
DB-CO	Double-blind, crossover
DB-P	Double-blind, parallel
DSM	Diagnostic and Statistical Manual
EM	Extensive metaboliser
ICC	Intraclass correlation
ICD	International Classification of Diseases
NNT	Number needed to treat
PM	Poor metaboliser
RCT	Randomised controlled trial
RD	Rate (risk) difference
RDC	Research Diagnostic Criteria
ROC	Receiver Operating Characteristic
RR	Rate (risk) ratio
SB-CO	Single-blind, crossover
SB-P	Single-blind, parallel
SD	Standard deviation

SE	Standard error
$T_{1/2}$	Half-life
T_{max}	Time to reach maximum concentration
V_d	Volume of distribution

Chapter 1

Introduction

1.1 Psychiatric disorders

A psychiatric disorder or mental illness can be regarded as an organic disease of the brain, either structural or chemical (Sims & Owens 1993). Mental disorder is conceptualised as a clinically significant behavioural or psychological syndrome or pattern that occurs in an individual, and that is associated with present distress, disability, or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom (American Psychiatric Association 1995). Specifically, it refers to a manifestation of a behavioural, psychological, or biological dysfunction in the individuals. The term includes a wide range of conditions ranging from those characterised by multiple cognitive deficits such as dementia to the minor emotional disorders. Psychiatric disorders are multifactorial in nature and are normally associated with biological, psychological, and social components.

Clinical presentations of mental disorders are heterogeneous. The symptoms and degree of severity, even within the same diagnostic category, can vary enormously and individual patients may present with different symptoms at different times. This causes problems for practitioners in recognising and diagnosing the different illnesses. Traditionally, psychiatric disorders can be differentiated in two ways (Goldberg *et al.* 1994). The first divides them into three groups according to clinical presentations, i.e. psychoses, neuroses, and personality disorders. Psychotic patients

seem to be less in touch with reality, to have less insight into their illness, and display psychotic symptoms such as delusions and hallucinations. In the absence of delusions or hallucinations, it is a neurosis. The differentiation between the two, however, is arbitrary and is based mainly on experience. The second method divides the various diseases according to aetiology. Organic disorders are secondary to brain disease, and functional disorders are those whose physical basis is unknown.

More restrictive and specific criteria for the diagnosis and classification for mental disease have been successfully developed and the two most widely used internationally are the Diagnostic and Statistical Manual of Mental Disorder and the International Classification of Diseases. Each diagnostic category, however, is not completely discrete nor immutable. More than one condition may coexist or follow each other in the same patient. The DSM-IV (American Psychiatric Association 1995) classifies mental disorders into a number of categories based on criteria sets with defining features. Some major groups include schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, mental disorders due to a general medical condition, personality disorders, and substance-related disorders.

1.2 Epidemiology

In a recent survey, nearly half of Americans were reported to have a psychiatric disorder at least once in their lifetime and almost 30% suffered a psychiatric disorder during the previous 12 months. The most common illnesses are major depression, alcohol dependence, social phobia, and simple phobia (Kessler *et al.* 1994). In contrast, approximately 6% of men and 12% of women living in London areas were

reported to have received a psychiatric diagnosis at some time during their lives. The 12-month prevalence of such illnesses, mainly anxiety and depression, is approximately 14% with just over 5% being new illnesses. (Goldberg *et al.*1994).

Up to 15-25% of adults are known to suffer from depressive symptoms, one third of whom have a diagnosis of depressive disorders. Females are found to have higher rates than males (Sims & Owens 1993). The impact of depression on patients and families is profound, with suicide probably being the most severe sequel. The direct and indirect costs of depression in the United States were estimated at $43 billion per year. Approximately 50% of which is due to absenteeism and lost productivity in the workplace (Hirschfeld *et al.* 1997). Bipolar disorders, characterised by mania or hypomania alternating irregularly or combining with depression, are reported with the lifetime prevalence of about 1% and is not significantly different among racial groups. Men and women are equally likely to develop the disease (Weissman *et al.* 1988, American Psychiatric Association 1994). The disorders, particularly mania, is also more likely to be associated with alcohol and/or substance abuse (Bucholz 1999). It has been estimated that one of every four to five untreated or inadequately treated patients commit suicide during the course of illness, particularly during depressive or mixed episodes (Janicak *et al.* 1997).

Anxiety is commonly seen in almost every psychiatric disorders and is more prevalent among women than men. The occurrence varies among several categories of anxiety disorders, with generalised anxiety disorder being the most frequently diagnosed (Janicak *et al.* 1997). The lifetime prevalence in the adult population is 5%

(American Psychiatric Association 1995). The impact of anxiety disorder is largely associated with impairment in the workplace (Greenberg *et al.* 1999).

An estimate suggests that about 1% of the world population is diagnosed as schizophrenic. The prevalence seems equal among men and women (Carpenter & Buchanan 1994). The annual incidence ranges from 0.11 to 0.70 per 1000 and is comparable in different populations (Ryan 1991). The illness is appreciably devastating to both patients and their families and imposes an enormous economic burden due to expenditure for hospitalisation, treatment and rehabilitation, and lost of productivity. For example, the annual direct and indirect costs of schizophrenia in the United States was estimated at $33 billion, and treatment costs accounted for 2.5% of total health care expenditure (Rupp & Keith 1993).

The prevalence of mental illness may differ substantially among different racial/ethnic groups. Substance abuse and affective disorders are more prevalent in white-Americans compared to African-Americans (Kessler *et al.* 1994). The prevalence of psychiatric disorders is lower in Asians than in British people (Lloyd 1998). Compared with the white population, Caribbeans were found to have higher rates of schizophrenia, and depression (Lloyd & Moodley 1990, Lloyd 1998). Admission rates for schizophrenia in immigrants from West Africa was almost 30 times as high as those of the native British population (Dein 1997). The personal and social pressures of belonging to any ethnic minority group may, in part, contribute to the higher incidence of psychotic disorders (King *et al.* 1994).

Socioeconomic factor plays an important part in epidemiology of mental disorders. Higher rates are reported in people in lower social classes, with low income and education. For example, schizophrenia and suicide are more frequently found among those in lower socioeconomic groups (Sims & Owens 1993). Poor standards of living may partly contribute to higher rates of depression and psychosis. Single mothers are found to have higher rates of mental illness, particularly depression, than those who are married or cohabiting (Lloyd 1998). Alcohol and drug abuse are generally high in those with lower income and lower education and those who have not been stably married (Bucholz 1999). Socioeconomic status appears to be more strongly related to anxiety disorders than to affective disorders or substance abuse (Kessler *et al.* 1994).

Apart from an epidemiologic effect, socioeconomic variables may influence the presentation of psychotic mental disorders. Delusions and hallucinations in Western schizophrenic patients are often related to technology, while those in African and Indian are mainly based on religious beliefs. Depressive illness among people from the Far East and from lower socioeconomic groups in the West may express primarily as somatic symptoms such as lethargy, weakness, and aching joints, rather than low mood, and poor appetite (Dein 1997).

1.3 Psychopharmacotherapy

Treatment in psychiatry is focused on the amelioration of symptoms, the prevention of relapse, and the social rehabilitation of the patient. Three treatment options can be considered; physical including psychopharmacotherapy and electroconvulsive

treatment, psychological, and social treatments (Goldberg *et al.* 1994). While pharmacotherapy may be considered as a first-line treatment, it is generally insufficient for a successful outcome. Education and psychological interventions such as cognitive–behavioural therapy and counselling may also be indicated. Drug treatments commonly used in psychiatry include antipsychotics, antidepressants, anxiolytics, hypnotics, stimulants, and mood stabilising drugs.

1.3.1 Antipsychotic drugs

The antipsychotic drugs were first used in the 1950s with the introduction of chlorpromazine which was developed as a pre-anaesthetic sedative and found to be useful in the treatment of psychosis (Jacobsen 1986). These drugs, also known as major tranquillizers or neuroleptics, are used in the treatment of psychotic symptoms such as delusions, hallucinations, thought disorders, and some nonpsychotic conditions such as emesis and movement disorders. They may also be effective in maintenance treatment to control symptoms and prevent the recurrence of acute psychotic episodes. For example, phenothiazines and butyrophenones have remained the mainstay for patients with schizophrenia (Kane 1996).

The antipsychotic effects are presumed to be associated with their action as dopamine receptor blockers in the mesolimbic and mesocortical pathways. The clinical efficacy is generally correlated with their ability to block dopamine D_2 receptors. All typical antipsychotics are thought to have comparable efficacy, but differ from one another in the risk of producing side-effects which seems to be based on the drugs'potency (Schwarts & Brotman 1992).

Despite their efficacy in a broad range of symptoms, antipsychotic drugs are less effective against negative schizophrenic symptoms. Further, up to 20% of patients are reported to respond poorly to traditional antipsychotics due to inadequate therapeutic effects or adverse effects (Carpenter & Buchanan 1994). Apart from limitations in efficacy, treatment with these agents is associated with a wide range of side-effects in the cardiovascular, gastrointestinal, and central nervous systems. These include sedation, weight gain, and extrapyramidal symptoms such as dystonia and akathesia. Side-effects are reported to be related to plasma levels of fluphenazine, perphenazine, and haloperidol (Van Putten & Marder 1995). High plasma levels of antipsychotics are also associated with behavioural toxicity which is often difficult to differentiate from schizophrenic symptoms. Tardive dyskinesia, a late-developing extrapyramidal symptoms, is a particularly serious complication commonly occur after long term treatment with an annual incidence rate of 5% (Fleischhacker & Hummer 1997). Therapeutic drug monitoring may be useful in optimising treatment, especially in those with poor response.

The limitations of typical antipsychotics have driven the development of newer agents. Clozapine is among the novel drugs which has lower affinity for D_2 dopamine receptors and higher affinity for D_1 and D_4 dopamine receptors. It is also a potent antagonist at serotoninergic, muscarinic, and alpha-adrenergic receptors (Kane 1996). Its weak affinity for D_2 receptors and its low activity in nigrostriatal tract probably account for the low incidence of extrapyramidal side-effects. Further, the drug may not be associated with tardive dyskinesia (Carpenter & Buchanan 1994). Its use, however, is limited by the association with agranulocytosis which occurs in 1-2% of patients (Baldessarini & Frankenburg 1991). The drug is specifically

indicated in patients with refractory psychosis who have inadequate response to traditional antipsychotic therapy either because they do not improve or because they cannot tolerate adverse effects of standard antipsychotics. Clozapine causes less motor side-effects, but more hypersalivation and drowsiness than conventional antipsychotics (Wahlbeck *et al.* 1999).

Risperidone has high affinity to serotonin, dopamine, and adrenergic receptors. It is a potent serotonin 5-HT_{2A}–receptor and dopamine D_2-receptor antagonist. The risk of extrapyramidal side-effects with risperidone is dose-dependent (Brown *et al.* 1999). It was claimed to have advantages over conventional antipsychotic agents in controlling negative symptoms of schizophrenia (Carman *et al.* 1995). However, a recent systematic review showed that risperidone appears to have little or no additional effect on the positive and negative symptoms of schizophrenia compared to typical neuroleptics, largely haloperidol. It is less likely to cause movement disorders, but has more tendency to cause weight gain (Kennedy *et al.* 1999).

Several atypical antipsychotic drugs including olanzapine, quetiapine, and sertindole have been developed based on pharmacological profile of clozapine but without the risk of agranulocytosis. The agents are at least as effective as haloperidol in the treatment of schizophrenia, with olanzapine being slightly superior to haloperidol against negative symptoms. Use of these drugs is associated with lower risk for extrapyramidal side-effects, but olanzapine produces significant weight gain when compared to other antipsychotics (Duggan *et al.* 1999, Leucht *et al.* 1999). Evidence suggests that the novel antipsychotics may produce antidepressant effect in schizophrenia and may be used as either adjunctive medications or alternatives to

mood stabilisers in patients with affective disorders (Collaborative Working group on Clinical Trial Evaluations 1998).

1.3.2 Antidepressant drugs

Antidepressants are effective in the treatment of depressive illness. They may be useful as monotherapy or adjunctive treatment in patients with schizophrenia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder, and those with panic attacks (Lydiard *et al* 1996). The major groups of antidepressants include tricyclic antidepressants (TCAs) and related drugs, selective serotonin reuptake inhibitors (SSRIs), and nonselective monoamine oxidase (MAO) inhibitors and monoamine oxidase-A (MAO-A) inhibitors. All classes seem to have similar efficacy in acute treatment of depression, but differ in their side effect profiles (Ballenger *et al*. 1999).

TCAs have been commonly used and have demonstrated efficacy in the treatment of depression. However, their action does not become apparent until 2-3 weeks after initiating treatment. Tricyclic drugs also have anticholinergic, antihistaminergic, and cardiotoxic effects and are associated with a wide range of adverse effects such as drowsiness, dry mouth, constipation, orthostatic hypotension, and cardiac arrhythmia. (Westenberg 1999). Additionally, the TCAs are generally toxic in overdose (Power 1995).

Several disadvantages of TCAs have led to the development of a number of second generation drugs. These include newer TCAs such as maprotiline and lofepramine

which cause fewer side-effects especially cardiotoxic and anticholinergic effects and are less toxic than more classical drugs. Nonselective monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine inhibit irreversibly the enzyme monoamine oxidase resulting in an increased concentration of cerebral serotonin, noradrenaline, and dopamine. They have been used as a second line treatment in patients with depression who are unresponsive to TCAs (Goldberg *et al.* 1994). Antidepressant effect is more rapid than TCAs. But their use is limited by side-effects which include agitation, hypomania and orthostatic hypotension, and by drug interactions with dietary agents and sympathomimetic amines which can lead to hypertensive crises (Balon *et al.* 1999). MAOIs are also associated with lethal toxicity in overdose (Power 1995).

Moclobemide is the first reversible inhibitor of monoamine oxidase A (RIMA). Others include brofaromine and toloxatone. Due to the reversibility and selectivity to monoamine oxidase A, dietary restrictions are not required during therapy and hypertensive crises are quite rare. Both brofaromine and moclobemide are as effective as the TCAs, but are better tolerated (Lotufo-Neto *et al.* 1999). Moclobemide has minimal sedative and anticholinergic side-effects, and its toxicity appears to be very low. The drug has been shown to be effective in psychotic and non-psychotic depression, endogenous depression (both unipolar and bipolar), and depression with and without melancholia (Priest *et al.* 1995). In agitated depression, the efficacy is comparable to imipramine, or sedative antidepressants (Delini-Stula *et al.* 1995).

The next generation of antidepressants includes the selective serotonin reuptake inhibitors (SSRIs), for example, citalopram, fluoxetine, fluvoxamine, and sertraline. These agents provide advantages over the older drugs in terms of lack of weight gain, anticholinergic effects and cardiovascular effects and safety in overdose. Major side-effects involve gastrointestinal problems particularly nausea and sexual dysfunction (Trindale *et al.* 1998). In depressed patients, the response rate to the SSRIs was reported to be no different to that of the TCAs, but more TCA-treated than SSRI-treated patients dropped out due to either lack of efficacy or adverse effects (Steffens *et al.* 1997). The SSRIs have become first-line treatment for depression primarily due to their improved side-effects profile (Ballenger *et al.* 1999). Inspite of their higher acquisition costs, the total cost of treating depression appears to be no higher with the SSRIs than with the TCAs (Conner *et al.*1999). The SSRIs have also been shown to be effective in panic disorder, anxiety disorder, obsessive-compulsive disorder, and alcoholism (Ballenger *et al.* 1999).

Recently the dual-acting drug mirtazapine has been introduced (Westenberg 1999). Its antidepressant effect appears to be related to dual enhancement of central noradrenergic and serotonergic neurotransmission by blockade of alpha2-autoreceptors. Mirtazapine also directly blocks 5-HT_2 and 5-HT_3 receptors which may account for its anxiolytic and sleep-improving properties as well as its lack of adverse events typical of SSRIs. It has been claimed to be effective at all levels of severity of depressive illness and in a broad range of symptoms associated with depression (Gorman 1999).

1.3.3 Anxiolytic and hypnotic drugs

Benzodiazepines are the most commonly used anxiolytics and hypnotics. These drugs have the advantages of lower toxicity and generally better tolerability than barbiturates previously used. Benzodiazepines possess, to greater or lesser extent, the pharmacological effects of anxiolytic, hypnotic, muscle relaxant, and anticonvulsant. They are effective in reducing anxiety, tension, and agitation and may be useful as an adjunct to antipsychotic drugs in schizophrenic patients. Their action is related to GABA-mediated inhibition of noradrenaline and 5-hydroxytriptamine system in the CNS (Sims & Owens 1993). Despite its efficacy and safety, the use of benzodiazepines as hypnotic agents is limited by the development of tolerance to hypnotic effect and rebound insomnia. Tolerance to anxiolytic effects may develop, but more slowly than does tolerance to hypnotic effects (Fraser 1998).

There seems to be little qualitative differences between the benzodiazepine derivatives. Their use is determined by pharmacokinetic characteristics, such as time of onset of action and peak action, and duration of action (Spiegel 1996). For example, long-acting drug such as diazepam, alprazolam, and bromazepam, may be used mainly in persistent severe anxiety, whereas short-acting drugs such as temazepam, lorazepam, and nitrazepam may be preferred in episodic or situational anxiety and insomnia.

Drowsiness, ataxia, confusion, and impaired cognitive and psychomotor functions normally occur during anti-anxiety treatment with benzodiazepines. A paradoxical

increase in hostility and aggression can be seen in some patients. One of the main concerns about use of benzodiazepines is the potential for dependence both physical and psychological. The short-acting drugs are more likely to cause dependence than the long-acting agents. Doses and duration of drug use, drug half-life, individual personality and diagnosis contribute to prevalence, severity and duration of the withdrawal syndrome (Norman *et al.* 1997). Although the risk is greater with high doses, benzodiazepine withdrawal syndrome can occur at low drug doses, even within the therapeutic range, with an incidence of 40% to 80% (Gudex 1990). Symptoms are often pronounced within a few days of stopping use and may last for up to 2 to 4 weeks. A wide range of symptoms include rebound insomnia, increased anxiety, anorexia, muscle twitching, tremor, palpitations and perceptual disturbance. Some of these symptoms may be similar to the original complaints which may encourage further prescribing and increase difficulty in withdrawal.

Buspirone, an azapirone anxiolytic, is an alternative to benzodiazepines in the treatment of anxiety. Unlike benzodiazepines, buspirone exerts anxiolytic effects through a partial agonist effect at 5-HT_{1A} receptors (Norman *et al.* 1997). It seems as effective as benzodiazepines in the treatment of generalised anxiety disorder (Enkelmann 1991, Strand *et al.* 1990). The major advantage is its lack of dependence and sedative effect. However, it has a slower onset of action with a one to two-week delay. Additionally, it may not be as effective in patients who have previously used benzodiazepines (Janicak *et al.* 1997). Buspirone appears not to have beneficial effects in patients with panic attacks (Norman *et al.* 1997).

1.3.4 Mood stabilising drugs

The antimanic effect of lithium was first discovered in 1949 (Cade 1949). For more than 40 years, it has been a mainstay in the treatment of mood disorders and has been universally considered as the treatment of choice in the prophylaxis of bipolar disorder (Schou 1997). The mechanism by which it exerts its clinical effect is still unclear (Price & Heninger 1994). It has also remained a standard against which new mood-stabilising drugs are measured (Price & Heninger 1994). Refractory depressed patients can potentially be treated by lithium augmentation (Rouillon & Gorwood 1998). Lithium can be useful in the treatment of alcoholism, schizoaffective disorder and as adjunctive treatment in treatment-resistant schizophrenia (Murray 1990, Pantelis & Barnes 1996).

Despite lithium's effectiveness in the mood disorders, some 10% to 20% of patients do not respond and a few cannot tolerate it (Schou 1988). In addition, its use is limited by potentially lethal toxicity and a narrow therapeutic index (Emilien *et al.* 1995). Some patients develop intoxication at conventional therapeutic concentrations. Thus therapeutic monitoring of plasma levels is crucial. One major side-effects with lithium is weight gain which occurs in up to 70% of patients (Janicak *et al.* 1997). Other common side-effects such as nausea, tiredness, fine tremor, thirst, polyuria, polydipsia, occur even at low plasma lithium levels. These side-effects are among the most common causes of lithium noncompliance, particularly in maintenance therapy (Gitlin & Altshuler 1997). More severe complications include neurotoxicity, metabolic disturbance, hypothyroidism, nontoxic goitre, impaired renal function, and dermatological eruptions.

There has been increasing recognition that lithium's efficacy in the acute treatment and the prophylaxis of bipolar disorder may not to be as high as previously reported. A recent controlled trial in acute mania showed that only half of the patients had 50% improvement after 3-week treatment (Bowden *et al.* 1994). Similar results were reported in the naturalistic studies of lithium prophylaxis in which poor outcome was observed in almost half of the patients taking lithium (Peselow *et al.* 1994, Goldberg *et al.* 1996). Furthermore, some subtypes of patients, for example those with rapid cycling and dysphoric mania, were reported to show poor response to lithium (Goodwin & Jamison 1990).

For these reasons there has been an ongoing attempt to develop alternative strategies and a number of drugs, often initially used for other conditions, have been evaluated for their efficacy in mania. Most of the clinical research has focused on carbamazepine and valproate. These drugs are reported to be effective alone or in combination with lithium in patients less responsive to lithium monotherapy including those with greater number of prior episodes, dysphoric mania, rapid cycling, co-morbid substance abuse or other associated medical problems. Both drugs are now widely used and are considered as therapeutic options for lithium-nonresponders (Post *et al.* 1996). Thus far divalproex sodium is the only drug other than lithium currently approved by the U.S. FDA for the treatment of acute mania (Janicak *et al.* 1997). Anticonvulsants may also be beneficial as alternatives or adjuncts to antipsychotic drugs in the treatment of schizophrenia and schizoaffective disorder (Pantelis & Barnes 1996).

Both carbamazepine and valproate are generally well tolerated. Major side-effects include drowsiness, dizziness, headache, gastrointestinal disturbance and ataxia. Leukopenia can be seen in 2% of patients on carbamazepine. The risk of blood dyscracia is lesser with valproate (Tohen *et al.* 1995). Regular haematological monitoring is necessary. Another disadvantage of carbamazepine is its enzyme-inducing property which would increase the elimination and reduce plasma levels of not only itself, but of other drugs which are the substrates of those enzymes.

Several controlled trials suggested the usefulness of clonazepam and lorazepam in the treatment of acute mania (Chouinard *et al.* 1983, Bradwejn *et al.* 1990). This is probably attributed to a non-specific sedating effect. Both drugs are commonly used adjunctively with lithium or anticonvulsant mood stabilisers as substitutes for antipsychotics in the treatment of manic breakthrough (Post *et al.* 1996). The evidence for their efficacy as the sole treatment is limited and further investigation is needed. Other anticonvulsant benzodiazepines such as intravenous diazepam are used clinically to control agitation in mania and other psychotic states (Small 1990).

1.3.5 Stimulants

Stimulants are usually sympathomimetic drugs structurally similar to endogenous catecholamine. Compounds in current use are thought to prevent the reuptake of catecholamines at synaptic sites and prevent the degradation of the amines at the nerve ending by monoamine oxidase (Biederman & Steingard 1991). Psychostimulant drugs have been used commonly in childhood psychiatric disorders mainly in attention deficit hyperactive disorder and have remained as the drugs of

first choice for this condition (Pliszka 1998). Dextroamphetamine, methylphenidate and pemoline are those normally prescribed. The compounds deminish motor hyperactivity and impulsive behaviours and improve attention and overall cognitive functioning. They can be helpful as adjunctive treatment in patients with depressive disorders (Janicak *et al.* 1997).

Insomnia and anorexia are reported as frequent side-effects. Of major concern are the risk of hepatic failure with pemoline and the effect of long-term use of stimulants on growth rate. Pimoline should generally be used only as a second-line agent and monitoring of hepatic enzymes is required (Pliszka 1998). Whether long-term therapy with psychostimulants reduces growth rate remains controversial (Gittelman-Klein *et al.* 1988, Spencer *et al.* 1996). Abrupt discontinuation can cause behavioural deterioration and tapering off is advisable (Biederman & Steingard 1991).

1.4 Need for evidence-based practice

Research and practice in psychiatry and mental health have attracted considerable attentions during the past years. Mental illness has been common and has accounted for a great amount of residual disability. In addition, the public have become more aware of and have expected more for their health and quality of life. For example, mental disorder accounts for over 15% of disease burden in established market economies worldwide (NIH publication No. 99-4586). Major depression, schizophrenia, bipolar disorder, and obsessive-compulsive disorder contribute significantly to the total disease burden. Advances in pharmaceutical research have

resulted in newer medications being more available with generally considerably higher costs. Many new agents have advantages over the older generations in terms of favourable side-effect profiles and lower toxicity, but may have the potential for more serious adverse effects, for instance, the risk of agranulocytosis with clozapine. With more treatment options but restricted budgets, clinicians need to take into consideration any benefit, risk and cost of treatment in order to achieve an optimal choice of treatment.

Rational decision-making requires the use of currently available resources in an optimal way to improve clinical practice and patient outcomes. Psychiatrists, like other specialists, have encountered difficulties in making decisions about diagnosis, therapy and prognosis. To inform their decision-making and to keep abreast of developments, psychiatrists traditionally turn to several sources of information including individual clinical skills, textbooks, reviews, and research reports. These sources, however, have a number of limitations and biases. For example, traditional reviews may be authoritative, but subjective and lack of rigorous scientific standards (Slavin 1995). On the other hand, the explosion of papers published in biomedical journals each year results in psychiatrists being inundated with information making it impractical to locate or identify those which are clinically important and scientifically sound. Moreover, clinical usefulness of many research findings in treatment studies are usually limited by their external validity and the applicability of outcome measures used in such studies to real-life clinical practice (Geddes 1996).

Clinical practices in psychiatry and mental health are generally influenced by many factors to include government policy, public demand, financial pressures, and

behaviour of psychiatrists (Geddes *et al.* 1997). These professionals often have widely disparate views about the nature of mental illness and the appropriate treatments. Given the knowledge gap, the limitations of traditional ways of keeping up to date, the disparity within the discipline and the pressures from purchasers and public demands, psychiatrists need a new strategy, evidence-based practice, to ensure that their decision-making is based on the best available evidence (Geddes & Harrison 1997).

Although some psychiatric interventions are evidence-based, a huge gap between research and clinical practice continues to exist (Geddes *et al.* 1996, Geddes & Harrison 1997). For example, the current use of high dose neuroleptics (Hirsch & Barnes 1994) and the variation in the treatment of depression (Hirschfeld *et al.* 1997). High quality evidence seems to be lacking regarding comparative efficacy or cost-effectiveness of treatment. This has led to several different drugs being used in specific disorders such as schizophrenia and affective disorders. In addition, many randomised controlled trials of psychotropic drugs are aimed at showing that new drugs are as effective as older drugs, but with less side-effects (Geddes *et al.* 1996). Also, applying research findings to clinical practice is apparently more problematic in psychiatry. Few clear-cut dichotomous outcomes exist and the cut-off points seem to be arbitrary. Continuous measures are normally reported making it difficult to interpret the results (Geddes 1996). Research in psychiatry and the systematic review of published randomised controlled trials remain to be expanded further. The presence of more clinically meaningful categorical outcomes and high quality evidence will help promote the practice of evidence-based psychiatry. This would

lead to greater uniformity, improve healthcare delivery and raise the standard of psychiatric care.

1.5 Focus of the thesis

This thesis focuses on evidence-based psychopharmacotherapy using affective disorder and schizophrenia as exemplars. Systematic reviews and meta-analyses of randomised controlled trials are performed to estimate therapeutic efficacy and safety of lithium compared to other pharmacotherapies, such as antipsychotics, antidepressants, and anticonvulsants, in the acute treatment of mania and for the prophylaxis of bipolar disorder. Difficulty in optimum dosing is a common problem in clinical practice. An evidence-based approach is adopted to investigate whether the plasma concentration of haloperidol is predictive of treatment response. Finally since response to pharmacotherapy often shows wide inter-individual variability, the literature on the pharmacogenetics of psychotropic drugs is critically appraised.

Chapter 2

Evidence-based pharmacotherapy and systematic reviews

2.1 Evidence-based pharmacotherapy

Evidence-based pharmacotherapy has been described as the systematic, explicit and judicious use of best available evidence in making decision about drug treatment for patients to ensure the most cost effective pharmacotherapy (Li Wan Po 1996). The area is part of evidence-based medicine and one in which pharmacists have a major role to play. The importance of this area has been increasingly recognised as greater demands are placed on health-care resources. Further, health-care providers have been inundated with vast amount of information which need to be critically appraised, synthesised, and the results integrated in order to be of maximal benefit to practitioners and patients.

Traditional reviews of research or "narrative reviews" summarise qualitatively the available studies and often deal with a broad range of issues related to a given topic rather than focusing on any particular question. This approach is subjective and lacks rigorous scientific standards (Slavin 1995). As a result, the systematic review/overview was introduced (Peto 1987). The term has been defined as "the application of scientific strategies that limit bias and random error in the systematic assembly, critical appraisal, and synthesis of primary studies on a specific problem" (Cook *et al.* 1995). When a systematic review employs statistical methods to

combine and summarise the results of several studies, it can be called a quantitative systematic review, or meta-analysis (Cook *et al.* 1995). Meta-analysis can increase power and precision of estimates of treatment effects or exposure risks (Mulrow 1994). The practices of evidence-based medicine and pharmacotherapy require the results of systematic reviews to guide practitioners towards rational decision-making.

2.2 Systematic review of randomised controlled trials

Systematic reviews are retrospective research and primarily address a specific, narrow clinical question which can be formulated explicitly regarding a specific population and setting, the condition of interest, an exposure to a test or treatment, and specific outcomes (Cook *et al.* 1997). The question will determine which evidence would be included and how it should be synthesised. The best available evidence may be obtained from non-randomised trials, case-control, and cohort studies, although the highest level of evidence, namely randomised controlled trial, is commonly regarded as gold standard for treatment efficacy (Li Wan Po 1996).

The systematic review process can be divided into six general steps: define study objectives, define relevant outcome measures, systematic retrieval of relevant studies, data collection, summarise the evidence using statistic method, if possible, and interpret the results (Li Wan Po 1997).

Principally, primary and sub-objectives of the study need to be clearly defined. More specifically, the questions posed should be answerable. Prior to defining outcome measures, the results of a clinical trial have to be evaluated as to whether the

outcome used in assessing efficacy is appropriate and valid. The choice of outcome measures can be obtained from published clinical trials. The appropriateness of the outcome measure needs to be confirmed with clinicians and with patients with the disease concerned. Instruments used for measuring clinical outcomes need to be validated in order for the results to be meaningful. The relevant studies can then be systematically retrieved after computerised searches and manual searches. Computerised searches may allow access to a number of references, but not all studies are included in electronic databases. In addition, many of relevant studies may be missed because of inadequate indexing (Sutton *et al.* 1998). The electronic database searching should be complemented by hand searching, follow-up of reference lists of articles retrieved and writing to appropriate manufacturers and investigators known to have an interest in the drug involved (Li Wan Po 1996).

A set of inclusion and exclusion criteria must be established for the studies to be included in a meta-analysis. This is based on the specific hypotheses being tested in the analysis and may include study design, specification of study sample, intervention, and outcomes (Cook *et al.*1995). Search methods and subsequent inclusion criteria may affect the results of a meta-analysis (Cook *et al.* 1995). In addition, study quality is also a major concern when conducting a meta-analysis. Poor quality studies may be excluded or their quality downweighted in the analysis. Thus far there has been no consensus regarding the most appropriate strategy (Sutton *et al.* 1999). Moreover, although numerous scales and checklists have been constructed to assess quality of each study, the majority of them are inadequately developed (Moher 1995, Sutton *et al.* 1999). However, quality assessment has been

suggested as being useful in examining the relation between quality and outcome for the particular group of trials (Dickersin & Berlin 1995).

Important information regarding design feature, study characteristics, and outcome needs to be extracted after retrieving the relevant studies. Data extraction forms should be used. It is recommended that two investigators extract data independently and that they be blinded to certain information, such as name of the journal, authors of the papers, and the institutions where a study was conducted (Berlin 1994). When the available evidence is homogeneous, the results of the studies should be statistically combined. However, the data are sometimes too sparse, too heterogeneous, or of too low quality to proceed with a statistical aggregation. In this case, a "best evidence" synthesis may be appropriate (Slavin 1995).

A systematic review should clearly summarise the available evidence and provide appropriate interpretation. The degree of generalisability, and the strength and weakness of the results should be highlighted. Recommendations may be made based on the results of the meta-analysis and the areas which need future research highlighted.

2.3 Measures of effect size

A variety of scales have been used in reporting treatment outcomes in individual studies. For the results to be compared and combined, they need to be transformed into a common measure. The measurements commonly used for continuous outcome variables are standardised mean difference, or effect size (Hedges 1981) and mean

difference, while rate ratio (RR), rate difference (RD), and odds ratio (OR) are general scales for binary outcomes (Whitehead & Whitehead 1991).

2.3.1 Standardised mean difference

Standardised mean difference allows pooling of studies in which different scales were used giving a dimensionless effect size. The effect size for the ith (θ_i) study is defined as

$$\theta_i = \frac{\mu_{1i} - \mu_{0i}}{\sigma_i}$$

The estimator $\hat{\theta}_i$ of θ_i is given by (Hedges 1981).

$$\hat{\theta}_i = \frac{\overline{X}_{1i} - \overline{X}_{0i}}{S_i}, \qquad i = 1, \ldots, k$$

where $\overline{X}_{1i}, \overline{X}_{0i}$ are the sample means of treatment and control groups for the ith study and S_i is the pooled within-groups standard deviation,

$$S_i = \sqrt{\frac{(n_{1i}-1)(S_{1i})^2 + (n_{0i}-1)(S_{0i})^2}{(n_{1i}+n_{0i}-2)}}$$

where n_{1i} and n_{0i} are sample sizes, and S_{1i} and S_{0i} are the standard deviations for the treatment and control groups in the ith study.

An unbiased estimator $\hat{\theta}_i$ can be given by (Hedges 1982)

$$\hat{\theta}_i = c(m)\frac{\overline{X}_{1i} - \overline{X}_{0i}}{S_i} \qquad , i = 1, \ldots, k$$

where $m = n_{1i} + n_{0i} - 2$, c(m) is approximated by

$$c(m) \approx 1 - \frac{3}{4m-1}$$

For a sample with normal distribution, the sampling variance for effect size can be estimated as

$$\upsilon_i = \frac{n_{1i} + n_{0i}}{n_{1i} n_{0i}} + \frac{\hat{\theta}_i^2}{2(n_{1i} + n_{0i})}$$

and standard error (SE_i) is $\sqrt{v_i}$. An approximate 95% confidence interval is defined by $\hat{\theta}_i \pm 1.96SE_i$ and the Z statistic for the null hypothesis that $\theta_i = 0$ is defined by $Z = \hat{\theta}_i / SE_i$.

2.3.2 Mean difference

When the outcomes of different studies are measured on the same scale, the mean difference can be used to express the difference in effect size between the treatment and control groups and is given by (Shadish & Haddock 1994)

$$\hat{\theta}_i = d_i = \overline{X}_{1i} - \overline{X}_{0i} \quad , i = 1,\ldots, k$$

where $\overline{X}_{1i}, \overline{X}_{0i}$ are sample means in the ith study for the treatment and control groups, respectively. The variance of the mean difference is

$$\upsilon_i = \sigma_i^2 (\frac{1}{n_{1i}} + \frac{1}{n_{0i}})$$

where n_{1i} and n_{0i} are sample sizes for the treatment and control groups. σ_i^2 is the assumed common variance and can be estimated by the pooled within-group variance.

$$S_i^2 = \frac{(n_{1i} - 1)(S_{1i})^2 + (n_{0i} - 1)(S_{0i})^2}{(n_{1i} + n_{0i} - 2)}$$

where S_{1i} and S_{0i} are the standard deviations of the treatment and control groups in the ith study. The standard error of the mean difference is $\sqrt{v_i}$. The Z statistic is $Z = d_i/SE(d_i)$ and the approximate 95% confidence interval $d_i \pm 1.96SE(d_i)$.

2.3.3 Rate ratio (RR)

Assume that the data arise from a series of k independent studies in which the outcome variable is binary. Each study compares a treatment group (1) with a control

group (0), the data can be presented in the form of a 2x2 table (Mantel & Haenszel 1959) as,

	Event	Without event	total
Treatment	a_i	c_i	n_{1i}
Control	b_i	d_i	n_{0i}
	m_{1i}	m_{0i}	T_i

Let p_{1i} and p_{0i} be the event rate on the ith study from the treatment and control groups of sample sizes n_{1i} and n_{0i}, respectively. The rate ratio is equal to

$$RR_i = \frac{p_{1i}}{p_{0i}} = \frac{a_i / n_{1i}}{b_i / n_{0i}}$$

RR values can vary from 0 to infinity. For statistical analysis, RR is transformed to the natural logarithm. The measure of treatment effect for the ith study is therefore given by $\ln RR_i$, $\hat{\theta}_i = \ln RR_i$, which is normally distributed with a standard error estimated as (Rothman 1986, Fleiss 1993)

$$SE(\ln RR_i) = \sqrt{\frac{1-p_{1i}}{n_{1i}p_{1i}} + \frac{1-p_{0i}}{n_{0i}p_{0i}}} = \sqrt{\frac{c_i}{a_i n_{1i}} + \frac{d_i}{b_i n_{0i}}}$$

An approximate 95% confidence interval of RR_i is given by

$$\exp[\ln RR_i \pm 1.96 SE(\ln RR_i)]$$

and the Z-statistic = $\ln RR_i / SE(\ln RR_i)$.

2.3.4 Rate difference (RD)

Rate or risk difference is the difference between the probabilities of an event in the two groups. RD is a particularly useful measure for studies of treatment efficacy as it measures actual gains which can be expected in terms of percentage of patients treated (DerSimonian & Laird 1986). The reciprocal of RD provides the number needed to treat (NNT), that is the number of patients who need to be treated to achieve one more desirable outcome (Cook & Sackett 1995). The rate difference in the ith study is

$$\hat{\theta}_i = RD_i = p_{1i} - p_{0i}$$

with the sampling variance estimated by

$$v_i = \frac{p_{1i}(1-p_{1i})}{n_{1i}} + \frac{p_{0i}(1-p_{0i})}{n_{0i}}$$

The standard error of RD_i is $\sqrt{v_i}$ and an approximate 95% confidence interval is

$$RD_i \pm 1.96 SE(RD_i)$$

The Z-statistic = $RD_i / SE(RD_i)$.

2.3.5 Odds ratio (OR)

From the above 2x2 table, odds ratio in the ith study is given as

$$OR_i = \frac{p_{1i}(1-p_{0i})}{p_{0i}(1-p_{1i})} = \frac{a_i d_i}{b_i c_i}$$

As rate ratio, odds ratio values range between 0 and infinity. The statistical analysis is performed on the natural logarithm of odds ratio. Therefore, the estimate of treatment effect, $\hat{\theta}_i = \ln OR_i$. When any of the numbers a_i, b_i, c_i, d_i, is large, the standard error of $\ln OR_i$ is

$$SE(\ln OR_i) = \sqrt{\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}}$$

To reduce the bias when one or more of the numbers are small, the amount 0.5 may be added to each cell before OR_i and $SE(\ln OR_i)$ are calculated (Fleiss 1993).

Alternatively, let a_i be the number of observed event in the treatment group. Under the null hypothesis of independence and conditional on the fixed values of the marginal frequencies, the number of expected value can be calculated by $E(a_i) = n_{1i}m_{1i}/T_i$ with the variance of the difference (a_i - E_i) given by (Yusuf *et al.*1985, Fleiss 1993)

$$V(a_i) = \frac{n_{1i}n_{0i}m_{1i}m_{0i}}{T_i^2(T_i - 1)}$$

where m_{1i} is the total number of event from both treatment and control groups, n_{1i} is the number of patients in the treatment group, and T_i is the total number of patients in the ith trial.

The natural logarithm of the odds ratio is estimated by

$$\ln OR_i = \frac{a_i - E(a_i)}{V(a_i)}$$

with an estimated variance of $1/V(a_i)$.

An approximate standard error of $\ln OR_i$ is thus given by

$$SE(\ln OR_i) = \frac{1}{\sqrt{V(a_i)}}$$

The Z statistic is $Z = \ln OR_i / SE(\ln OR_i)$ and associated 95% confidence interval is

$$\exp[\ln OR_i \pm 1.96 SE(\ln OR_i)]$$

The odds ratio is popular because of its suitability in both retrospective and prospective studies, while the rate ratio is usually not estimable from data collected in retrospective studies. The odds ratio provides an approximation to the rate ratio when the events are comparatively rare and when the rate ratio cannot be estimated directly, such as in case-control studies (Altman 1998). However, the meaning of the odds ratio is not intuitively clear nor clinically meaningful. The choice of a measure depends on its relevance and statistical efficiency. What needs to be taken into

account are whether it is statistically convenient to work with, and whether it conveys the necessary clinically useful information (DerSimonian & Laird 1986, Sutton *et al.* 1998).

2.4 Approaches to combining data

2.4.1 Fixed effects model

The fixed effects model assumes that each of the study sample has the same effect size (Whitehead & Whitehead 1991). Consider a series of k independent studies each comparing a treatment (1) with a control (0) group. The response variable of interest in each study is the same. Let θ_i, the population effect size, denote the value of the chosen measure of treatment effect, i.e. the effect of the treatment relative to the control, in the ith study. This may, for example, be the log-odds-ratio for binary data or the mean difference for normally distributed data. Let $\hat{\theta}_i$, the observed effect size, denote an estimate of θ_i from the ith study and w_i be the inverse of the asymptotic variance of θ_i. Assume that $\hat{\theta}_i \sim N(\theta_i, w_i^{-1})$ for $i = 1, \ldots, k$, then $\hat{\theta}_i w_i \sim N(\theta_i w_i, w_i)$ and under the null hypothesis H_{0i}: $\theta_i = 0$, $\hat{\theta}_i w_i \sim N(0, w_i)$. The combined null hypothesis is $H_0 : \theta_1 = \ldots = \theta_k = 0$, $\Sigma\hat{\theta}_i w_i \sim N(0, \Sigma w_i)$ and so the statistic U to test H_0,

$$U = \frac{(\Sigma \hat{\theta}_i w_i)^2}{\Sigma w_i}$$

follows a χ^2 distribution with 1 degree of freedom.

Assume that all population effect sizes are equal, that is $\theta_1 = \ldots = \theta_k = \theta$, $\Sigma\hat{\theta}_i w_i \sim N(\theta\Sigma w_i, \Sigma w_i)$. Then θ can be estimated from $\hat{\theta}$ where

$$\hat{\theta} = \frac{\Sigma\hat{\theta}_i w_i}{\Sigma w_i}$$

with a standard error of $SE(\hat{\theta}) = \sqrt{1/\Sigma w_i}$

An approximate 95% confidence interval for the population effect size is given by $\hat{\theta} \pm 1.96\sqrt{1/\Sigma w_i}$.

The homogeneity test statistics Q is:

$$Q = \Sigma w_i(\hat{\theta}_i - \hat{\theta})^2$$

which is a weighted sum of squared deviations. When treatment effects are homogeneous, Q follows a χ^2 distribution with (k-1) degree of freedom (Cochran 1954).

The quality of an individual study can be incorporated into the analysis, by assigning a weight given by (Klein *et al.* 1986)

$$w_i = \frac{q_i}{v_i}$$

where q_i is the quality index for the ith study.

If heterogeneity exists across the studies, the possible sources should be investigated. The problem can be accommodated by various approaches including transforming the outcome variable to a different scale, meta-regression, sensitivity analysis, and subgroup analysis (Sutton *et al.* 1998). When the source of variation cannot be identified, the random effects model can be used (DerSimonian & Laird 1986).

2.4.2 Random effects model

In this model, each study is considered to be from a different population, the treatment effects vary from study to study, and differences are due to within-study and between-study variability. Assume that the treatment effects from the k studies ($\theta_1, \ldots, \theta_k$) are a sample of independent observations from N (θ, τ^2). Suppose, as before, that the estimate $\hat{\theta}_i$ satisfies the distributional relationship $\hat{\theta}_i \sim N(\theta_i, w_i^{-1})$ where now $\theta_i \sim N(\theta, \tau^2)$. The marginal distribution of $\hat{\theta}_i$ follows $\hat{\theta}_i \sim N(\theta, w_i^{-1} + \tau^2)$. When $\tau^2 = 0$, the model would reduce exactly to the fixed effects model. For the random effects, homogeneity test statistic Q is used to derive a noniterative estimate of τ^2 by equating the sample statistic with the corresponding expected value (DerSimonian & Liard 1986), yielding a weighted estimator

$$\hat{\tau}^2 = \max\left[0, \frac{Q-(k-1)}{\sum w_i - (\sum w_i^2 / \sum w_i)}\right]$$

The homogeneity test statistic Q is a test of H_0: $\tau^2 = 0$ and equals to

$$Q = \Sigma w_i (\hat{\theta}_i - \hat{\theta})^2$$

The estimate of θ is given by

$$\hat{\theta}^* = \frac{\Sigma \hat{\theta}_i w_i^*}{\Sigma w_i^*}$$

where $w_i^* = (w_i^{-1} + \hat{\tau}^2)^{-1}$

The asymptotic standard error of $\hat{\theta}^*$ is SE $(\hat{\theta}^*) = \sqrt{1/\Sigma w_i^*}$ and corresponding approximate 95% confidence interval is $\hat{\theta}^* \pm 1.96 \sqrt{1/\Sigma w_i^*}$.

The statistic to test the null hypothesis H_0: $\theta = 0$,

$$U^* = \frac{(\Sigma \hat{\theta}_i w_i^*)^2}{\Sigma w_i^*}$$

follows a χ^2 distribution with 1 degree of freedom (Whitehead & Whitehead 1991).

The quality of each study can be incorporated and weight is given by (Klein *et al.* 1986)

$$w_{iq}^* = w_i^* q_i$$

2.5 Problems in meta-analysis

Meta-analysis, by combining results from multiple studies, can increase statistical power for primary end points and for subgroups, resolve uncertainty when studies disagree, and improve estimates of effect size. It can be used to answer questions not posed at the beginning of individual trials (Sack 1987). However, meta-analysis has been subject to criticisms which have included bias, inclusion of unpublished data, and combinability of studies (Berlin 1994, Li Wan PO 1996).

2.5.1 Bias

Meta-analysis may be subject to several types of bias. The first is publication bias. Studies with statistically significant results are more likely to be submitted and published than those with nonsignificant results. Uncritical combining of these studies may produce an overestimate of effect. Various approaches have been proposed for dealing with publication bias. An early method, the file-drawer method, was described by Rosenthal (1979). The method uses Z scores corresponding to the p-values from the individual trials included in a meta-analysis to calculate the number of unpublished nonsignificant studies that would be required to overturn the current pooled result. A modification of the file drawer method was produced by Klein *et al.* (1986) so that the OR scale, instead of the p-values, can be used.

Orwin (1983) later proposed a method analogous to that of Rosenthal's file-drawer calculation, for dealing with the standardised mean difference. The fail-safe N can be calculated as follows:

$$N_{fs} = \frac{N_0(\bar{d}_0 - d_c)}{d_c - \bar{d}_{fs}}$$

where N_0 is the number of studies, $\bar{d}_0$ is the mean effect size for the N_0 studies, d_c is the criterion value that $\bar{d}_0$ would equal to when N_{fs} studies were added. $\bar{d}_{fs}$ is the mean effect size of the studies to be added and is assumed to be zero. For example, $N_0 = 10$, $\bar{d}_0 = 0.85$ and is supposed to be decreased to 0.5. Then the $N_{fs} = 10\ (0.85\text{-}0.5)/(0.5\text{-}0) = 7$, which means 7 missing studies with negative results need to be added in order to reduce the mean effect size from 0.85 to 0.50.

An important aspect of publication bias is that positive trials are more likely to be published more than once. Duplicating data could yield excessively precise and inflated effect size estimates. As such it is essential that only one report on the same patients be accepted into a meta-analysis (Berlin 1994, Naylor 1997).

Other types of potential bias include: (i) retrieval bias, arising from non-exhaustive searches of the literature, (ii) selection bias, arising from inappropriate criteria for inclusion and exclusion of studies, and (iii) data-extraction bias, arising from errors in interpretation by readers and from careless reporting in the original trials. A properly conducted systematic review would ensure that all biases are minimised.

2.5.2 Inclusion of unpublished data

The selection of data presented in published studies, or publication bias, poses a major threat to the validity of meta-analysis. To avoid this problem, the data from unpublished studies should be obtained and included. However, it seems uncertain whether including unpublished data would reduce or increase bias as one cannot be sure that all such studies have been identified. Further, the problem may arise regarding the willingness of investigators to provide unpublished data (Smith & Egger 1998).

Additional concern with regard to the inclusion of unpublished data is that they may be methodologically flawed. However, the most valid synthesis would be obtained when such studies are subjected to the same rigorous methodological evaluation as the published studies and the analysis is performed with and without the unpublished data (Cook *et al.* 1993, Smith & Egger 1998).

2.5.3 Combinability of studies

Theoretically, pooling of data from different trials would enhance the precision and accuracy of the results given that the differences among trials are primarily due to chance. A major issue in pooling is whether the results of each trial can be meaningfully combined. Indeed, the trials may differ in their study quality, design and implementation, such as blinding, randomisation, eligibility criteria, variation in treatment, length of follow-up, and outcome measures. The assessment of heterogeneity is therefore crucial. Pooling of heterogeneous studies may lead to

inappropriate results. On the other hand, the heterogeneity of studies, if properly handled, may help in the interpretation of the existing data and in planning future studies (Li Wan Po 1996).

2.6 Conclusion

Systematic reviews and meta-analyses are increasingly common, and when properly conducted may provide the best estimates of treatment effect through summarising all available evidence. They offer valuable information for medical decision-making and for the setting of clinical policies. The reviews may help investigators to define future research agendas. Meta-analyses, however, can be misleading and interpretation of the same evidence may lead to different conclusions. The results, therefore, need to be interpreted carefully and critically. Used increasingly in clinical practice, systematic reviews may strengthen the link between best research evidence and optimal health care.

Chapter 3

Measuring mania: a critical appraisal of rating scales

3.1 Introduction

Manic-depressive illness (bipolar disorder) is a chronic recurrent disease. For example, a recent survey suggests that about 1% of the population of the United States is affected (Regier *et al.* 1990). Manic symptoms include explosive temper, impaired judgement, hypersexuality, grandiosity and disorganised behaviour. The symptoms are often disruptive enough to lead to breakdown of relationships and job loss. Suicide mortality in untreated patients has been reported to be about 15% (Bowden *et al.* 1994). Few effective drugs are available and lithium is generally regarded as the gold standard therapy for acute mania. Lithium is often perceived as poorly tolerated drug with a narrow therapeutic index (Emilien *et al.* 1995). For this reason there has been a search for alternative treatments and a number of drugs, often initially used for other conditions have been evaluated for their efficacy in mania. A systematic review was conducted with regard to the comparative efficacy of anti-manic drugs because there does not appear to have been any published and because of the increasing recognition of the value of such reviews for informing treatment decisions in current clinical practice.

One of the critical issues in determining the usefulness of clinical reports about the efficacy of particular treatments is whether appropriate and meaningful treatment outcomes were used. Different methods have been used to measure treatment outcomes in clinical trials of acute mania. These include determining the number of patients with

remission, evaluating the degree of improvement, and assessing reduction in symptoms (Keck & McElroy 1996). The available instruments for measuring mania fall into two broad categories: global rating scales and symptom rating scales. Global rating evaluates the severity of the total condition, in one single assessment. Symptom rating scales assess the severity or presence of signs and/or symptoms and then integrate the individual scores, to provide an overall score for the disease. It is obvious that both types of rating scales need to be validated. In other words we need to ensure that they measure what they are intended to measure and are sensitive to clinically meaningful changes. In this report we describe our attempts to identify rating scales in common use for the evaluation of the severity of mania in randomised controlled trials and provide a critical and systematic appraisal of their quality.

3.2 Methods

3.2.1 Identification of studies

Relevant studies were searched through the reports of randomised controlled trials of lithium in acute mania and the reports of rating scales identified through a systematic search comprising; (i) Electronic searches of MEDLINE and BIDS (Science Citation Index and EMBASE). The computerised searches covered the period 1970 to February 1999. A medical subject headings (MeSH) search in MEDLINE was undertaken first, followed by a keyword search using "mania" and "rating scales" as keywords. (ii) Historical searches through the reference lists of all retrieved studies, review articles, and textbooks.

Our intention was to identify and assess any rating scales for mania reported in the literature. Assessing the quality of the rating scales: We focused on the dimensions of quality identified by the American Psychological Association (1974) and assessed the extent to which the authors have endeavoured to establish the validity and reliability of their scales.

3.2.2 Evaluating rating scales: reliability and validity

Reliability concerns the extent to which a test yields the same results on repeated measurements. The common tests of reliability include inter-rater reliability, test-retest reliability, and internal consistency. Test-retest reliability is much less common in rating of psychopathology as psychiatric conditions vary over time (Endicott & Spitzer 1978, Bech 1993). Validity is the extent to which a measuring instrument measures what it is intended to measure. The instrument may be measuring symptoms severity reliably, i.e. yield similar score under identical conditions, but may not be measuring accurately what it is purported to measure, i.e. manic symptomatology. Scale items concerning their sources and assessment and the utility of the scale, such as completion time, training of rater, and scoring, need to be taken into account when evaluating rating scales (Bech 1993, Streiner 1993).

Correlation analysis is commonly used to estimate reliability and validity. However, Pearson (r), or Spearman's rank (r_s) correlation coefficient only shows the degree of association, but does not indicate agreement, i.e. provides no information on whether one rater differs systematically from the other. The intraclass correlation coefficient (ICC), in contrast, is sensitive to systematic biases and provides more accurate estimate

of reliability (Streiner 1993). Alternative approaches for assessing agreement between two methods of clinical measurement are available (Bland & Altman 1986, McDowell & Newell 1996).

3.3 Results and discussion

A total of 13 scales were identified (Beigel *et al.* 1971, Petterson *et al.* 1973, Research Group on Treatment of Mania 1974, Blackburn *et al.* 1977, Bech *et al.* 1978, Young *et al.* 1978, Secunda *et al.* 1985, Brierley *et al.* 1988, Bauer *et al.* 1991, Shugar *et al.* 1992, Altman *et al.* 1994, 1997, Zheng & Lin 1994). Five were identified through reports of randomised controlled trials of lithium in acute mania. Six through computerised database searches of articles other than randomised controlled trials and two through historical searches of reference lists of articles retrieved. Four self-rating scales (Bauer *et al.* 1991, Shugar *et al.* 1992, Zheng & Lin 1994, Altman *et al.* 1997) were among the 13 retrieved but were eliminated from further detailed evaluation because it is now widely recognised that such scales are unreliable in this condition. Manic patients cannot be relied on to provide robust data. One scale in Japanese was not further evaluated (Research Group on Treatment of Mania 1974). Table 3.1 summarises the similarities and differences in their item profiles while Table 3.2 summarises some of their metric properties, detailed below.

Table 3.1 Item profiles of rating scales for mania

Item	MS 26-item	Petterson† 7-item	MMS† 28-item	MRS† 11-item	BRMS† 11-item	MADS* 23-item	MNRS-M† 9-item	CARS-M† 15-item
is active	●	motor activity	●	increased motor activity-energy	activity (motor)	energetic (2)	●	energetic
moves from one place to another	●		restless			increase in activity		motor hyperactivity
is talking	●	pressure of speech	●	speech	activity (verbal)	●	●	pressured speech
is argumentative	●					●	interfering	
is distractable	●	flight of idea	●	language-thought disorder	flight of thought	●	●	distractibility
jumps from one subject to another	●		●			●	●	flight of idea
is irritable	●	aggressive ness	●	irritability	hostility/ destruc tiveness		●	irritability/ aggres siveness
is angry	●		●	disruptive-aggressive behaviour		● (2)		
is combative/ destructive	●						antisocial or disinhibited	
makes threats	●		●					
looks happy & cheerful	●	elevated mood	●	elevated mood	mood (feelings of well-being)	elevated mood, elated (2)	●	elevated/ euphoric mood
verbalises feeling of well-being	●		●					
has grandiose ideas	●		●	content	self-esteem	grandio sity (4)	●	grandiosity
makes unrealistic plans	●		●					
is delusional	●		●					delusion
is suspicious	●		●			guarded		
dresses inappropriately	●			appearance				
is careless about dress and grooming	●		●					
talks about sex	●			sexual interest	sexual interest			poor judge-ment
is sexually preoccupied	●		●					
has poor judgement	●		●			● (2)		
has diminished impulse control	●		●			●		
demands contact with others	●		●		contact			
seeks out others	●		●			●		
looks depressed	●		depressed					
verbalises depressive feelings	●							
noisinesss		●			●			
orientation		●						●

Table 3.1 Item profiles of rating scales for mania (continued)

Item	MS 26-item	Petterson† 7-item	MMS† 28-item	MRS† 11-item	BRMS† 11-item	MADS* 23-item	MNRS-M† 9-item	CARS-M† 15-item
decreased sleep			●	●	●	●		●
hallucinating			●					●
has delusion of persecution			●					
shows flight of idea			●					
emotionally liable			●					
is religiose			●					
is disinhibited			●					
insight				●		●		●
working activity					●			
negativism						●		
disordered thinking								●

MS, Manic State Rating Scale; MMS, Modified Manic State Rating Scale; MRS, Mania Rating Scale; BRMS, Bech-Rafaelsen Mania Scale; MADS, Manic Diagnostic and Severity Scale; MNRS-M, Manchester Nurse Rating Scale for Mania; CARS-M, Clinician-Administered Rating Scale for Mania
* Number in bracket indicates number of items
† Some item constructs assess more than one symptom

Table 3.2 Summary of the psychometric properties of mania rating scales

		Reliability		Validity	
Instrument	**Influential factor**	**Interrater**	**Internal consistency**	**Content**	**Construct**
MS Scale (26-item)	4 factors accounting for 34%, 19%, 8%, and 7% of variance, respectively 3 rotated factors: (1) motor and speech disturbance, (2) aggressiveness, (3) unrealistic expansiveness of mood	Using intraclass correlation: ICC = 0.895-0.996 for 25 items among 12 raters, $p < 0.001$ (n = 13) Using Rank correlation: $r_s = 0.60$, $p < 0.001$ (n = 35) Using Friedman test: n = 3, p = 0.43 among 4 raters	N/R	Literature review and clinical experience	Comparison of MS Scale scores with (1) 15-point global rating, (2) nurses' symptom checklist score, (3) 8-point global rating, (4) Petterson Scale, (5) 11-point global assessment
Petterson Scale (7-item, 2-global rating)	N/R	Using Pearson correlation: before treatment; r = 0.48-1.00, for 8 items (n = 20) Using Rank correlation: $r_s = 0.88$, $p < 0.001$ (n = 35)	N/R	Literature review and pilot study	Comparison of manic scores with (1) clinical improvement as judged by clinician, (2) global rating, (3) MS Scale
MMS (28-item)	N/R	Using Pearson correlation: $r > 0.37$, $p < 0.01$ for individual item scores r = 0.79-0.85 for total scores (n = 45)	N/R	Derived from MS Scale	Comparison of MMS scores with (1) nurses'global rating, (2) physicians' global rating
MRS (11-item)	3 factors accounting for 59% of variance. 3 rotated factors (1) thought disturbance, (2) overactive and aggressive behaviour, (3) elevated mood and vegetative symptoms	Using Rank correlation: $r_s = 0.93$, $p < 0.001$ for total score $r_s = 0.66$-0.95, $p < 0.001$ for individual item scores (n = 35)	$\alpha = 0.80$ (n = 30)	Literature review and clinical experience	Comparison of MRS scores with (1) global rating, (2) MS Scale, (3) Petterson Scale, (4) Clinical Global Impression -Mania

Table 3.2 Summary of the psychometric properties of mania rating scales (continued)

		Reliability		Validity	
Instrument	**Influential factor**	**Interrater**	**Internal consistency**	**Content**	**Construct**
BRMS (11-item)	N/R	Using Kendall concordance: W = 0.95, $p < 0.001$ among 4 raters (n = 12) Using intraclass correlation: ICC = 0.98 (n = 84)	$\alpha = 0.93$ (n = 84)	Derived from MS Scale and Petterson Scale	N/R
MADS (4-subscale)	N/R	Using intraclass correlation: ICC; ADRS Score 1 = 0.85, ADRS Score 2 = 0.91, VIBES Score B2 = 0.89 (n = 19)	N/R	Items from SADS-C Scale 17, VIBES Factor B2, ADRS-Factor 1 and 2	N/R
MNRS-M (9-item)	N/R	Using Pearson correlation: $r = 0.813$-0.993, $p < 0.05$ for total scores (n = 7-10) among 4 pairs of raters $\tau = 0.381$-0.780, $p < 0.001$ for individual items (n = 36)	N/R	Derived from MS Scale	Comparison of MNRS-M scores with (1) MRS, (2) global rating of mania
CARS-M (15-item)	2 factors accounting for 49% of variance; (1) mania factor, (2) psychosis factor	Using intraclass correlation: ICC = 0.83 (0.66-0.94) for individual items and 0.93 for total scores (n =14) among 5 raters	$\alpha = 0.88$ for factor 1 $\alpha = 0.63$ for factor 2	Derived from SADS	Comparison of CARS-M total scores with the MRS total scores

ADRS, Affective Disorder Rating Scale; BRMS, Bech-Rafaelsen Mania Scale; CARS-M, Clinician-Administered Rating Scale for Mania; ICC, intraclass correlation; MADS, Manic Diagnostic and Severity Scale; MMS, Modified Manic State Rating Scale; MNRS-M, Manchester Nurse Rating Scale for Mania; MRS, Mania Rating Scale; MS Scale, Manic-State Rating Scale; N/R, not reported; SADS-C, Schedule for Affective Disorders and Schizophrenia, change version; VIBES, Video Interview Behaviour Evaluation Scale

3.3.1 Manic-State Rating Scale (MS)

The first published rating scale for manic symptomatology was constructed for research in affective disorders (Beigel *et al.* 1971). The scale consists of 26 items which are graded for frequency and severity, each on a 5-point scale. Multiplication of these two ratings yields an item score ranging from 0 to 25. This rating represents the total impression of the patient's behaviour during the previous eight hours. It is designed for assessing inpatients by trained nursing staff.

Inter-rater reliability for all items was high. Intraclass correlation coefficient was 0.862-0.996 ($p < 0.001$) in 13 manic and depressed patients (Beigel *et al.* 1971, Murphy *et al.* 1974). Spearman correlation, r_s of 0.60 ($p < 0.001$, $n = 35$) was reported (Young *et al.* 1978). Significant Pearson correlation was found between individual item scores and the total MS scores for 6 item: moves from one place to another ($r = 0.855$, $p < 0.05$), has poor judgement ($r = 0.849$, $p < 0.05$), is distractable ($r = 0.888$, $p < 0.02$), is active ($r = 0.846$, $p < 0.05$), is angry ($r = 0.858$, $p < 0.05$), and jumps from one subject to another ($r = 0.916$, $p < 0.02$) ($n = 6$) (Beigel *et al.* 1971). Rotation of factors identified 3 factors concerning motor and speech disturbance, aggressiveness, and unrealistic expansiveness of mood (Double 1990).

Construct validity was assessed by comparing MS total scores against:15-point psychiatrists' global rating ($r = 0.96$, $p < 0.001$, $n = 13$) (Beigel *et al.* 1971), ($r = 0.70$, $p < 0.001$, $n = 22$) (Murphy *et al.* 1974), nurses' manic symptom checklist scores ($r = 0.959$, $p < 0.001$, $n = 13$) (Beigel *et al.* 1971) , 8-point global ($r_s = 0.66$, $p < 0.001$, $n = 35$) (Young *et al.* 1978), Petterson score ($r_s = 0.65$, $p < 0.001$, $n = 35$) (Young *et al.*

1978), 11-point global assessment ($r_s = 0.90$, $p < 0.001$, $n = 19$) (Bech *et al.* 1975). Only a subgroup of the items (moves from one place to another, looks happy and cheerful, seeks out others, is distractable, has diminished impulse control, and demands contact with others) was relevant for assessing the severity of mania when scale item validity was tested against the 11-point global rating ($n = 19$) (Bech *et al.* 1975). The MS Scale was able to differentiate patients before and after 2 weeks of treatment and to distinguish between degrees of severity based on global ratings (Young *et al.* 1978).

The limitation of this scale is its extensiveness. Rating on 26 items according to frequency (0 to 5) and intensity (1 to 5) requires too much time. In addition, items and scale steps are not explicitly defined and certain characteristics of mania, such as sleep disturbance and lability of mood, are not included (Petterson *et al.* 1973, Blackburn *et al.* 1977).

3.3.2 Petterson Scale

Petterson *et al.* (1973) attempted to overcome some of the shortcomings of the MS. This scale consists of seven symptom-rating items and two global ratings scored on 5-point scale. The item constructs include motor activity, pressure of speech, flight of ideas, noisiness, aggressiveness, orientation, and elevated mood. Patients are rated by psychiatrists based on an approximately 30-minute non-structured interview.

Reliability and validity were determined in 20 manic patients (Peterson *et al.* 1973). Significant interjudge reliability was reported for both item scores and the sum of seven items scores ($r = 0.48$-1.00; $n = 20$) (Petterson *et al.* 1973), and for total scores ($r_s =$

0.88, $p < 0.001$, $n = 35$) (Young *et al.* 1978). Sum of scores reflected change in clinical state as judged by an independent clinician, indicating validity and sensitivity of the scale for rating mania of various intensities. The mean score ($n = 20$) before treatment was 17.48 (SE 3.50) which decreased to 8.40 (SE 1.46, $p < 0.001$) after 10 days when patients were considered as markedly improved. Construct validity was examined against global rating ($r_s = 0.80$, $p < 0.001$) and Beigel's MS Scale ($r_s = 0.65$, $p < 0.001$, $n = 35$) (Young *et al.* 1978). For predictive validity the scores were correlated with the number of days of continued stay in hospital ($r = 0.50$, $p < 0.01$) (Young *et al.* 1978).

The Petterson Scale defines the degree of severity of the signs and symptoms more explicitly than the MS scale. Its brevity makes it useful for serial ratings. However, the scale does not distinguish between mood and self-esteem and several features of mania, such as social contact, sleep and work disturbance, are not assessed (Young *et al.* 1978, Bech *et al.* 1979, Goodwin & Jamison 1990).

3.3.3 Modified Manic State Rating Scale (MMS)

Blackburn *et al.* (1977) modified Beigel's MS purportedly to overcome the need for specially trained nursing staff to assess the patient. Unfortunately, the instrument is even more extensive, consisting of 28 items. While a useful feature is a detailed glossary to aid scoring on 6-point scale (0-5), rating still requires a psychiatrist, being based on both a clinical interview and nursing reports.

Inter-rater agreement was assessed using 45 ratings by 3 psychiatrists. Significant correlation of individual item was reported for each pair of raters ($r > 0.37$, $p < 0.01$).

The overall correlation between each pair of raters were in the range 0.79-0.85 (n = 45). Examination of scale homogeneity revealed significant correlations between all individual items, except that relating to depression, and MMS total score. Testing of construct validity included comparison of total MMS score and global rating by physicians ($r = 0.801$, $n = 44$, $p < 0.001$) and by nurses ($r = 0.654$, $n = 44$, $p < 0.001$). The MMS also demonstrated sensitivity to changes in scores following inpatient treatment (Blackburn *et al.* 1977).

3.3.4 Mania Rating Scale (MRS)

Young *et al.* (1978) developed a clinician-administered scale with broader scope and greater sensitivity than the Petterson Scale, but shorter and more explicit in its rating of item severity than the Beigel MS Scale. The scale measures 11 constructs based on published descriptions of the core symptoms of mania: elevated mood, increased motor activity (energy), sexual interest, decreased sleep, irritability, speech (rate and amount), language-thought disorder, content, disruptive-aggressive behaviour, appearance, and insight. The 5-point severity score is based on the patient's subjective report and on the clinician's observations of the behaviour of the patient during the interview which lasts for 15 to 30 minutes.

Assessment of inter-rater reliability was based on 35 ratings (Young *et al.* 1978) and significant correlations were reported for both the total scores ($r_s = 0.93$, $p < 0.001$) and the item scores ($r_s = 0.66$-0.95, $p < 0.001$). All individual item scores were significantly correlated with the total scores ($r_s = 0.41$-0.85), suggesting scale homogeneity. The internal consistency was evaluated in 30 prepubertal patients. A Cronbach's α

coefficient of 0.80 was reported (Fristad *et al.* 1995). Factor analysis identified three factors representing thought disturbance, overactive and aggressive behaviour, and elevated mood and vegetative symptoms (Double 1990).

The construct validity was determined against 3 rating scales (n = 35): global rating were $r_s = 0.88$ ($p < 0.001$), the Petterson Scale $r_s = 0.89$ ($p < 0.001$), and the MS Scale $r_s = 0.71$ ($p < 0.001$) (Young *et al.* 1978). In a recent study which included 30 prepubertal patients with bipolar disorder and those with attention deficit hyperactivity disorder, the correlation between the Clinical Global Impression-Mania and mania scores was $r = 0.82$ ($p < 0.0001$, n = 30) (Fristad *et al.* 1995). The correlation between the scores and the number of days of subsequent stay in hospital was evaluated for predictive validity ($r_s = 0.66$, $p < 0.001$) (Young *et al.* 1978). The MRS yielded pre- and post-treatment scores which were significantly different at the 0.005 level, following 2-week treatments (n = 15) and was able to differentiate groups of patients with various degrees of severity based on global severity levels (n = 35) (Young *et al.* 1978).

3.3.5 Bech-Rafaelsen Mania Scale (BRMS)

Bech *et al.* (1978) constructed a brief mania rating scale based on the Beigel Manic-State Rating Scale (Beigel *et al.* 1971) and the Petterson Scale (Petterson *et al.* 1973). The BRMS consists of 11 items: motor activity, verbal activity, flight of thoughts, voice/noise level, hostility/destructiveness, mood level (feeling of well-being), self-esteem, contact, sleep change, sexual interest, and work activity. Each item is assessed based on the condition in the 3 days preceding the test on a 5-point Likert scale (0-4). The range of possible scores is between 0 and 44. The rating is undertaken by a

clinician, based on a 15 to 30 minute interview administered at a fixed time during the day in order to avoid diurnal variation.

Inter-observer reliability calculated as Kendal coefficient of concordance (W) was 0.95, $p < 0.001$ ($n = 12$) (Bech *et al.* 1979). Intra-class coefficient of 0.98 and Cronbach α of 0.93 were reported ($n = 84$) (Bech 1993, Bech *et al.* 1993). The homogeneity of the BRMS was indicated by significant correlation between the item scores and the total scores ($r_s = 0.72$-0.94, $p < 0.001$, $n = 23$) except for sleep and total score ($r_s = 0.48$, $p < 0.05$) (Bech *et al.* 1979). Licht and Jensen (1997) assessed the internal validity of the scale using latent structure analysis based on ratings of 100 patients. All items, except work activity, were included. Mood level, self-esteem, sleep, and sexual interest were found not to reflect severity of illness to the same extent as the remaining six items; $r_s = 0.24$-0.44 for those four items compared to 0.64-0.78 for the other six (Licht & Jensen 1997).

3.3.6 Manic Diagnostic and Severity Scale (MADS)

The MADS was originally developed for use with hospitalised patients in a study as part of the National Institute of Mental Health Collaborative Study of Depression (Secunda *et al.* 1985). In order to obtain greater breadth and sensitivity, the authors included four subscales integrating items from existing physician- and nurse-rated measurements. The symptom characteristics as assessed by the clinician are captured by the SADS-C-17 Scale (Spitzer & Endicott 1978) and the Video Interview Behaviour Evaluation Scale (VIBES) Factor B-2 scale (Katz & Itil 1974). The former profiles the major manic features while the latter focuses on the anger and negativity associated with the

syndrome. The nurse perspective is captured using two factors derived from the nurse-rated Affective Disorder Rating Scale (ADRS) (Murphy *et al.* 1980). Factor 1, which includes nine items assesses the paranoid-destructive features while Factor 2 captures the elation-grandiose features. The average intraclass correlation coefficients (ICC) of the MADS subscales based on 19 manic patients were reported as follows: ADRS Factor 1, 0.85; ADRS Factor 2, 0.91, and VIBES Factor B2, 0.89 (Secunda *et al.* 1985). Discriminant validity testing included the ability of the scale to differentiate among the various diagnostic groups compared to the standard diagnostic instrument, Schedule for Affective Disorders and Schizophrenia (SADS). Both measures adequately separated manic patients from the other groups. The sensitivity to change was demonstrated by assessing patients before and after four weeks' treatment. In responsive patients (n = 11), the mean MADS scores decreased from 4.49 (SD 1.50) to 1.06 (SD 0.23, $p < 0.01$), while there was no difference between pre- and post-treatment scores (5.00±2.16 vs 4.67±0.61) in nonresponders (n = 5) (Secunda *et al.* 1985).

3.3.7 Manchester Nurse Rating Scale for Mania (MNRS-M)

MNRS-M is a brief nurse-rated scale, based on the MS. Unlike MS, the MNRS-M contains fewer items to allow relatively easy daily administration. Moreover, it does not require specially trained nurses. Evaluation is based solely on observations of the patient's behaviour (Brierley *et al.* 1988). 9 items are included and each is scored on a 0-3 scale based on the frequency of occurrence (0 = never, 1 = seldom, 2 = often, 3 = usually) during a nursing shift. Rating is made at 24-hour intervals. Mania scores are obtained by summing scores for all items.

Inter-rater reliability was obtained from 4 pairs of raters with each pair providing 7-10 ratings. The product-moment correlation coefficient ranged from 0.813 to 0.993 ($p < 0.05$). Significant Kendall's τ was found for inter-rater reliability of each item (τ = 0.381-0.780, $p < 0.001$, $n = 36$). Item consistency was examined with Kendall's correlation between individual item scores and the total scores (τ = 0.373-0.670, $p < 0.001$, $n = 50$). Construct validity was assessed by comparing the MNRS-M total scores with the MRS ($r = 0.790$, $p < 0.001$) and global rating of mania ($r = 0.650$, $p < 0.001$, $n = 52$) (Brierley *et al.* 1988).

3.3.8 Clinician-Administered Rating Scale for Mania (CARS-M)

The 15-item scale is primarily derived from the Schedule for Affective Disorders and Schizophrenia (SADS) and adopts a standardised format to allow clinicians to elicit information in a consistent and reliable way. 14 of the items are scored from 0 (absent) to 5 (severe) and 1 item is scored 0 to 4. Rating is based on a 15 to 30 minute, semi-structured interview, and observations of behavioural symptoms over the previous 7 days.

Inter-rater reliability was assessed using a sample of 14 patients with schizophrenia, major depression, bipolar mania, and bipolar depression (Altman *et al.* 1994). The mean ICC for the five raters for individual items was 0.83 (0.66-0.94), and for total scores, 0.93. Testing of construct validity included a comparison of the CARS-M total scores with the total scores obtained with the MRS ($r = 0.94$, $n = 96$). Factor analysis identified 2 factors accounting for 49% of the total variance. One, referred to as the mania factor, consists of the first ten items and assesses manic symptoms. The other, referred to as

the psychosis factor, consists of the remaining five items and assesses psychotic features. Reliability of the factor subscales was examined using test-retest reliability (Pearson correlation coefficients of 0.78, $n = 16$, $p < 0.01$ and 0.95, $n = 16$, $p < 0.01$) and internal consistency (Cronbach's α of 0.88 and 0.63) for factor 1, and 2, respectively. The two subscales demonstrated sensitivity to change with patients before and after inpatient treatment (Altman *et al.* 1994).

3.4 Conclusion

There are now at least eight mania rating scales. The Mania Rating Scale, developed by Young *et al.*, is the most widely used for assessing treatment response. It is often regarded as the gold standard by scale developers who use it for assessing concurrent validity for new scales (Brierley *et al.* 1988, Altman *et al.* 1994). Despite this, its validation is still limited. For example, inter-rater reliability was assessed by comparing the scores assigned by only two physicians and involving only twenty patients who provided thirty five sets of ratings. Nonetheless, wide experience of its use suggests that it is sufficiently sensitive to detect changes in severity of mania following treatment and because of this extensive in-practice validation, it should be retained as a comparator even if an alternative scale is used as first choice. Lithium therapy consistently gives reduction in scores of over ten units over treatment periods of a few weeks. This magnitude of change is clinically significant based on comparison against ratings obtained with the Clinical Global Impression Scale (Segal *et al.* 1998). The two more recent rating scales for mania, the MNRS-M and the CARS-M hold much promise. However, the MNRS-M requires much more extensive validation. For example, its

sensitivity to change has yet to be established. CARS-M is at a more advanced stage and has generally been well validated. What has yet to be established is the relationship between its scores and global ratings. Until this is defined, interpretation of observed changes in scores in terms of clinical significance is not reliable. Rating scales are generally used to obtain a single integrated score. This reductionist approach may mask differential effects of treatments on the different subscales or individual items. Increased emphasis on item and subscale score analysis may well be justified. Indeed, the developers of CARS-M suggest that the mania and the psychosis factors within their scale should be interpreted independently, a recommendation which we fully endorse. Indeed, the pharmacological profiles of antimanic drugs differ substantially. Masking their effects within a single score may lead to failure to identify differences in effectiveness profiles. This in turn may lead to suboptimal choice of therapy, for a disease in which individual variability in symptomatology is substantial.

Irrespective of which scale is used, the traditional approach to the analysis of patient responses is that of cross-sectional analysis at fixed time points, typically collected at the beginning of therapy and at the end. In many instances, scores are collected at regular intervals and the analysis then adopts a repeated measures analysis of variance. We would suggest that analysis of the data integrated over time, as has been recently suggested for assessing treatment outcomes in multiple sclerosis, would make better use of such data. The use of generalised estimating equations as suggested by Zeger and Liang (1986) would be useful. In view of the increasing importance of cost-effectiveness assessments in the evaluation of alternative therapies, translating observed changes in scores, obtained with the various mania rating scales, into clinically meaningful categories requires further exploration. To do this, there may be a need to

establish whether the assignment of equal weights to every item on any particular scales is valid. Although the MRS does include some differential weighting, the approach used appears to have been arbitrary and requires further validation.

Further work is needed both to identify the most relevant and sensitive core characteristics of mania, and to define how to weight the different symptoms so that any integrated score more accurately reflects the disease severity, as perceived by both observer and patient. Measuring disease severity in mania presents many challenges, not least the fact that capturing the patient's perspective reliably is almost impossible because of the nature of the disease. Instruments which capture the independent observer's perception reliably and responsively are a useful first step.

Chapter 4

Systematic review of lithium treatment in acute mania

4.1 Introduction

Mania is an abnormal condition of mood which affects approximately 1% of the population (Daly 1997). The essential feature of mania is the distinctive mood which is elevated, expansive, or irritable. The associated symptoms include inflated self-esteem, impaired judgement, decreased need of sleep, flight of ideas, distractibility, and psychomotor agitation. The disturbance can cause considerable impairment in both social and occupational functioning, even during clinical recovery (Daly 1997).

Lithium has been used as an antimanic agent for decades since its antimanic effects was first discovered in 1949 (Cade 1949). Although it remains the mainstay of the treatment against mania, about 10% to 20% of patients are reported to be unresponsive to lithium and some are unable to tolerate it (Schou 1988). Antipsychotics such as chlorpromazine and haloperidol have been widely used as alternatives or adjuncts to lithium in early stage acute mania to control agitation and psychotic features. Although they are claimed to produce more rapid response than lithium, their efficacy compared with lithium is still unclear. Similarly the anticonvulsants carbamazepine and valproate have recently been claimed to be effective in patients who were reported to have failed to respond adequately to lithium or were intolerant of lithium. They have become increasingly used as alternatives to, or in combination with lithium, in place of antipsychotics (Mitchell & Parker 1991, Keck & McElroy 1996). However, there appears to be inconsistencies

in their efficacy compared to lithium (Lerer *et al.* 1987, Okuma *et al.* 1990, Small *et al.* 1991, Freeman *et al.* 1992, Bowden *et al.* 1994). Other agents investigated for their potential antimanic effects include verapamil (Dubovsky *et al.* 1986, Höschl & Kozeny 1989) and clonazepam (Edwards *et al.* 1991, Bottai *et al.* 1995), but again their efficacy compared to lithium remains to be established.

The results of the controlled trials of lithium in the treatment of mania appear to be discrepant. Several possible contributory factors include methodological issues (open/blind, and parallel/crossover study design), sample size, variability in diagnostic criteria, duration of treatment, variability in rating scales used, concurrent medications, and differences in patient sample characteristics such as age, sex, and severity of illness (King 1990a, Keck & McElroy 1996). Further, a recent narrative review by Moncrieff (1997) has called into question lithium's effectiveness.

We therefore undertook a systematic review of trials of lithium in the treatment of acute mania in an attempt to resolve the apparent inconsistencies and to better define the position of lithium in relation to other pharmacotherapies including chlorpromazine, haloperidol, carbamazepine, and valproate.

4.2 Materials and methods

4.2.1 Identification of studies

Reports of randomised controlled trials of lithium were identified through a systematic literature search comprising of; (i) Electronic searches of MEDLINE, BIDS (EMBASE

and Science Citation Index), and the Cochrane Library (issue 1, 1999). The computerised searches covered the period 1966 to the end of June 1999. A medical subject headings (MeSH) search was undertaken using "lithium", "bipolar disorder" and "clinical trial". This was followed by a keyword search using "mania" and "acute treatment" as keywords. (ii) Historical searches through the reference lists of the randomised controlled trials and of narrative and systematic reviews of lithium retrieved through the computer searches.

4.2.2 Inclusion and exclusion criteria

A two level inclusion protocol was used. At the first level, for a trial to be included in the systematic overview, it had to be a randomised controlled trial dealing with the use of lithium as an acute treatment of mania. At the second level, studies were included in the statistical pooling if they (a) used a single or double-blind design and (b) provided efficacy data in terms of the improvement in symptom severity as measured by the Brief Psychiatric Rating Scale (BPRS) or the improvement in global severity as measured by the Clinical Global Impression (CGI), or in terms of response rate. When there were more than one publication based on the same group of patients, the publication with the more comprehensive and relevant data was used as the primary source. Specific exclusions and inclusions are described in detail further on.

4.2.3 Data extraction

Data abstracted were the year of publication, study design (double or single blind, crossover or parallel), rating scales, duration of the study, sample characteristics, sample

size, severity scores, and response rates. In addition, the incidence of any side-effects was also recorded.

4.2.4 Statistical analysis

Improvement in severity of illness is the outcome measure commonly reported in the assessment of lithium efficacy studies in acute mania. Various symptom rating scales have been used for measuring severity and/or presence of psychiatric symptoms (Poolsup *et al.* 1999). The Brief Psychiatric Rating Scale (BPRS) was the most widely used metric scale while the Clinical Global Impression (CGI) was the most widely used global scale.

The effect of each treatment was calculated as the reduction in the severity scores from baseline to final assessment. The mean difference in effect (d_i) between lithium and control treatment was then estimated. Standard errors were abstracted from the individual studies if provided. When the standard errors or standard deviations and sample sizes were not provided or the calculation based on the data reported was not possible, the pooled interstudy standard error from studies reporting variances was used for imputation.

Pooled standard deviations between lithium and control treatment were calculated first, and the standard error of the difference was then obtained from this pooled estimate. The inverse of the squared standard error of the difference in response between lithium and control treatment was used as the weight (w_i). The same approach was applied for both the BPRS and the CGI. The estimation of the pooled effect difference (d) between

lithium and control treatments was calculated by the following formula (Zhang & Li Wan Po 1996).

$$d = \Sigma(w_i d_i)/ \Sigma w_i \qquad i = 1, 2, 3, ..., k$$

Efficacy was also estimated in the form of the response rate ratio. This is defined as the ratio of the proportion of patients with marked improvement or remission during the observation period in the treatment group relative to the control group. The incidence of adverse effects was compared using rate ratio. The individual rate ratio and rate difference were calculated as described in Rothman (1986).

In the pooling of rate ratios, the individual log rate ratio weighted by the inverse of the variance was used. The 95% confidence intervals of the pooled estimates were calculated as described by Whitehead and Whitehead (1991). The number needed to treat was calculated from the pooled rate difference (Cook & Sackett 1995). A random effects model was used where the results were heterogeneous on the basis of the Q-statistic for heterogeneity at the 0.05 level of significance (DerSimonian & Laird 1986).

4.3 Results

4.3.1 Study characteristics

The trial flow is summarised in Figure 4.1. Twenty two trials (Schou *et al.* 1954, Maggs 1963, Johnson *et al.* 1968, 1971, Spring *et al.* 1970, Platman 1970, Prien *et al.* 1972b,

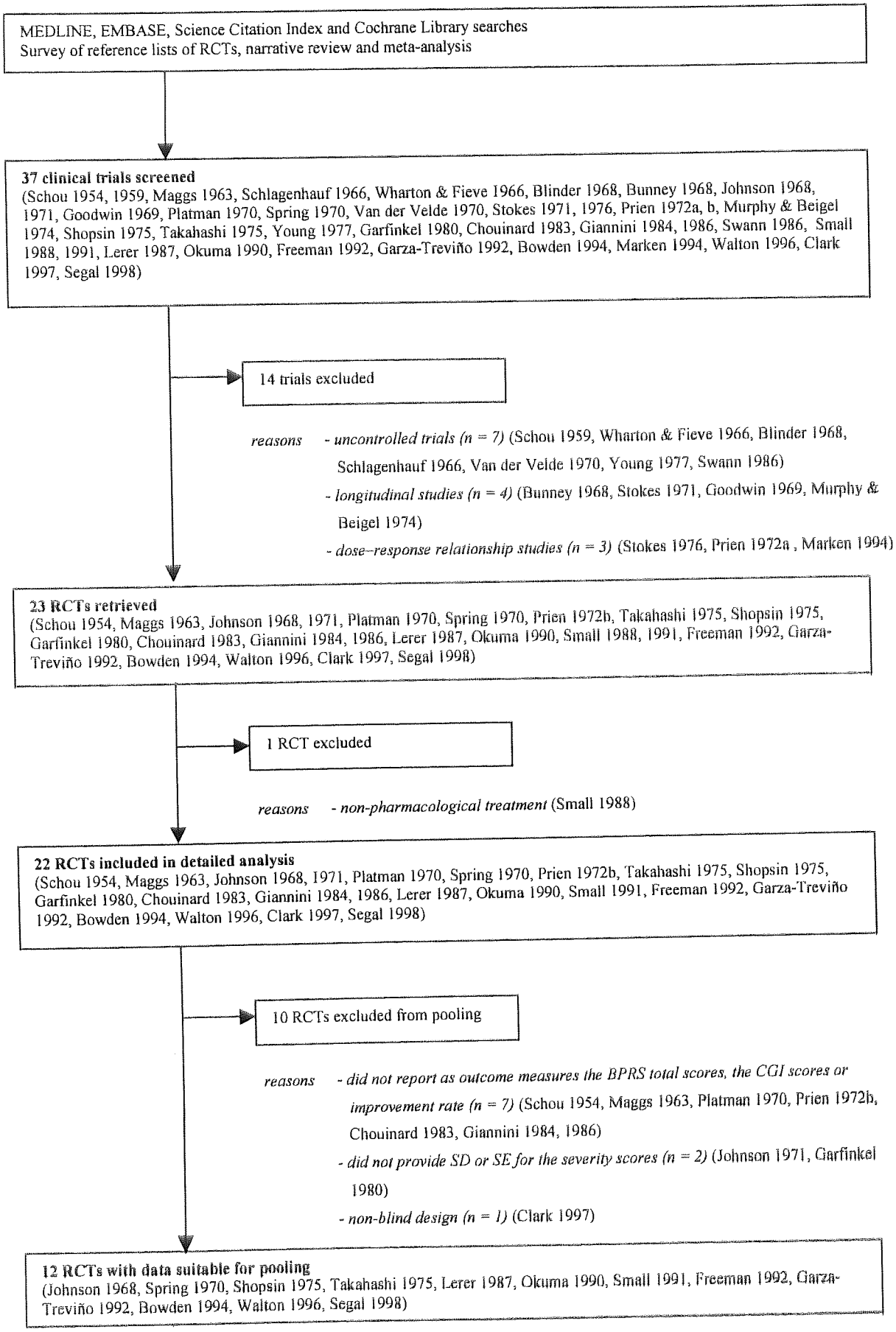

Figure 4.1 Summary of trial flow. References in brackets.

Shopsin *et al.* 1975, Takahashi *et al.* 1975, Garfinkel *et al.* 1980, Chouinard *et al.* 1983, Giannini *et al.* 1984, 1986, Lerer *et al.* 1987, Okuma *et al.* 1990, Small *et al.* 1991, Freeman *et al.* 1992, Garza-Treviño *et al.* 1992, Bowden *et al.* 1994, Walton *et al.* 1996, Clark *et al.* 1997, Segal *et al.* 1998) were subjected to detailed analysis as they met the first level inclusion criteria. Two (Schou *et al.* 1954, Maggs 1963) were comparisons with placebo only. Twenty trials (Johnson *et al.* 1968, 1971, Spring *et al.* 1970, Platman 1970, Prien *et al.* 1972b, Shopsin *et al.* 1975, Takahashi *et al.* 1975, Garfinkel *et al.* 1980, Chouinard *et al.* 1983, Giannini *et al.* 1984, 1986, Lerer *et al.* 1987, Okuma *et al.* 1990, Small *et al.* 1991, Freeman *et al.* 1992, Garza-Treviño *et al.* 1992, Bowden *et al.* 1994, Walton *et al.* 1996, Clark *et al.* 1997, Segal *et al.* 1998) included at least one active control arm. Of those, one (Bowden *et al.* 1994) also contained a placebo arm. The details of the studies and their assessment measures are presented in Table 4.1.

Twelve trials reported data suitable for pooling (Johnson *et al.* 1968, Spring *et al.* 1970, Shopsin *et al.* 1975, Takahashi *et al.* 1975, Lerer *et al.* 1987, Okuma *et al.* 1990, Small *et al.* 1991, Freeman *et al.* 1992, Garza-Treviño *et al.* 1992, Walton *et al.* 1996, Bowden *et al.* 1994, Segal *et al.* 1998) and their characteristics are summarised in Tables 4.2 and 4.3. Table 4.4 lists trials which included outcome measures other than response rate, BPRS score or CGI score, or which had design features which made them unsuitable for direct comparisons with the 12 trials identified above.

Not all the trials reporting values for the reduction in severity scores also reported improvement response rates for efficacy. Therefore, the trials included in different analyses do not necessarily match. The detailed definitions of response rate among different trials are listed in Table 4.5.

Table 4.1 Clinical trials of lithium in acute mania and their assessment measures

Trial	Duration (weeks)	Design	N	Assessment measures																
				BPRS	BMS	CGI	CPRG-M	GAF	GAS	GIS	GSM	MRS	MS	PEF	PS	SCI	SDMS	SADS-C mania	TRAM	TS	WS
Two-armed trials																					
Lithium v placebo																					
Schou 1954	N/R	DB-CO*	38							●											
Mages 1963	6	DB-CO	28																		●
Lithium v chlorpromazine																					
Johnson 1968	3-4	DB-P	29	●						●						●			●		●
Johnson 1971	3	DB-P	21	●						●						●			●		
Platman 1970	3	DB-P	23											●						●	
Spring 1970	3	DB-P	14																		
Prien 1972b	3	DB-P	255	●																	
Takahashi 1975	5	DB-P	80				●			●											
Lithium v carbamazepine																					
Lerer 1987	4	DB-P	34	●		●							●								
Okuma 1990	4	DB-P	105				●			●											
Small 1991	8	DB-P	52	●		●			●	●		●					●				

Table 4.1 Clinical trials of lithium in acute mania and their assessment measures (continued)

Trial	Duration (weeks)	Design	N	Assessment measures																
				BPRS	BMS	CGI	CPRG-M	GAF	GAS	GIS	GSM	MRS	MS	PEF	PS	SCI	SDMS	SADS-C mania	TRAM	TS	WS
Lithium v valproate																					
Freeman 1992	3	DB-P	27	●					●									●			
Lithium v verapamil																					
Gianini 1984	60 days	SB-CO	12	●											●						
Garza-Treviño 1992	4	DB-P	23	●		●															
Walton 1996	4	SB-P	40	●	●	●		●													
Lithium v clonazepam																					
Chouinard 1983	20 days	DB-CO	12								●									●	
Clark 1997	4	open	30	●	●	●		●													
Lithium v clonidine																					
Giannini 1986	60 days	DB-CO	24	●																	
Three-armed trials																					
Lithium v haloperidol v chlorpromazine																					
Shopsin 1975	3	DB-P	30	●		●										●					

Table 4.1 Clinical trials of lithium in acute mania and their assessment measures (continued)

Trial	Duration (weeks)	Design	N	Assessment measures																
				BPRS	BMS	CGI	CPRG-M	GAF	GAS	GIS	GSM	MRS	MS	PEF	PS	SCI	SDMS	SADS-C mania	TRAM	TS	WS
Lithium v haloperidol v lithium-haloperidol combination																				
Garfinkel 1980	3	DB-P	21	●															●	
Lithium v placebo v valproate																				
Bowden 1994	3	DB-P	179						●									●		
Lithium v haloperidol v risperidone																				
Segal 1998	4	DB-P	45	●		●		●				●								

BPRS, Brief Psychiatric Rating Scale; BMS, Bech-Rafaelsen Mania Scale; CGI, Clinical Global Impression; CPRG-M, Clinical Psychopharmacology Research Group rating scale for mania; GAF, Global Assessment of Functioning; GAS, Global Assessment Scale; GIS, global improvement scale; GSM, global severity of mania; MRS, Mania Rating Scale; MS, Manic State Rating Scale; PEF, Psychiatric Evaluation Form; PS, Petterson Scale; SADS-C, Schedule for Affective Disorders and Schizophrenia, change-version; SCI, Structured Clinical Interview; SDMS, Symptoms of Depression and Mania Scale; TRAM, Treatment Response Assessment Method; TS, Target symptom scale; WS, Wittenborn scale

DB-P, double-blind, parallel; DB-CO, double-blind, crossover; N/R, not reported; SB-P, single-blind, parallel; SB-CO, single-blind, cross-over

* For only some patients was the study double-blind

Table 4.2 Study characteristics of 12 randomised-controlled trials of lithium in acute mania

Trial	Design	N	Duration (weeks)	Response rate	Incidence of any side-effects
Two-armed trials					
Lithium v chlorpromazine					
Johnson *et al.*(1968)	DB-P	18 v 11	3-4	14 v 4	Not reported
Spring *et al.*(1970)	DB-P	9 v 5	3	6 v 3	Not reported
Takahashi *et al.* (1975)	DB-P	38 v 42	3	10 v 3	No. of cases of each symptoms
Lithium v verapamil					
Garza-Treviño *et al.* (1992)	DB-P	11 v 12	4	Not reported	3 v 1
Walton *et al.*(1996)	SB-P	19 v 21	4	Not reported	4 v 0
Lithium v carbamazepine					
Lerer *et al.*(1987)	DB-P	19 v 15	4	Not reported	4 v 4
Okuma *et al.*(1990)	DB-P	54 v 51	4	15 v 14	23 v 31
Small *et al.*(1991)	DB-P	27 v 25	4	Not reported	Not reported
Lithium v valproate					
Freeman *et al.* (1992)	DB-P	13 v 14	3	12 v 9	Not reported
Three-armed trials					
Lithium v haloperidol v chlorpromazine					
Shopsin *et al.* (1975)	DB-P	10 v 10 v 10	3	7 v 2 v 1	N/R v 3 v 7
Lithium v valproate v placebo					
Bowden *et al.*(1994)	DB-P	36 v 69 v 74	3	18 v 33 v 19	33 v 58 v 58
Lithium v haloperidol v risperidone					
Segal *et al.* (1998)	DB-P	15 v 15 v 15	4	Not reported	Not reported

DB-P, double-blind, parallel; N/R = not reported; SB-P, single-blind, parallel

Table 4.3 Inclusion and exclusion criteria of 12 randomised-controlled trials

Trial	Inclusion criteria	Exclusion criteria
Two-armed trials		
Lithium v chlorpromazine		
Johnson *et al.* (1968)	- Mayer-Gross criteria for manic-depressive illness, manic phase	Not reported
Spring *et al.* (1970)	- Pure mania - No serious organic illness	Not reported
Takahashi *et al.* (1975)	- Bipolar disorder, manic episode or monopolar mania - First attack of mania without history of depression - Age 13-65 years	- Manic state associated with schizophrenia, organic disorders, oligophrenia, or epilepsy
Lithium v verapamil		
Garza-Treviño *et al.* (1992)	- DSM-III criteria for acute mania - Age 18-65 years	- Pregnancy - Recently treated with depot neuroleptics
Walton *et al.* (1996)	- DSM-IV criteria for acute mania	- Abnormal liver function, thyroid function, haematological findings - Pre-existing cardiac disease - Acute systemic medical disorder - Previous month use of depot antipsychotic - Substance abuse
Lithium v carbamazepine		
Lerer *et al.* (1987)	- DSM-III criteria for bipolar disorder, manic episode - Age 21-65 years - Physically healthy	Not reported
Okuma *et al.* (1990)	- DSM-III criteria for bipolar disorder, manic or mixed episode - Age 13-65 years	- Renal disease, cardiovascular disease, liver disease, haematological disorders - Pregnancy
Small *et al.* (1991)	- DSM-III-R criteria for bipolar disorder, manic or mixed episode - A history of at least one affective episode within previous 2.5 years - Not resistance to lithium or carbamazepine - A score of ≥ 7 on the manic subsection of the Depression and Mania Scale and of ≤ 60 on Global Assessment Scale	- Significant medical problems - Affective episode associated with physical illness - Substance abuse

Table 4.3 Inclusion and exclusion criteria of 12 randomised-controlled trials (continued)

Trial	Inclusion criteria	Exclusion criteria
Lithium v valproate		
Freeman *et al.* (1992)	- DSM-III-R criteria for manic episode	- Abnormal EEG, liver function, thyroid function, haematologic findings - Positive urine drug screen - Focal neurological abnormalities - Drug or alcohol dependence or abuse
Three-armed trials		
Lithium v haloperidol v chlorpromazine		
Shopsin *et al.* (1975)	- Bipolar disorder - Age 21-68 years - Had multiple episodes in the past	- Schizophrenic illness characterological cyclothymia - Brain syndromes, alcoholism, drug addiction, epilepsy, serious medical illness - Pregnancy
Lithium v valproate v placebo		
Bowden *et al.* (1994)	- RDC criteria for mania - Age 18-65 years - Mania Rating Scale scores ≥ 14 with scores ≥ 2 on at least four items - Undetectable serum lithium levels prior to randomisation	- History of severe side-effects from lithium - Prior treatment with divalproex or valproic acid - Schneider first-rank symptoms occurring throughout the day without manic symptoms for several days or intermittently for more than a week - Central nervous system or neuromuscular disorders - Uncontrolled diseases - Drug-induced mania or mania induced by acquired immunodeficiency syndrome - Substance abuse - A positive result on any toxicology screening tests - Concomitant treatment with medications that would confound the results - Pregnancy
Lithium v haloperidol v risperidone		
Segal *et al.* (1998)	- DSM-IV criteria for bipolar disorder, manic episode	- Abnormal liver function, thyroid function, haematologic findings - Last month use of depot neuroleptics - 24 hours use of oral psychotropics - Acute systemic medical disorder - Pre-existing cardiac disease - Psychoactive substance abuse

DSM-III, Diagnostic and Statistical Manual, 3rd edition; DSM-III-R, Diagnostic and Statistical Manual, 3rd edition, revised; DSM-IV, Diagnostic and Statistical Manual, 4th edition; EEG, electroencephalogram; RDC, Research Diagnostic Criteria

Table 4.4 Trials which required separate assessment

Trial	Reasons
Lithium v placebo	
Schou *et al.* (1954)	Assessed efficacy based on total response classified as "+ effect", "possible effect", and "- effect"
Maggs (1963)	Evaluated clinical symptom using Wittenborn scale
Lithium v chlorpromazine	
Platman *et al.* (1970)	Evaluated clinical symptoms using Psychiatric Evaluation Form
Johnson *et al.* (1971)	Did not provide SD or SE for the BPRS scores
Prien *et al.* (1972b)	Classified patients as highly active and mildly active
	Evaluated clinical symptoms based on some of the BPRS items
Lithium v haloperidol	
Garfinkel *et al.* (1980)	Data in lithium group were not available at the end of treatment period
	Not clear whether SD or SE was provided
Lithium v verapamil	
Giannini *et al.* (1984)	12 items of the BPRS were used instead of 18 items
	Did not provide SD or SE
Lithium v clonazepam	
Chouinard *et al.* (1983)	Assessed clinical symptoms using the scale derived from the Inpatient Multidimensional Psychiatric Scale
Clark *et al.* (1997)	Non-blind design
Lithium v clonidine	
Giannini *et al.* (1986)	Reported the mean BPRS item scores instead of total scores

BPRS, Brief Psychiatric Rating Scale; SD, standard deviation; SE, standard error

Table 4.5 Definition of response rate in clinical trials of lithium in acute mania

Trial	Definition
Lithium v placebo	
Bowden *et al.* (1994)	Proportion of patients with marked improvement (at least 50% improvement in SADS-C, mania factor)
Lithium v chlorpromazine	
Johnson *et al.* (1968)	Proportion of patients with complete or nearly complete remission
Spring *et al.* (1970)	Proportion of patients with complete or nearly complete remission
Shopsin *et al.* (1975)	Proportion of patients with remission
Takahashi *et al.* (1975)	Proportion of patients with marked improvement
Lithium v haloperidol	
Shopsin *et al.* (1975)	Proportion of patients with remission
Lithium v carbamazepine	
Okuma *et al.* (1990)	Proportion of patients with marked improvement
Lithium v valproate	
Freeman *et al.* (1992)	Proportion of patients with at least 50% improvement in SADS-C, mania factor
Bowden *et al.* (1994)	Proportion of patients with marked improvement (at least 50% improvement in SADS-C, mania factor)

SADS-C = Schedule for Affective Disorders and Schizophrenia, change version

4.3.2 Lithium versus placebo

Only one placebo-controlled trial reported results which could be transformed to improvement response rate (Bowden *et al.* 1994). Lithium was more effective than placebo, with an estimated positive rate ratio of 1.95 (95% CI 1.17 to 3.23), a rate difference of 0.24 (95% CI 0.05 to 0.43) corresponding to a mean NNT of 5 (Table 4.6, Figure 4.2).

Two other placebo-controlled trials (Schou *et al.* 1954, Maggs 1963) used a cross-over design and did not report the response rate. One reported results in terms of total response to the treatment classified as "+ effect", "possible effect", and "- effect" (Schou *et al.* 1954). 84 % of patients showed "+ effect" or "possible effect" when treated with lithium. The additional study evaluated the clinical symptoms using the Wittenborn scale (Maggs 1963). The severity of mania was reduced significantly during lithium treatment compared to placebo. The mean scores on cluster III (manic states) before and after treatment with lithium were 12.0 and 4.33, respectively after 2 weeks'treatment. The corresponding values for placebo were 16.11 and 11.22.

Lithium was associated with more side-effects than placebo (Table 4.7 and Figure 4.3). The pooled estimate of the risk ratio for adverse effects was 1.17 (95% CI 1.00 to 1.37). The number needed to treat was 8 (95% CI 4 to 334). On average, treating 8 patients with lithium will result in one more patient experiencing a side effect.

Table 4.6 Comparison of response rate with lithium and controls

Trial (ref) (Length of study in weeks)	No of patients (Lithium/Control)	Crude rate		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		Lithium	Control			
Lithium v placebo						
Bowden *et al.* (1994) (3)	36/74	18/36	19/74	1.95† (1.17 to 3.23)	0.24* (0.05 to 0.43)	5 (3 to 20)
Lithium v chlorpromazine						
Spring *et al* (1970) (3)	9/5	6/9	3/5	1.11 (0.47 to 2.60)	0.07 (-0.46 to 0.60)	N/A
Shopsin *et al.* (1975) (3)	10/10	7/10	1/10	7.00* (1.04 to 46.95)	0.60† (0.26 to 0.94)	2 (2 to 4)
Takahashi *et al.* (1975) (3)	38/42	10/38	3/42	3.68* (1.10 to 12.40)	0.19* (0.03 to 0.35)	6 (3 to 32)
Pooled	57/57	23/57	7/57	1.96* (1.02 to 3.77)	0.25† (0.11 to 0.39)	4 (3 to 9)
Johnson *et al.* (1968) (3-4)	18/11	14/18	4/11	2.14 (0.94 to 4.86)	0.41* (0.07 to 0.76)	3 (2 to 15)
Lithium v haloperidol						
Shopsin *et al.* (1975) (3)	10/10	7/10	2/10	3.50 (0.95 to 12.90)	0.50† (0.12 to 0.88)	2 (2 to 9)
Lithium v carbamazepine						
Okuma *et al.* (1990) (4)	54/51	15/54	14/51	1.01 (0.54 to 1.88)	0.003 (-0.17 to 0.17)	N/A
Lithium v valproate						
Freeman *et al.* (1992) (3)	13/14	12/13	9/14	1.44 (0.94 to 2.19)	0.28 (-0.01 to 0.57)	N/A
Bowden *et al.* (1994) (3)	36/69	18/36	33/69	1.05 (0.69 to 1.57)	0.02 (-0.18 to 0.22)	N/A
Pooled	49/83	30/49	42/83	1.22 (0.91 to 1.64)	0.11 (-0.06 to 0.27)	N/A

N/A, not applicable; NNT, number needed to treat; RD, rate difference; RR, rate ratio
* $P < 0.05$
† $P < 0.01$

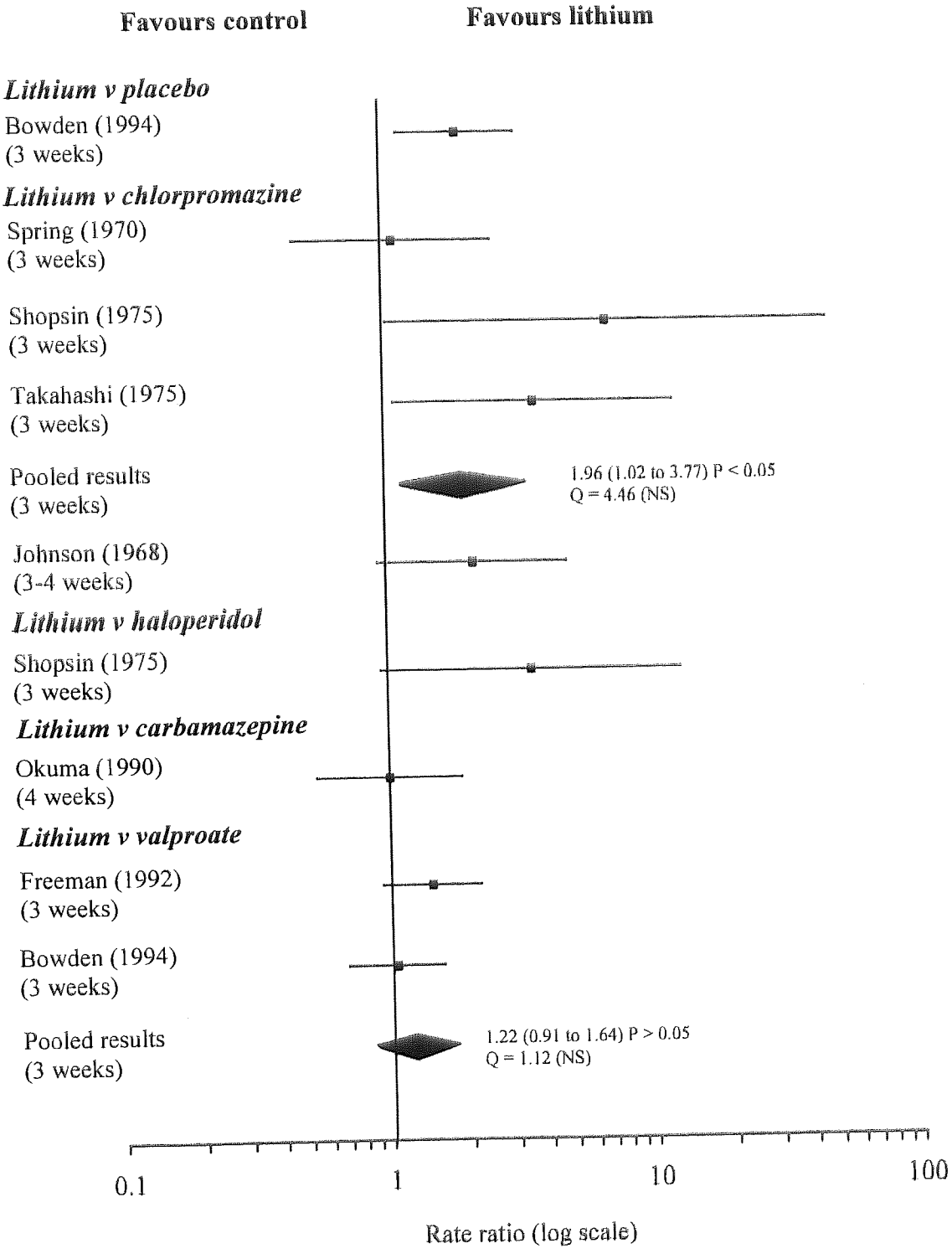

Figure 4.2 Rate ratios (95% confidence interval) for improvement with lithium and controls. Individual rate ratios (—) are shown along with the pooled estimate of effect (◆). Times of assessment shown in brackets.

Table 4.7 Comparison of risk of side-effects with lithium and controls

Trial	No of patients (Lithium/Control)	Crude rate§		RR (95%CI)	RD (95%CI)
		Lithium	Control		
Lithium v placebo					
Bowden *et al.* (1994)	36/74	33/36	58/74	1.17* (1.00 to 1.37)	0.13*† (0.003 to 0.26)
Lithium v carbamazepine					
Lerer *et al.* (1987)	19/15	4/19	4/15	0.79 (0.24 to 2.65)	-0.06 (-0.35 to 0.23)
Okuma *et al.* (1990)	54/51	23/54	31/51	0.70 (0.48 to 1.02)	-0.18 (-0.37 to 0.01)
Pooled	73/66	27/73	35/66	0.71 (0.49 to 1.02)	-0.14 (-0.30 to 0.01)
Lithium v verapamil					
Garza-Treviño *et al.* (1992)	11/12	3/11	1/12	3.27 (0.40 to 27.00)	0.19 (-0.12 to 0.50)
Walton *et al.* (1996)	19/21	4/19	0/21	9.90 (0.57 to 172.59)	0.20* (0.01 to 0.40)
Pooled	30/33	7/30	1/33	4.84 (0.89 to 26.41)	0.20*‡ (0.04 to 0.36)
Lithium v valproate					
Bowden *et al.* (1994)	36/69	33/36	58/69	1.09 (0.95 to 1.26)	0.08 (-0.05 to 0.20)

RD, risk difference; RR, risk ratio
★ $P < 0.05$
† Number needed to treat was 8 (4 to 334)
‡ Number needed to treat was 6 (3 to 28)
§ percentage of patients with any side-effects

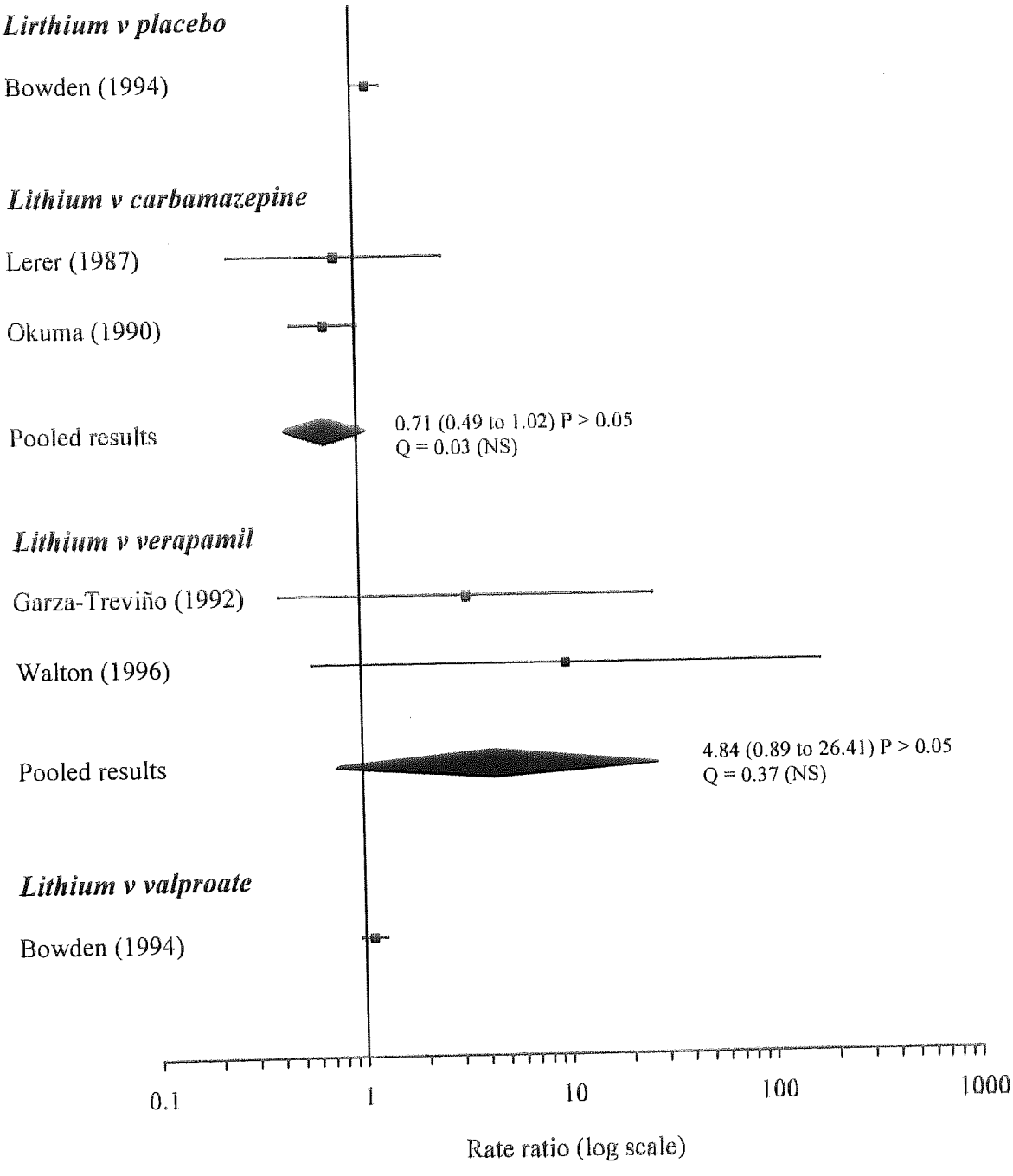

Figure 4.3 Rate ratios (95% confidence interval) for side-effects with lithium and controls. Individual rate ratios (——) are shown along with the pooled estimate of effect (◀▬▶).

4.3.3 Active-controlled trials

Lithium versus chlorpromazine

A total of 143 patients from 4 trials (Johnson *et al.* 1968, Spring *et al.* 1970, Shopsin *et al.* 1975, Takahashi *et al.* 1975) were included in the comparison of lithium versus chlorpromazine. Lithium was more effective than chlorpromazine. The mean number needed to treat was 4 (95% CI 3 to 9). On average, four patients will need to be treated with lithium for one more patient to obtain remission than when they were treated with chlorpromazine [pooled rate ratio 1.96 (95% CI 1.02 to 3.77); Figure 4.2 and Table 4.6].

The two other trials meeting our first level inclusion criteria compared lithium against chlorpromazine in a double-blind manner and reported the change in score on the BPRS as a treatment outcome, but the standard deviations were unobtainable (Johnson *et al.* 1971, Prien *et al.* 1972b) and only some items of the BPRS were used (Prien *et al.* 1972b). Manic patients treated for 3 weeks with lithium appeared to lead greater improvement than those treated with chlorpromazine. The initial mean severity score was 39.92 and the final score was 21.42 in the patients treated with lithium. The corresponding scores were 41.60 and 26.50 in those treated with chlorpromazine (Johnson *et al.* 1971). In Prien and colleagues' study (1972b), manic patients were prospectively classified as highly active or mildly active based on degree of motor activity shown at admission. In highly active patients, chlorpromazine was clearly superior to lithium. Chlorpromazine rapidly controlled manic symptoms, produced significantly fewer drop-outs (8% vs 38%), and was associated with a lower incidence of severe side-effects (18% vs 31%). The difference was less pronounced among mildly

active patients. But lithium appeared to be the better treatment as it produced fewer severe side-effects than chlorpromazine (10% vs 25%)(Prien *et al.* 1972b). The one other trial assessed efficacy based on rating on the Psychiatric Evaluation Form (Platman 1970). Improvement with lithium was better, but not significantly so, than that with chlorpromazine in all measures, i.e. belligerence-negativism, somatic complaints, grandiosity, denial, sleep, and severity of illness.

Lithium versus haloperidol

A total of 50 patients enrolled in the two trials of lithium and haloperidol which provided poolable data with respect to BPRS score. The results were heterogeneous (Figure 4.4). Haloperidol was no better than lithium in reducing manic symptom. The pooled estimate effect was -2.14 (95% CI -6.57 to 2.30) (Table 4.8).

Individual estimates of efficacy expressed as the mean differences in the reduction in the CGI score are shown in Table 4.9 and Figure 4.5. Haloperidol was no better than lithium in reducing the global severity of mania. The pooled estimate effect was 0.19 (95% CI -0.06 to 0.44). The response rate was also not statistically higher with lithium than with haloperidol [rate ratio 3.50 (95% CI 0.95 to 12.90)] (Table 4.6).

One other trial compared lithium versus haloperidol and the combination of lithium and haloperidol, and evaluated the treatment effect based on the BPRS (Garfinkel *et al.* 1980). The results suggested that haloperidol was superior to lithium for treating severe acute mania. The mean scores at baseline and after 2 weeks treatment were 33.95 and 33.14, respectively, in the lithium group compared to 32.98 and 20.04 in the haloperidol

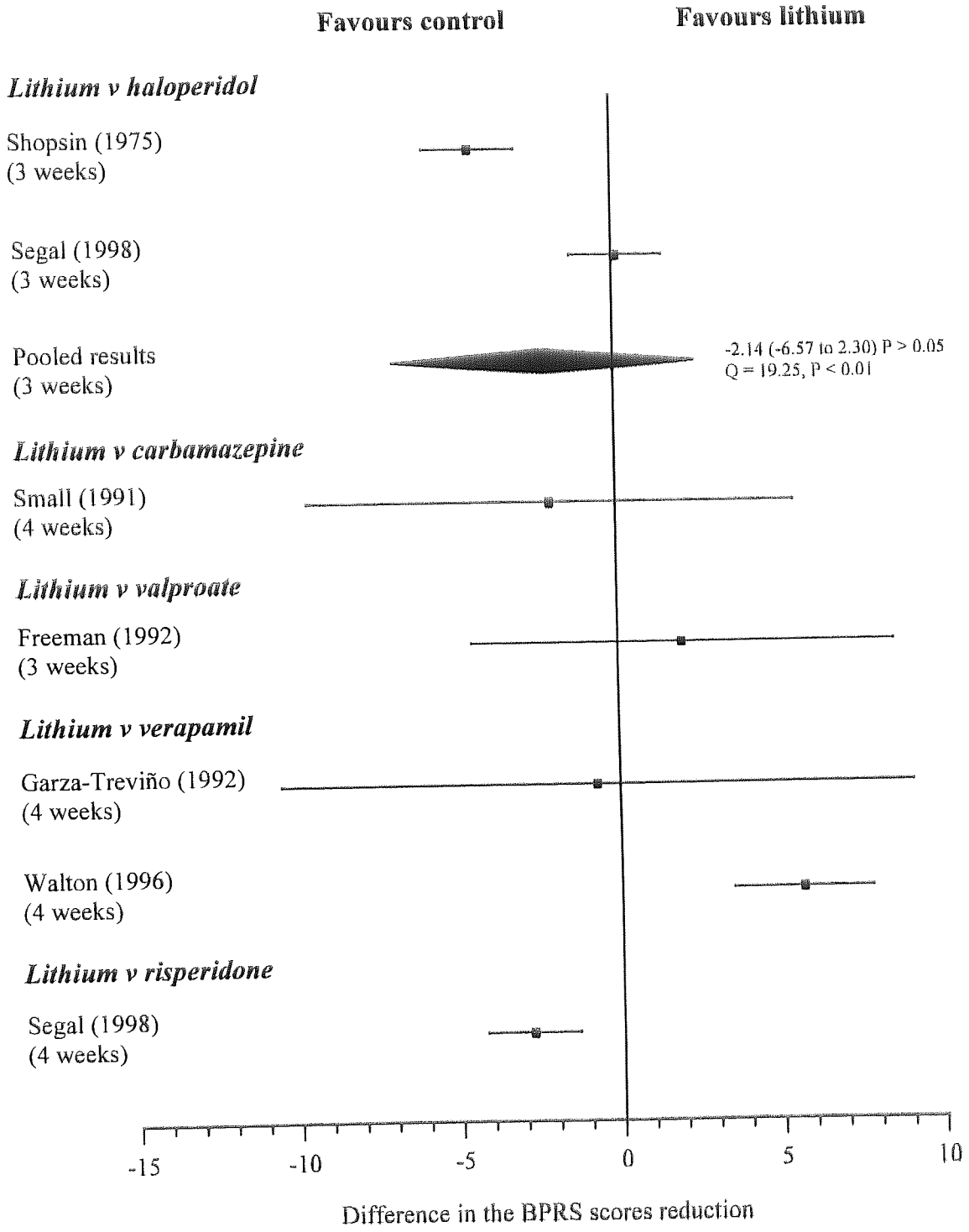

Figure 4.4 Mean difference (95% confidence interval) in the reduction in BPRS score with lithium and controls. Individual rate ratios (——) are shown along with the pooled estimate of effect (◀▬▶). Times of assessment shown in brackets.

Table 4.8 Comparison of the reduction in symptom severity scores with lithium and controls

Trials (ref) (Length of study in weeks)	No of patients (Lithium/Control)	BPRS		
		d	SE	95% CI
Lithium v haloperidol				
Shopsin *et al.* (1975) (3)	10/10	-4.40†	0.73	-5.83 to -2.97
Segal *et al.* (1998) (3)	15/15	0.13	0.73	-1.30 to 1.56
Pooled	25/25	-2.14	2.27	-6.57 to 2.30
Lithium v carbamazepine				
Small *et al.* (1991) (3)	20/23	-2.04	3.85	-9.59 to 5.51
Lithium v valproate				
Freeman *et al.* (1992) (3)	13/14	2.0	3.33	-4.53 to 8.53
Lithium v verapamil				
Garza-Treviño *et al.* (1992) (4)	8/12	-0.72	5.00	-10.52 to 9.08
Walton *et al.* (1996) (4)	18/18	5.65†	1.09	3.51 to 7.79
Lithium v risperidone				
Segal *et al.* (1998) (4)	15/15	-2.79†	0.73	-4.22 to -1.36

BPRS, Brief Psychiatric Rating Scale; CI, confidence interval; d, mean difference in effect between lithium and controls; SE, standard error of d
† $P < 0.01$

Table 4.9 Comparison of the reduction in global severity scores with lithium and controls

Trial (ref) (Length of study in weeks)	No of patients (Lithium/Control)	CGI		
		d	SE	95% CI
Lithium v haloperidol				
Shopsin *et al.* (1975) (3)	10/10	0.40*	0.18	0.05 to 0.75
Segal *et al.* (1998) (3)	15/15	-0.02	0.18	-0.37 to 0.33
Pooled	25/25	0.19	0.13	-0.06 to 0.44
Lithium v carbamazepine				
Lerer *et al.* (1987) (4)	14/14	1.10*	0.46	0.20 to 2.00
Small *et al.* (1991) (4)	20/23	-0.15	0.36	-0.86 to 0.56
Pooled	34/37	0.44	0.62	-0.78 to 1.67
Lithium v verapamil				
Garza-Treviño *et al.* (1992) (4)	8/12	-0.25	0.65	-1.52 to 1.02
Walton *et al.* (1996) (4)	18/18	0.98†	0.17	0.65 to 1.31
Lithium v risperidone				
Segal *et al.* (1998) (4)	15/15	-0.76†	0.18	-1.11 to -0.41

CGI, Clinical Global Impression; CI, confidence interval; d, mean difference in effect between lithium and controls; SE, standard error of d

★ $P < 0.05$

† $P < 0.01$

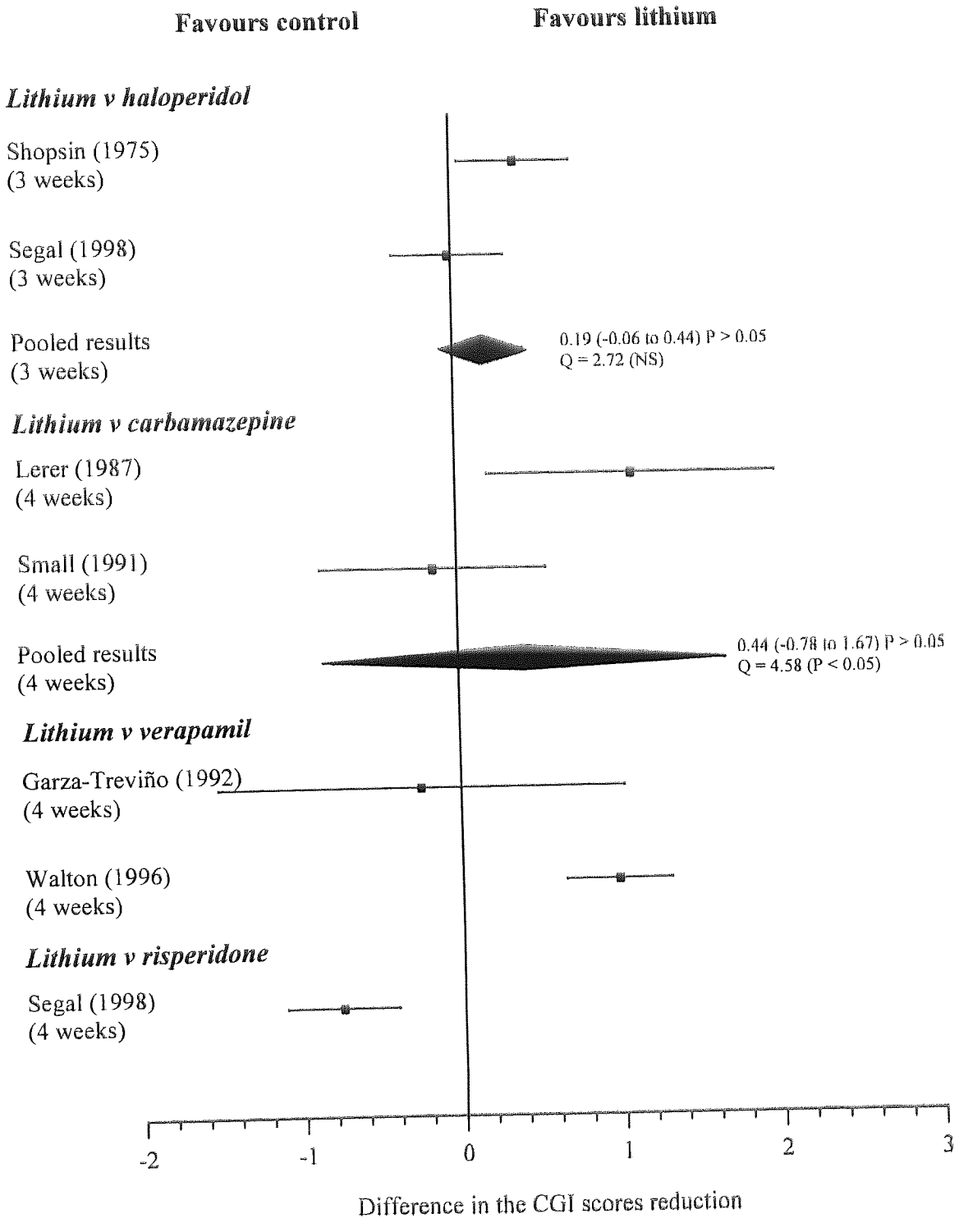

Figure 4.5 Mean difference (95% confidence interval) in the reduction in CGI score with lithium and controls. Individual mean differences (——) are shown along with the pooled estimate of effect (◆). Times of assessment shown in brackets.

group. No week-three data were available for the lithium-treated group because in the words of the investigator "because of the number of drop-outs in this group".

Lithium versus carbamazepine

In the only trial comparing lithium versus carbamazepine and involving 43 patients (Small *et al.* 1991), carbamazepine was no better than lithium. The mean difference in the reduction in BPRS score was -2.04 (95% CI -9.59 to 5.51) (Table 4.8, Figure 4.4). The two trials (Lerer *et al.* 1987, Small *et al.* 1991) of lithium against carbamazepine yielded heterogeneous results with respect to CGI score. Individual estimates of effect are shown in Table 4.9 and Figure 4.5. Carbamazepine was no better than lithium in reducing the global severity of mania. The pooled estimate of effect was 0.44 (95% CI -0.78 to 1.67) (Table 4.9).

Comparison of lithium against carbamazepine using the response rate ratio as a measure of efficacy yielded results which were consistent with those based on the BPRS score (Table 4.6 & 4.8). Carbamazepine was no more effective than lithium as shown by the response rate ratio of 1.01 (95% CI 0.54 to 1.88) and the response rate difference of 0.003 (95% CI -0.17 to 0.17) (Table 4.6, Figure 4.2). The incidence of side-effects was not statistically different with lithium and carbamazepine (Table 4.7, Figure 4.3).

Lithium versus valproate

In the only trial of lithium versus valproate reporting BPRS scores (Freeman *et al.* 1992), valproate was no more effective than lithium as shown by the mean difference

in score of 2.0 (95% CI -4.53 to 8.53) (Table 4.8). Two trials (Freeman *et al.* 1992, Bowden *et al.* 1994) involving132 patients provided response rate data. No significant difference was found between the two agents as shown by the pooled response rate ratio of 1.22 (95% CI 0.91 to 1.64) and the pooled rate difference of 0.11 (95% CI -0.06 to 0.27) (Table 4.6, Figure 4.2). There was no significant difference in the rate of adverse effects between lithium and valproate (Bowden *et al.* 1994). The rate (risk) ratio was 1.09 (95% CI 0.95 to 1.26) and the rate difference was 0.08 (95% CI -0.05 to 0.20) (Table 4.7, Figure 4.3).

Lithium versus verapamil

Two trials compared lithium against verapamil (Garza-Treviño *et al.* 1992, Walton *et al.* 1996). In the only trial using a double-blind design (Garza-Treviño *et al.* 1992), verapamil was no more effective than lithium. The mean difference in the reduction in BPRS score was -0.72 (95% CI -10.52 to 9.08). In a second trial using a single-blind design (Walton *et al.* 1996) lithium was superior to verapamil in reducing the psychiatric symptoms with an estimated difference in reduction in BPRS score of 5.65 (95% CI 3.51 to 7.79) (Table 4.8, Figure 4.4). In the only published and eligible double-blind randomised controlled trial, verapamil was no better than lithium (Garza-Treviño *et al.* 1992). The point estimate for the difference in the reduction of global severity scores was -0.25 (95% CI -1.52 to 1.02) (Garza-Treviño *et al.* 1992). Lithium was superior to verapamil in a further single-blind trial comparing the two drugs with point estimate of 0.98 (95% CI 0.65 to 1.31) (Walton *et al.* 1996) (Figure 4.5). The risk of side-effects was higher with lithium than with verapamil. The pooled risk difference yielded a mean number needed to treat of 6 (95% CI 3 to 28). On average treating 6 patients with

lithium will cause one more patient to complain of a side effect when compared with verapamil.

An additional trial comparing lithium versus verapamil adopted a single-blind cross-over design (Giannini *et al.* 1984). The symptoms were assessed using 12 out of 18 items of the BPRS and the standard deviations or standard errors were unobtainable. The authors reported that no significant differences were seen between lithium and verapamil. The mean BPRS ratings were 19.25 at day 0 and 6.16 at day 30 in verapamil-treated patients and 14.9 and 4.0, respectively, in lithium-treated patients.

Lithium versus risperidone

In the only published randomised controlled trial comparing lithium with risperidone, the estimated difference in reduction in symptom severity score for lithium versus risperidone was -2.79 (95% CI -4.22 to -1.36) in favour of risperidone (Table 4.8, Figure 4.4). The estimated mean reduction in global severity scores also suggested that risperidone was better than lithium [-0.76 (95% CI -1.11 to -0.41)] (Table 4.9, Figure 4.5).

Lithium versus clonazepam

Two reports compared lithium versus clonazepam and met our first inclusion criteria (Chouinard *et al.* 1983, Clark *et al.* 1997). One used double-blind, cross-over design and assessed the symptoms based on the global impression and the scale derived from the Inpatient Multidimensional Psychiatric Scale (Chouinard *et al.* 1983). Clonazepam was

found to be more effective than lithium on two manic symptoms, motor overactivity and logorrhoea, with an overall trend for superiority on the three other symptoms, elevated mood, pressure of speech and insight. The mean score ± SD for item motor overactivity at the beginning of treatment was 5.0 ± 0.07 and the final scores were 1.8 ± 0.09 and 2.8 ± 1.4 after 10 days' treatment with clonazepam and lithium, respectively. The baseline score for item logorrhoea was 5.3 ± 0.8 and reduced to 2.2 ± 1.3 after treatment with clonazepam, and 2.9 ± 1.5 after treatment with lithium (Chouinard *et al.* 1983). The other reported the efficacy using the BRPS and the CGI, but used a non-blind design (Clark *et al.* 1997). There were no significant differences between the two groups at the end of a 4-week treatment period, irrespective of which outcome measure was used. The BPRS mean scores ± SD before and after treatment were 17.93 ± 4.71 and 6.27 ± 7.52 in lithium-treated patients. The corresponding scores were 22.93 ± 5.90 and 7.79 ± 6.89 in the clonazepam group. The CGI mean scores ± SD were 4.73 ± 0.46 and 2.07 ± 1.67 before and after 4 weeks'treatment with lithium, respectively. The corresponding scores were 4.53 ± 0.74 and 2.71 ± 1.68 in the clonazepam group (Clark *et al.* 1997).

Lithium versus clonidine

Only one trial compared lithium against clonidine and used a double-blind, cross-over design (Giannini *et al.* 1986). Lithium-treated patients improved significantly more than those treated with clonidine. The mean BPRS item score before and after treatment with lithium were 1.27 ± 1.02 (SD) and 0.41 ± 0.43, respectively after 30 days'treatment. The corresponding values were 1.17 ± 1.28 and 0.67 ± 0.59 in those treated with clonidine. It is important to note that in this study mean item score rather than total BPRS score was reported for each subject. These individual scores were then used to

calculate group mean score.

4.4 Discussion

A wide range of rating scales have been used in measuring the severity of mania (Table 4.1), hence a variety of outcome measures in assessing the efficacy of lithium. In this meta-analysis, antimanic efficacy was estimated (i) by the difference in the reduction in severity of illness as measured by the BPRS, or the CGI, (ii) by the global response rate ratio. The definition of improvement response rate differed somewhat from trial to trial, but was generally defined as the proportion of patients obtaining marked improvement or remission (Table 4.5), the criterion used in our study. The results of this meta-analysis support the conclusion arrived at by Goodwin and Jamison (1990) and Davis et al (1993) that lithium is an effective antimanic agent.

Pooling of the trials of lithium versus chlorpromazine produced results compatible with those reported by Davis *et al.* (1993) suggesting that lithium is more effective than chlorpromazine. Our findings suggest that neither carbamazepine nor valproate is better than lithium irrespective of which outcome measure was used (Table 4.6 & 4.8). Emilien *et al.* (1996), in their meta-analysis, included lithium trials relating to both acute treatment of mania and prophylaxis of bipolar disorder. They also pooled studies dealing with both carbamazepine and valproate (Emilien *et al.* 1996). Their conclusions that carbamazepine and valproate were no better than lithium were consistent with ours.

The treatment effects of lithium and haloperidol reported in the trials were

heterogeneous. It is possible that the BPRS may not be sensitive enough to capture total psychopathology in some patients. Despite control of some of the psychotic symptoms which are translated into a significant reduction in the BPRS score, control of other symptoms may not be enough for the patients to be rated globally as being in remission. The superiority of risperidone over lithium may be due to its better antipsychotic effect since many patients participating in the trial were psychotic as evidenced by the higher BPRS scores in the published trial (Segal *et al.* 1998) than in other lithium trials.

Lithium was associated with more side-effects than placebo and verapamil, but no more than carbamazepine nor valproate (Table 4.7). Tremor, thirst, drowsiness, fatigue, nausea, and dizziness were frequent problems associated with lithium and carbamazepine, while nausea, vomiting, pain, headache, and dizziness were reported as side-effects of valproate. As adverse events were reported as secondary outcomes, the studies do not have the power to exclude potentially important differences in event rates.

Meta-analysis was difficult due to the inconsistencies in the reported outcome measures used in the trials. Clinical improvement in acute treatment of mania is primarily defined by a decrease in symptom severity or a reduction in global severity using validated rating instruments. Several rating scales were used in the lithium trials (Table 4.1) making it impossible to pool the results of many of the trials into a meaningful statistic, thus suggesting a need for greater consistency in future trials. Luckily, a few trials were consistent in using the BPRS and the CGI. These trials suggest that lithium is an effective agent for the treatment of acute mania.

4.5 Conclusion

Lithium is more effective than placebo and chlorpromazine. Carbamazepine, valproate and verapamil were no better than lithium either in terms of response rate or reduction in severity of illness. Lithium was associated with more acute adverse effects than placebo and verapamil, but no more than carbamazepine nor valproate. It is our view that based on estimates of efficacy, lithium should remain the first line treatment for mania.

Chapter 5

Systematic review of lithium prophylaxis in bipolar disorder

5.1 Introduction

Mood disorders, which can be described as the episodic disturbance in mood, can be divided into unipolar depression (depressive disorders) and bipolar disorder (manic-depressive illness) (Emilien *et al.* 1995). Bipolar disorder is a recurrent illness with the lifetime prevalence of approximately 1%. The onset of symptoms generally starts in late adolescence or early adulthood, although late-age onset may be seen (Mitchell & Parker 1991, Daly 1997). Pharmacological treatment of bipolar disorder involves both the acute treatment of manic and depressive episodes and prophylactic (maintenance) therapy to prevent the recurrence of further episodes.

Lithium has been widely used in the acute treatment of the disease and is often considered to be a prophylactic agent of first choice, although anticonvulsants such as valproate and carbamazepine are increasingly being used as alternatives. Lithium was first introduced in psychiatry over fifty years ago and Cade (1949) was among the first to report on its use in mania. A popular description of personal experience of its use and effects in manic depression is given by Jamison (1996), a psychologist herself, in her acclaimed book. In addition to the claimed reduction in the frequency, severity, and duration of both manic and depressive episodes, long term lithium treatment has been

reported to reduce mortality rates in those with bipolar disorder, mainly from suicide (Jefferson & Greist 1994, Schou 1995, Muller-Oerlinghausen *et al.* 1992). However, about 10% to 20% of patients are reported not to respond to lithium and some do not tolerate it (Schou 1988).

Attempts to establish the prophylactic efficacy of lithium in bipolar disorder have been undertaken in two different ways; placebo-controlled parallel group maintenance study and intra-individual comparison of the course of the disease during control periods and during prophylactic treatment periods of similar lengths (Grof *et al.* 1970). In lithium maintenance studies, treatment response is usually measured in terms of a reduction in number, severity, and duration of episodes (Jefferson & Greist 1994). As many as 70% or more of bipolar patients have been reported to remain free of relapses when maintained on lithium for periods lasting up to 30 months (Goodwin & Jamison 1990). However, more recent uncontrolled naturalistic studies, in which lithium treatment was started in ordinary clinical settings and patients followed up for long periods, suggested a lower level of effectiveness (50%-60%) for lithium (O'Connell *et al.* 1991, Paselow *et al.* 1994, Goldberg *et al.* 1996). This has led to the therapeutic value of lithium being questioned (Moncrieff 1995, 1997) and newer agents being recommended instead.

There appears to be discrepancies in the results of controlled trials of lithium for the prophylaxis of bipolar disorder. Several possible contributory factors include methodological issues (lithium discontinuation trials and parallel/crossover study designs), variability in diagnostic criteria and outcome measures, the degree of assessment of comorbid psychiatric and medical illness, and differences in the severity of illness, duration of follow-up, and compliance (Emilien *et al.*1995, Keck &

McElroy1996). Moncrieff (1995, 1997) in particular has suggested that the randomised trials of lithium have perhaps been invalid.

We therefore undertook a systematic review of trials of lithium in the prophylaxis of bipolar disorder in an attempt to resolve the apparent inconsistencies and to establish the position of lithium in relation to other pharmacotherapies including carbamazepine, valproate, imipramine, and combination treatments.

5.2 Materials and methods

5.2.1 Identification of studies

Reports of randomised controlled trials of lithium were identified through a systematic literature search including searching of MEDLINE covering the period 1966 to end of June 1999, BIDS (EMBASE and Science Citation Index) from 1980 to June 1999, and the Cochrane Library (Issue 1, 1999). We used the terms "lithium", "bipolar disorder", "mood disorder", "prophylaxis" and "clinical trials" as keywords for the electronic searches. The MeSH terms automatically included "manic-depression", "bipolar affective disorder" and "affective disorder". The reference lists of randomised controlled trials and of narrative and systematic reviews of lithium retrieved through the computer searches were also scanned to identify possible systematic reviews and randomised controlled trials.

5.2.2 Inclusion and exclusion criteria

We used a two-tiered inclusion strategy. At the first level, the only inclusion criteria were that the study had to be a randomised controlled trial dealing with the use of lithium as a prophylactic in bipolar disorder. At the second level, studies were excluded from the statistical pooling if they (a) used a non-double-blind design; (b) did not provide efficacy data in terms of relapse rates; (c) admitted patients other than those with bipolar disorder making abstracting of data specific to bipolar patients impossible. When there were more than one publication based on the same group of patients, the publication with the more comprehensive and relevant data was used as the primary source. Specific exclusions and inclusions are described in detail in the text. Studies not included in the meta-analysis but thought to be of significance in an overall assessment of lithium as a prophylaxis in bipolar disorder were identified for qualitative assessments. The two-tiered approach enabled us to use data, which contribute to the evidence-base but are not homogeneous enough to be included in statistical pooling.

5.2.3 Data extraction

Data were extracted on the year of publication, study design (double or single blind, crossover or parallel, prospective or discontinuation), duration of the study, sample characteristics, sample size, and drop out and relapse rates. In addition, the incidence of any side-effects was also recorded.

5.2.4 Statistical analysis

Relapse is the outcome measure most commonly used in the assessment of lithium in prophylactic efficacy studies in bipolar disorder. The definition of relapse is slightly different from trial to trial. Typically, it refers to the occurrence of manic or depressive episodes requiring supplementary drug treatment or hospital admission.

Efficacy was estimated using relapse risk ratio, defined as the proportion of patients relapsing in the treatment group relative to the control group, and risk difference. Adverse effects were also estimated with rate ratio and rate difference. Individual risk ratios and risk differences were estimated as described by Rothman (1986). The number needed to treat was calculated as the inverse of the pooled risk difference. In the pooling of risk ratio and risk difference as well as the estimation of 95% confidence interval, the inverse variance method was used (DerSimonian & Laird 1986, Whitehead & Whitehead 1991). A random effects model was used where the results were heterogeneous on the basis of the Q-statistic for heterogeneity (DerSimonian & Laird 1986), and there was no clinical basis for inferring heterogeneity in patient population studied or trial design.

5.3 Results

5.3.1 Study characteristics

29 trials (Basstrup *et al.* 1970, Melia 1970, Coppen *et al.* 1971, 1976, Cundall *et al.* 1972, Prien *et al.* 1973a, b, 1984, 1988, Stallone *et al.* 1973, Dunner *et al.* 1976, Ahlfors

et al. 1981, Dunner & Stallone 1982, Fieve *et al.* 1976a, b, Quitkin *et al.* 1978, 1979, 1981a, b, Kane *et al.* 1981, 1982, Placidi *et al.* 1986, Watkins *et al.* 1987, Lusznat *et al.* 1988, Simhandl *et al.* 1993, Coxhead *et al.* 1997, Greil *et al.* 1997, Solomon *et al.* 1997, Denicoff *et al.* 1997) (Table 5.1) were included for detailed analysis. Ten (Basstrup *et al.* 1970, Melia 1970, Coppen *et al.* 1971, Cundall *et al.* 1972, Prien *et al.* 1973a, Stallone *et al.* 1973, Dunner *et al.* 1976, Dunner & Stallone 1982, Fieve *et al.* 1976a, b) were comparisons with placebo only. Nineteen trials (Prien *et al.* 1973b, 1984, 1988, Coppen *et al.* 1976, Quitkin *et al.* 1978, 1979, 1981a, b, Ahlfors *et al.* 1981, Kane *et al.* 1981, 1982, Placidi *et al.* 1986, Watkins *et al.* 1987, Lusznat *et al.* 1988, Simhandl *et al.* 1993, Coxhead *et al.* 1997, Greil *et al.* 1997, Solomon *et al.* 1997, Denicoff *et al.* 1997) included at least one active control arm. Of those, five (Prien *et al.* 1973b, Quitkin *et al.* 1978, 1979, 1981b, Kane *et al.* 1982) also contained a placebo arm. The study characteristics and treatment outcomes are summarised in Table 5.1.

13 trials gave relapse data suitable for the statistical pooling (Baastrup *et al.* 1970, Melia 1970, Cundall *et al.* 1972, Prien *et al.* 1973b, 1984, Stallone *et al.* 1973, Fieve *et al.* 1976a, Quitkin *et al.* 1981a, Kane *et al.* 1982, Placidi *et al.* 1986, Luzsnat *et al.* 1988, Coxhead *et al.* 1992, Solomon *et al.* 1997). Characteristics of these trials are presented in Table 5.2 & 5.3 and the reported definition of relapse in Table 5.4. Table 5.5 lists trials which included outcome measures other than risk of relapse or which had design features which make them unsuitable for direct comparisons with the 13 trials identified above.

Table 5.1 Study characteristics and treatment outcomes of randomised-controlled trials of lithium prophylaxis in bipolar disorder

Trial	Design	N	Duration (month)	Outcome							
				%time spent in hospital	%time spent with outpatient episode	% time ill	time in remission	occurrence of episodes (no. of patients with episode)	mean no. of episodes/ patient year	mean no. of episodes/ year	affective morbidity index
Placebo-controlled trials											
Baastrup 1970	DB-P	50	5					●			
Melia 1970	DB-P	14	24				●	●			
Coppen 1971	DB-P	65	24	●	●						
Cundall 1972	DB-CO	13	12					●			
Prien 1973a	SB-P	205	24					●			
Stallone 1973	DB-P	52	mean 15				●	●	●		
Dunner 1976, 1982	DB-P	38	mean 29						●		
Fieve 1976a, b	DB-P	18	mean 25					●	●		
Active-controlled trials, two-armed											
Lithium v lithium-imipramine combination											
Quitkin 1981a, Kane 1981	DB-P	44	24					●			
Lithium v lithium-divalproate combination											
Solomon 1997	DB-P	12	12					●			

Table 5.1 Study characteristics and treatment outcomes of randomised-controlled trials of lithium prophylaxis in bipolar disorder (continued)

Trial	Design	N	Duration (month)	Outcome							
				% time spent in hospital	% time spent with outpatient episode	% time ill	time in remission	occurrence of episodes (no. of patients with episodes)	mean no. of episodes/ patient year	mean no. of episodes/ year	affective morbidity index
Lithium v maprotiline											
Coppen 1976*	DB-P	39	12								●
Lithium v flupenthixol											
Ahlfors 1981*	Open	81	mean 16			●			●		
Lithium v carbamazepine											
Placidi 1986†	DB-P	83	34					●			
Watkins 1987*	DB-P	52	mean 18				●				
Lusznat 1988†	DB-P	54	12					●			
Simhandl 1993*	Open	84	24					●		●	
Coxhead 1992	DB-P	31	12					●			●
Greil 1997	Open	144	30					●			●
Active-controlled trials, three-armed											
Lithium v imipramine v placebo											
Prien 1973b	DB-P	44	24					●			
Lithium v imipramine v lithium-imipramine combination											
Prien 1984, 1988	DB-P	114	24					●			

Table 5.1 Study characteristics and treatment outcomes of randomised-controlled trials of lithium prophylaxis in bipolar disorder (continued)

Trial	Design	N	Duration (month)	Outcome							
				% time spent in hospital	% time spent with outpatient episode	% time ill	time in remission	occurrence of episodes (no. of patients with episodes)	mean no. of episodes/ patient year	mean no. of episodes/ year	affective morbidity index
Lithium v carbamazepine v lithium-carbamazepine combination											
Denicoff 1997	DB-CO	52	36			●				●	
Active-controlled trials, four-armed											
Lithium v imipramine v lithium-imipramine combination v placebo											
Quitkin 1978, 1979, 1981b	DB-P	22	mean 11					●			
Kane 1982											

DB-CO, double-blind, cross-over; DB-P, double-blind, parallel; SB-P, single-blind, parallel
Bolds for trials from which data were extracted
★ Included unipolar patients
† Included major recurrent depressive, schizoaffective, and schizophreniform patients
✦ Included schizoaffective patients

Table 5.2 Study characteristics of 13 randomised controlled trials of lithium in bipolar disorder

Trial	Design	Duration in months	Side-effects profiles
Two-armed trials			
Lithium v placebo			
Baastrup *et al.* (1970)	DB-P Discontinuation	5	Not reported
Melia (1970)	DB-P Discontinuation	24	Not reported
Cundall *et al.* (1972)	DB-CO Discontinuation	12	Not reported
Stallone *et al.* (1973)	DB-P Discontinuation design in some subjects	mean 15*	Not reported
Fieve *et al.* (1976a)	DB-P	mean 25*	Not reported
Lithium v lithium-imipramine combination			
Quitkin *et al.* (1981a)	DB-P	mean 19	Not reported
Lithium v carbamazepine			
Placidi *et al.* (1986)	DB-P	34	Number of cases of each symptom
Lusznat *et al.* (1988)	DB-P	12	Not reported
Coxhead *et al.* (1992)	DB-P Discontinuation	12	Side-effects checklist; Li = 14/16 CBZ = 12/15
Lithium v lithium-divalproate combination			
Solomon *et al.* (1997)	DB-P	12	Treatment Emergent Symptom Scale Li = 3/7 Li+ (divalproate) = 5/5
Three-armed trials *(Li, IMP, Li+IMP or P)*			
Prien *et al.* (1973b)	DB-P	24	Not reported
Prien *et al.* (1984)	DB-P	24	Li = 34/42 IMP = 22/36 Li+IMP = 34/36
Four-armed trial *(Li, IMP, Li+IMP, P)*			
Kane *et al.* (1982)	DB-P	mean 11	Not reported

CBZ, carbamazepine; DB-CO, double-blind, crossover; DB-P, double-blind, parallel; IMP, imipramine; Li, lithium; P, placebo
Discontinuation: patients on lithium prophylaxis for some time before randomisation
*Patients entered the study at different time points

Table 5.3 Inclusion and exclusion criteria of 13 randomised controlled trials

Trial	Inclusion criteria	Exclusion criteria
Two-armed trials		
Lithium v placebo		
Baastrup *et al.* (1970)	- Manic-depressive disorder - On lithium ≥ 1 year	- Recurrent mania* - Schizoaffective
Melia (1970)	- ICD criteria for manic-depressive, bipolar type - Normothymia , no single period > 9 months in 2 years before starting lithium	- Schizophrenic symptoms, when normothymic - Alcoholism or drug addiction
Cundall *et al.* (1972)	- Manic-depressive disorder - On lithium 1-3 years	- Not reported
Stallone *et al.* (1973)	- Manic-depressive disorder - At least 2-weeks' duration 3 previous episodes, at least one was manic	- Schizoaffective
Fieve *et al* (1976a)	- Feighner criteria for primary affective disorder (depression with hypomania) - At least 2 episodes in previous 2 years	- Not reported
Lithium v lithium-imipramine combination		
Quitkin *et al.* (1981a)	- RDC for bipolar I disorder - Euthymic ≥ 6 weeks on lithium - Age 18-65 years	- Medical illness
Lithium v carbamazepine		
Placidi *et al.* (1986)	- In previous 3 years, experiencing at least 2 major affective, schizoaffective, or schizophreniform episodes as defined by DSM-III	- Not reported
Lusznat *et al.* (1988)	- Mania or hypomania at the time of admission - DSM-III for bipolar or schizoaffective disorder - Age 17-64 years	- Pregnancy - Sensitivity to carbamazepine or lithium - Medical condition contra-indicating carbamazepine or lithium therapy
Coxhead *et al.* (1992)	- DSM-III for bipolar disorder - On no other psychotropic medication	- Medical condition contra-indicating carbamazepine or lithium therapy

Table 5.3 Inclusion and exclusion criteria of 13 randomised controlled trials (continued)

Trial	Inclusion criteria	Exclusion criteria
Lithium v lithium-divalproate combination		
Solomon *et al.* (1997)	- Current episode of mania or major depression and diagnosis of bipolar I disorder (DSM-III-R) - History of at least one prior mood episode in the previous 3 years - Age 18-65 years	- Treatment of acute episode with valproate or carbamazepine - Contraindication to lithium or divalproex sodium - Terminal illness, mental retardation or encephalopathy - Presence of focal neurologic signs on physical examination - History of seizure or paroxysmal activity on EEG within the past 2 years - Structural brain damage - Pregnancy, lactating, or inadequate contraception if sexually active
Three-armed trials *(Li, IMP, Li+IMP or P)*		
Prien *et al.* (1973b)	- Bipolar disorder - Under 60 years - At least one episode requiring hospitalisation in previous 2 years and two episodes requiring hospitalisation in previous 5 years - On stable maintenance dose of lithium or imipramine	- Schizophrenia - Schizoaffective - Organic brain syndrome - History of cardiovascular, adrenocortical disease, renal disease, or hypothyroidism
Prien *et al.* (1984)	- RDC for bipolar I disorder - At least one episode in previous 2.5 year - Age between 21 and 60 years - On stable maintenance doses of lithium and imipramine for 2 months - GAS score > 60 - RSDM total depression score and a total mania score < 7	- Medical illness precluding use of lithium or imipramine - Other psychiatric illness
Four-armed trial *(LI, IMP, Li+IMP, P)*		
Kane *et al.* (1982)	- RDC for bipolar II disorder - At least two episodes in previous 7 years - Euthymic for 6 months - Age 18-65 years	- Medical illness

DSM-III, Diagnostic and Statistical Manual (3rd ed.); DSM-III-R, Diagnostic and Statistical Manual (3rd ed.-revised); EEG, electroencephalogram; GAS, Global Assessement Scale; ICD, International Classification of Disease; RDC, Research Diagnostic Criteria, RSDM, Raskin Severity of Depression and Mania Scale

* Recurrent not defined

Table 5.4 Definition of relapse in clinical trials of lithium in bipolar disorder

Trial	Definition
Lithium v placebo	
Baastrup *et al.* (1970)	Mania or depression requiring hospitalisation or supplementary drugs
Melia (1970)	Mania or depression requiring hospitalisation
Cundall *et al.* (1972)	Mania or depression requiring hospitalisation or supplementary drugs
Stallone *et al.* (1973)	Mania or depression requiring supplementary drugs
Fieve *et al.* (1976a)	Mania or depression requiring supplementary drugs
Lithium v lithium-imipramine combination	
Quitkin *et al.* (1981a)	Episode meeting RDC criteria for major depressive disorder or hypomania for 1 week, minor depressive disorder for 4 weeks, or mania regardless of duration
Lithium v carbamazepine	
Placidi *et al.* (1986)	Mania or depression requiring hospitalisation
Lusznat *et al.* (1988)	Mania or depression requiring hospitalisation
Coxhead *et al.* (1992)	No definition provided
Lithium v lithium-divalproate combination	
Solomon *et al.* (1997)	Definite mood episode meeting DSM-III-R criteria
Lithium v imipramine v placebo	
Prien *et al.* (1973b)	Mania or depression requiring hospitalisation or supplementary drugs
Lithium v imipramine v lithium-imipramine combination	
Prien *et al.* (1984)	Mania or depression meeting RDC and GAS scores of 60 or less
Lithium v imipramine v lithium-imipramine combination v placebo	
Kane *et al.* (1982)	Episode meeting RDC criteria for major depressive disorder or hypomania for 1 week, minor depressive disorder for 4 weeks, or mania regardless of duration

DSM-III-R, Diagnostic and Statistical Manual, 3rd ed.-revised; GAS, Global Assessment Scale; RDC, Research Diagnostic Criteria,

Table 5.5 Trials which required separate assessment

Trial	Reasons
Lithium v placebo	
Coppen *et al.* (1971)	Assessed prophylactic efficacy based on length and severity of episodes
Prien *et al* (1973a)	Single-blind design
Dunner *et al.* (1976, 1982)	Reported results in terms of mean number of episodes per patients year
Lithium v maprotiline	
Coppen *et al.* (1976)	Reported affective morbidity as an outcome
	Included unipolar patients
Lithium v flupenthixol decanoate	
Ahlfors *et al.* (1981)	Reported results in terms of mean number of episodes per patient per year and per cent time the patients was ill
	Non-blind design
	Included unipolar patients
Lithium v carbamazepine	
Watkins *et al.* (1987)	Assessed prophylactic efficacy based on time in remission period
	Included unipolar patients
Simhandl *et al.* (1993)	Non-blind design
	Included unipolar patients
Greil *et al.* (1997)	Non-blind design
Lithium v carbamazepine v lithium-carbamazepine combination	
Denicoff *et al.* (1997)	Assessed prophylactic efficacy based on number and severity of episodes

5.3.2 Lithium versus placebo

Risk of relapse

A total of 202 patients from 7 trials were included in the comparison of lithium versus placebo. Lithium was superior to placebo (Table 5.6, Figure 5.1). Individual estimates of efficacy expressed as the risk ratios are shown in Figure 5.1. Only trials of the same lengths (24 months) (Melia 1970, Prein *et al.* 1973b) were pooled. For those trials, the pooled risk ratio of patients relapsing was 0.47 (95% CI 0.26 to 0.86). The risk difference yielded a mean number needed to treat of 3. On average, treating 3 patients will prevent one more patient from relapse when receiving lithium rather than placebo. The relapse rates at the different time points reported in the other trials also showed that lithium was more effective than placebo although this did not reach statistical significance at the 5% level for two of the trials (Kane *et al.* 1982, Fieve *et al.* 1976a).

The other placebo-controlled studies (Coppen *et al.* 1971) reported results in terms of length and severity of episodes rather than the number of patients who relapsed over the study period. The percentage of time the patients on lithium spent in an affective episode was less than did patients on placebo (16.7% v 56.7%, $p < 0.001$). A further two trials reported the occurrence of hypomanic and depressive episodes separately and reported the results as mean number of episodes per patient year (Dunner *et al.* 1976, Dunner & Stallone 1982). The mean rate of hypomanic episodes for patients receiving lithium did not differ from those receiving placebo (0.00 v 0.12 episodes per patient-year). Depressive episodes were fewer in the lithium group than in the placebo group (0.19 v 0.45 episodes per patient-year, $p < 0.05$) (Dunner *et al.* 1976, Dunner & Stallone

Table 5.6 Comparison of risk of relapse with lithium and placebo

Trial (ref) (Length of study in months)	No of patients (Lithium/Placebo)	Crude rate		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		Lithium	Placebo			
Melia (1970) (24)	6/8	3/6	6/8	0.67 (0.27 to 1.63)	-0.25 (-0.75 to 0.25)	N/A
Prien *et al.* (1973b) (24)	18/13	5/18	10/13	0.36★ (0.16 to 0.81)	-0.49† (-0.80 to -0.18)	3 (2 to 6)
Pooled	24/21	8/24	16/21	0.47★ (0.26 to 0.86)	-0.42† (-0.69 to -0.16)	3 (2 to 7)
Baastrup *et al.*(1970) (5)	28/22	0/28	12/22	0.03★ (0.002 to 0.51)	-0.53† (-0.74 to -0.32)	2 (1 to 3)
Kane *et al.* (1982) (11)	4/7	1/4	5/7	0.35 (0.06 to 2.04)	-0.46 (-1.00 to 0.08)	N/A
Cundall *et al.* (1972) (12)	13/13	4/13	10/13	0.40★ (0.17 to 0.95)	-0.46† (-0.80 to -0.12)	2 (1 to 8)
Stallone *et al.* (1973) (15)	25/27	11/25	25/27	0.48† (0.30 to 0.75)	-0.49† (-0.70 to -0.27)	2 (1 to 8)
Fieve *et al.* (1976a) (25)	7/11	4/7	8/11	0.78 (0.38 to 1.64)	-0.16 (-0.61 to 0.30)	N/A

CI, confidence interval; N/A, not applicable; NNT, number needed to treat; RD, risk difference; RR, risk ratio
★ $P < 0.05$
† $P < 0.01$

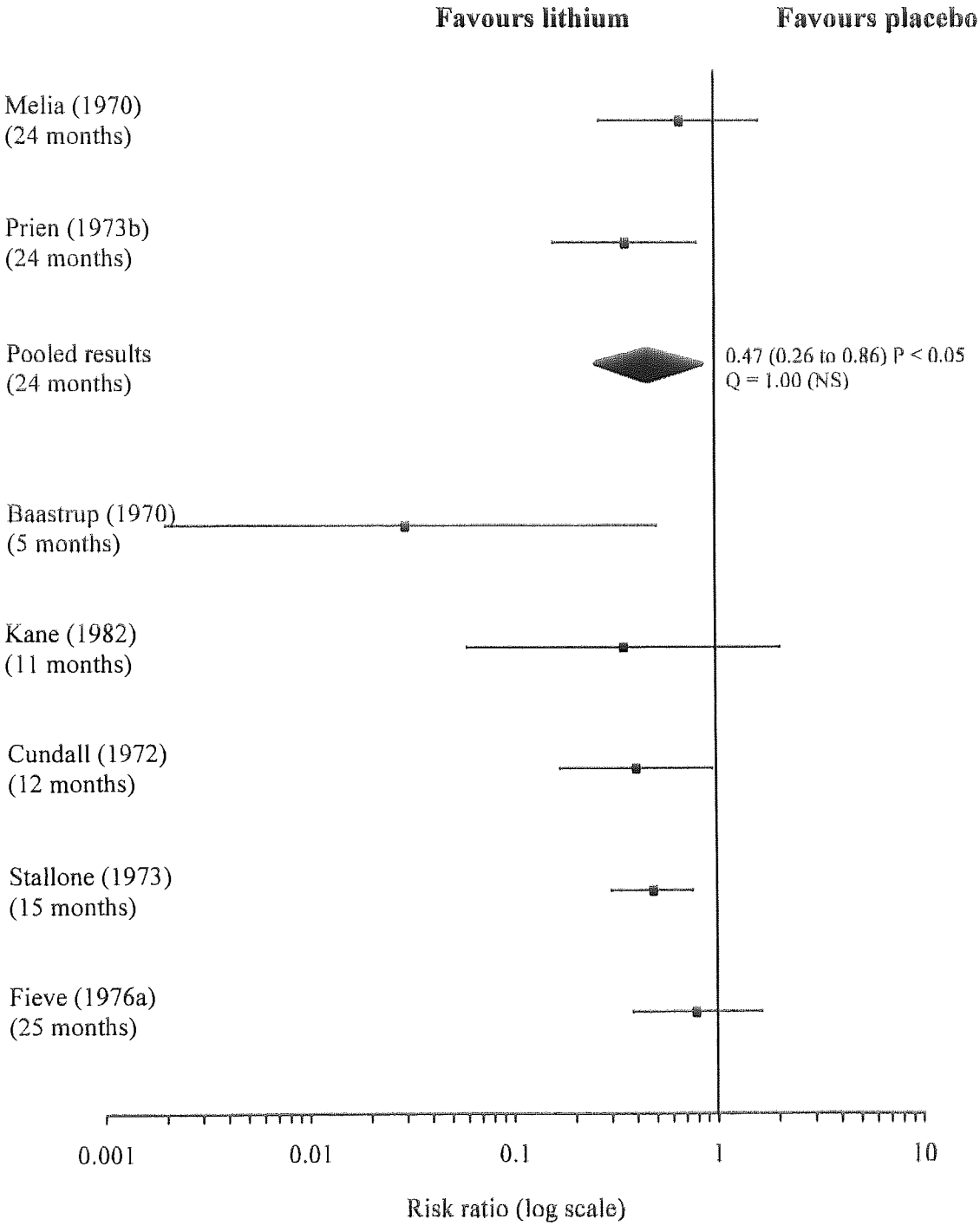

Figure 5.1 Risk ratios (95% confidence interval) for relapse with lithium and placebo. Individual risk ratios (——) are shown along with the pooled estimate of effect (◆). Times shown in brackets.

1982).

Risk of drop-out

Comparison of drop-out rates as a surrogate for lack of efficacy showed that more patients withdrew from the placebo group than did the patients treated with lithium (Table 5.7, Figure 5.2). The mean risk difference was in favour of lithium in the trials of at least 15 months (Prien *et al.* 1973b, Stallone *et al.* 1973, Fieve *et al.* 1976a). Different result was obtained in the other trials (Kane *et al.* 1982) although this failed to reach statistical significance at the 5% level. One of the trials used a cross-over design and there was no difference in drop-out rates (Cundall *et al.* 1972).

5.3.3 Active-controlled trials

Risk of relapse

Lithium versus imipramine

Overall, 118 patients enrolled in the trials comparing lithium with imipramine. Lithium was more effective than imipramine (Table 5.8, Figure 5.3). In the 24-month trials (Prien *et al.* 1973b, 1984), the pooled estimate risk ratio for relapse was 0.62 (95% CI 0.46 to 0.84). On average, treating 4 patients with lithium will prevent one more relapse than if they were treated with imipramine. In the 11-month trial (Kane *et al.* 1982), lithium tended to be superior to imipramine although it failed to reach the statistical significance at 5% level (Risk ratio 0.42, 95% CI 0.07 to 2.63).

Table 5.7 Comparison of risk of drop-out with lithium and placebo

Trial (ref) (Length of study in months)	No of patients (Lithium/Placebo)	Crude rate		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		Lithium	Placebo			
Kane *et al.* (1982) (11)	4/7	3/4	2/7	2.63 (0.71 to 9.64)	0.46 (-0.08 to 1.00)	N/A
Cundall *et al.* (1972) (12)	13/13	1/13	1/13	1.00 (0.07 to 14.34)	0.00 (-0.20 to 0.20)	N/A
Stallone *et al.* (1973) (15)	25/27	9/25	22/27	0.44† (0.25 to 0.77)	-0.45† (-0.69 to -0.22)	2 (1 to 5)
Prien *et al.* (1973b) (24)	18/13	5/18	9/13	0.40* (0.18 to 0.92)	-0.41* (-0.74 to -0.09)	3 (2 to 12)
Fieve *et al.* (1976a) (25)	7/11	1/7	7/11	0.22 (0.03 to 1.45)	-0.49* (-0.88 to -0.11)	2 (1 to 9)

CI, confidence interval; N/A, not applicable; NNT, number needed to treat; RD, risk difference; RR, risk ratio
★ $P < 0.05$
† $P < 0.01$

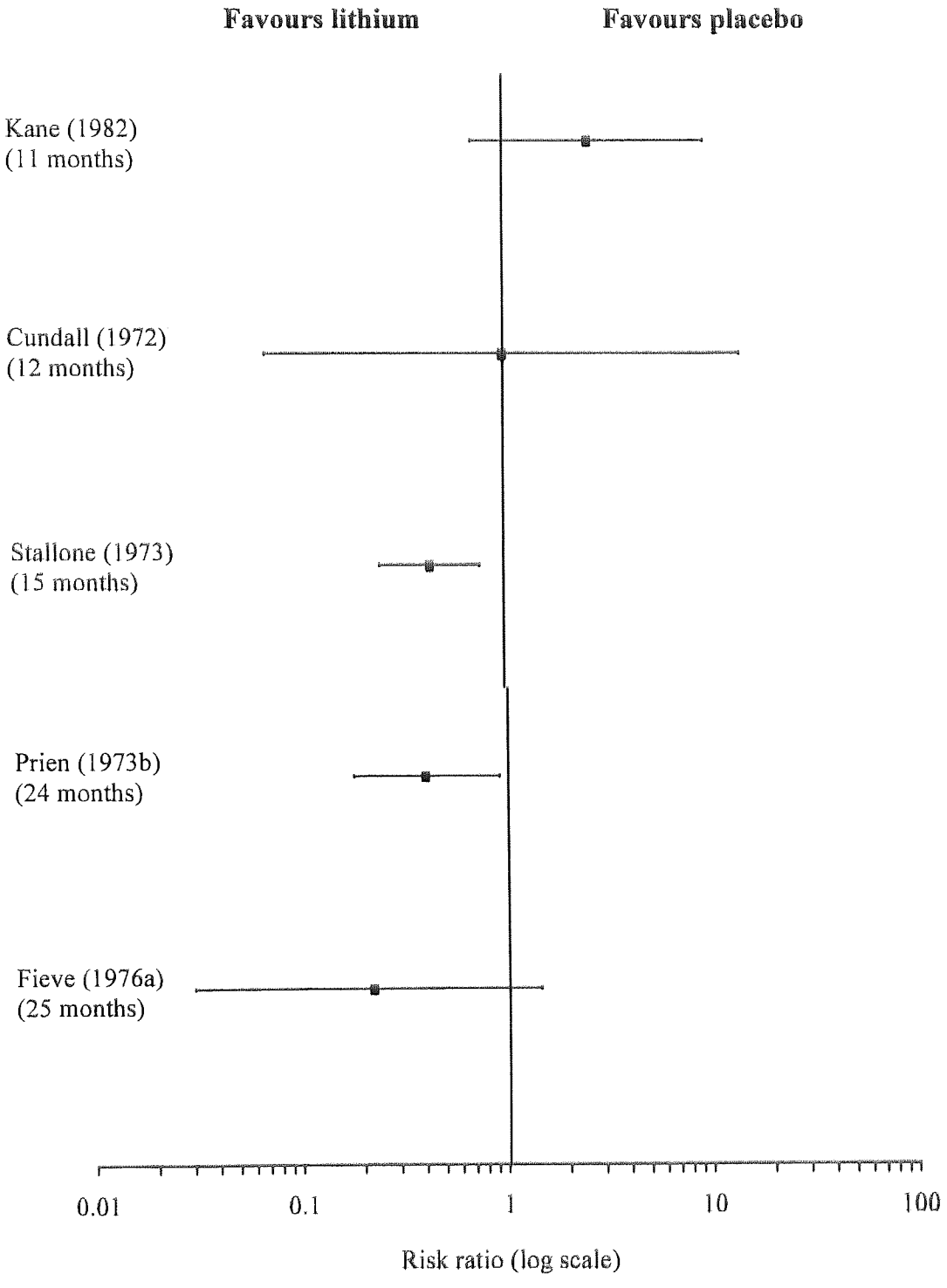

Figure 5.2 Risk ratios (95% confidence interval) for drop-out with lithium and placebo. Times shown in brackets.

Table 5.8 Comparison of risk of relapse with lithium and controls

Trial (ref) (Length of study in months)	No of patients (Lithium/Control)	Crude rate		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		Lithium	Control			
Lithium v imipramine						
Prien *et al.* (1973b) (24)	18/13	5/18	10/13	0.36* (0.16 to 0.81)	-0.49† (-0.80 to -0.18)	3 (2 to 6)
Prien *et al.* (1984) (24)	42/36	23/42	29/36	0.68* (0.49 to 0.93)	-0.26* (-0.46 to -0.06)	4 (3 to 17)
Pooled	60/49	28/60	39/49	0.62† (0.46 to 0.84)	-0.33† (-0.49 to -0.16)	4 (3 to 7)
Kane *et al.* (1982) (11)	4/5	1/4	3/5	0.42 (0.07 to 2.63)	-0.35 (-0.95 to 0.25)	N/A
Lithium v lithium-imipramine combination						
Quitkin *et al.* (1981a) (19)	38/37	8/38	12/37	0.65 (0.30 to 1.40)	-0.11 (-0.31 to 0.09)	N/A
Kane *et al.* (1982) (11)	4/6	1/4	1/6	1.50 (0.13 to 17.67)	0.08 (-0.44 to 0.60)	N/A
Prien *et al.* (1984) (24)	42/36	23/42	18/36	1.10 (0.71 to 1.68)	0.05 (-0.17 to 0.27)	N/A
Lithium v carbamazepine						
Placidi *et al.* (1986) (34)	27/29	7/27	8/29	0.94 (0.39 to 2.24)	-0.02 (-0.25 to 0.22)	N/A
Lusznat *et al.* (1988) (12)	20/20	10/20	5/20	2.00 (0.83 to 4.80)	0.25 (-0.04 to 0.54)	N/A
Coxhead *et al.* (1992) (12)	16/15	8/16	6/15	1.25 (0.57 to 2.75)	0.10 (-0.25 to 0.45)	N/A
Lithium v lithium-divalproate combination						
Solomon *et al.* (1997) (12)	7/5	5/7	0/5	8.25 (0.56 to 122.10)	0.60† (0.21 to 0.99)	2 (1 to 5)

CI, confidence interval; N/A, not applicable; NNT, number needed to treat; RD, risk difference; RR, risk ratio

* $P < 0.05$

† $P < 0.01$

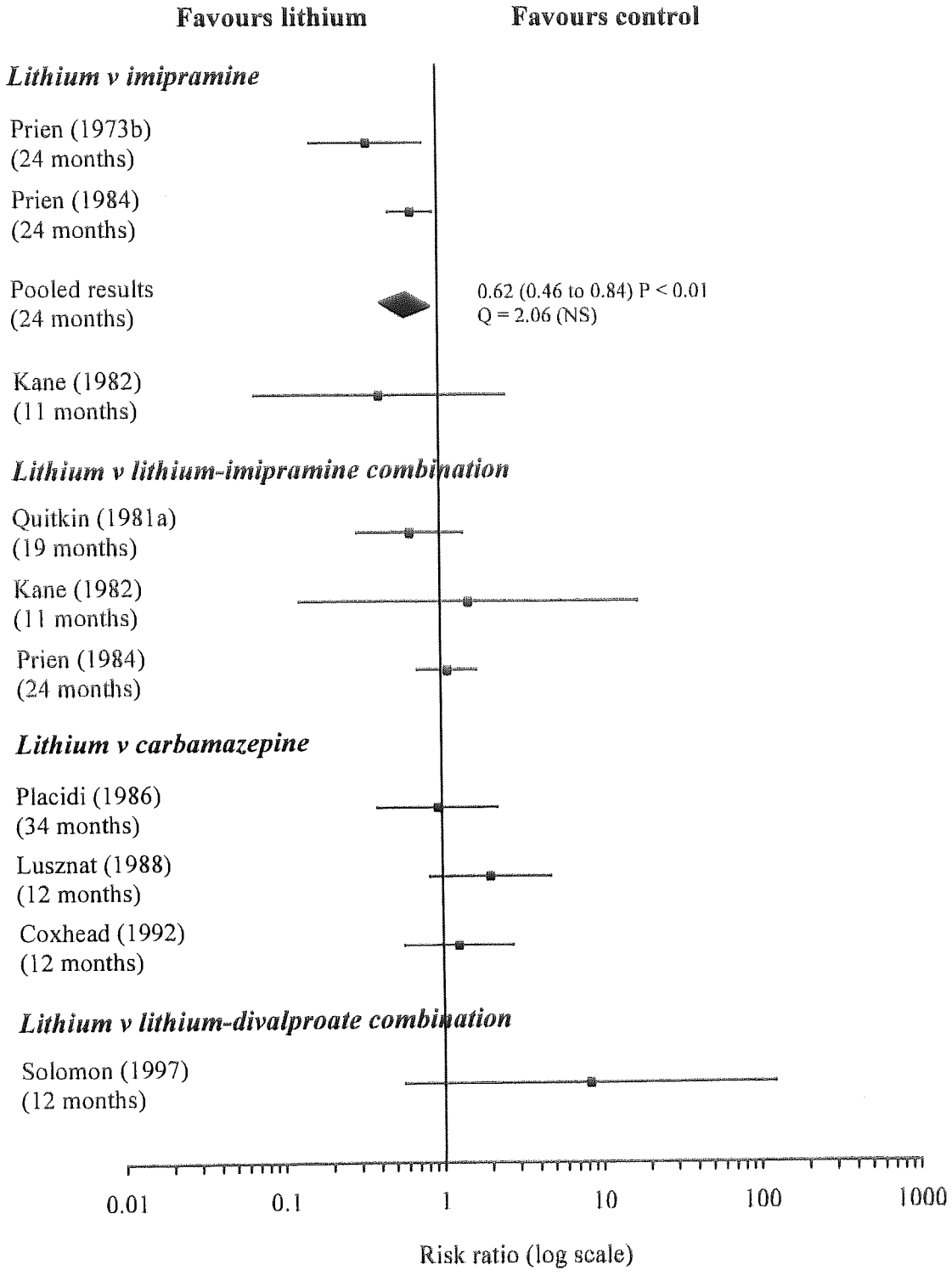

Figure 5.3 Risk ratios (95% confidence interval) for relapse with lithium and controls. Individual risk ratios (—) are shown along with the pooled estimate of effect (◆). Times shown in brackets.

In their study, Prien *et al.* (1973b) used a three-armed design comparing lithium, imipramine, and placebo. The relapse rate with imipramine was no different to that obtained in the placebo arm (Risk ratio 1.00, 95% CI 0.66 to 1.52).

Lithium versus lithium-imipramine combination

A total of 163 patients participated in the lithium versus lithium-imipramine combination trials (Quitkin *et al.* 1981a, Kane *et al.* 1982, Prein *et al.* 1984). The risk of relapse at the different time points reported in those trials are shown in Figure 5.3. There was no significant differences in prophylactic efficacy between the two regimens.

Lithium versus carbamazepine

127 patients participated in three randomised double-blind trials (Placidi *et al.* 1986, Lusznat *et al.* 1988, Coxhead *et al.* 1992) comparing lithium against carbamazepine. One study included patients with major recurrent depressive, schizoaffective, and schizophreniform disorder (Placidi *et al.* 1986) and a second study included schizoaffective patients (Lusznat *et al.* 1988). Statistical pooling of results was therefore not appropriate and neither trials reported a significant difference in effect between lithium and carbamazepine (Table 5.8, Figure 5.3).

Two other studies of lithium versus carbamazepine used a randomised but non-blinded design (Simhandl *et al.* 1993, Greil *et al.* 1997). The number of patients with affective episodes was used as outcome measure and one of the trials included unipolar patients (Simhandl *et al.* 1993). Their results suggested no significant differences in the efficacy of the two drugs (Simhandl *et al.* 1993, Greil *et al.* 1997). One other trial also including both unipolar and bipolar patients reported outcome in terms of remission period

(Watkins *et al.* 1987). The mean times (± SE) in remission were longer during lithium than carbamazepine treatment (16.0 ± 2.4 months v 9.4 ± 1.3 months) (Watkins *et al.* 1987).

In a cross-over trial comparing lithium against carbamazepine and the combination of lithium and carbamazepine (Denicoff *et al.* 1997), the efficacy was expressed as the mean number of affective episodes per year and the percentage of time the patient was ill. The mean number of episodes was significantly lower during the combination treatment compared with the lithium and the carbamazepine treatments. The percentage of time spent in a manic state was found to be significantly lower with lithium therapy and the combination therapy than with carbamazepine treatment. No differences were observed across the three treatments with regard to the percentage of time spent in depressive episodes.

Lithium versus lithium-divalproate combination

In the only trial comparing lithium and the combination of lithium and divalproate, the latter was more effective than lithium alone as shown by the mean difference in risk of 0.60 (95% CI 0.21 to 0.99) (Table 5.8). On average, treating 2 patients with lithium-divalproate combination will prevent one more patient from relapse than if they were given lithium alone.

In a randomised non-blinded trial including patients with unipolar disorder and using mean number of episodes per patient per year and mean per cent time the patient was ill as outcomes, lithium and flupenthixol decanoate were equivalent (Ahlfors *et al.* 1981). One trial compared lithium against maprotiline (Coppen *et al.* 1976). Patients with both

unipolar and bipolar disorders were included and the affective morbidity index was used as outcome. Lithium-treated patients had lower, but not significantly so, affective morbidity index than maprotiline-treated patients (0.10 ± 0.05 v 0.24 ± 0.08) (Coppen *et al.* 1976).

Risk of drop-out

Risk of drop-out with lithium and active controls at different time points are shown in Figure 5.4. More patients treated with imipramine withdrew from the trials over a 24-month period than did patients treated with lithium. There were no significant differences in risk of drop-out with lithium and the lithium-imipramine combination, or the lithium-divalproate combination as shown by the individual confidence intervals for both risk ratio and risk difference (Table 5.9, Figure 5.4). Drop-outs from the trials among patients treated with lithium did not differ from patients treated with carbamazepine.

Adverse effects

Risk of adverse effects with lithium and active controls are shown in Table 5.10 and Figure 5.5. While there was no significant difference in risk ratio of adverse effects for lithium versus imipramine, risk difference was marginally significant [0.20 (95% CI 0.00 to 0.40)]. On average, treating 5 patients with lithium will cause one more patient to report an adverse effect than if they were treated with imipramine.

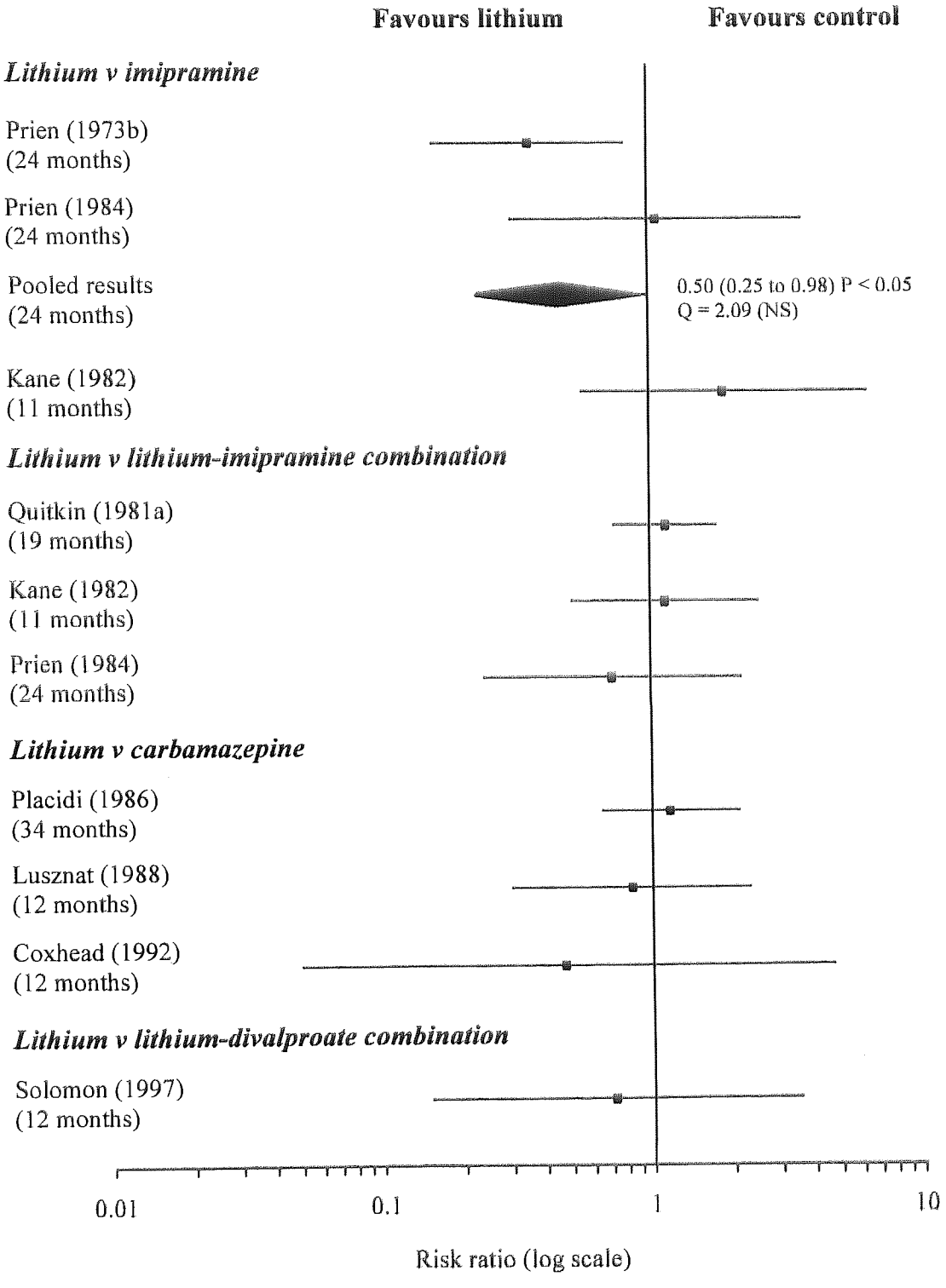

Figure 5.4 Risk ratios (95% confidence interval) for drop-out with lithium and controls. Individual risk ratios (——) are shown along with the pooled estimate of effect (◆). Times shown in brackets.

Table 5.9 Comparison of risk of drop-out with lithium and controls

Trial (ref) (Length of study in months)	No of patients (Lithium/Control)	Crude rate		RR (95% CI)	RD (95% CI)
		Lithium	Control		
Lithium v imipramine					
Prien *et al.* (1973b) (24)	18/13	5/18	10/13	0.36* (0.16 to 0.81)	-0.49† (-0.80 to -0.18)
Prien *et al.* (1984) (24)	42/36	5/42	4/36	1.07 (0.31 to 3.69)	0.01 (-0.13 to 0.15)
Pooled	60/49	10/60	14/49	0.50* (0.25 to 0.98)	-0.22 (-0.71 to 0.27)
Kane *et al.* (1982) (11)	4/5	3/4	2/5	1.87 (0.56 to 6.31)	0.35 (-0.25 to 0.95)
Lithium v lithium-imipramine combination					
Quitkin *et al.* (1981a) (19)	38/37	21/38	18/37	1.14 (0.73 to 1.76)	0.07 (-0.16 to 0.29)
Kane *et al.* (1982) (11)	4/6	3/4	4/6	1.13 (0.51 to 2.50)	0.08 (-0.48 to 0.65)
Prien *et al.* (1984) (24)	42/36	5/42	6/36	0.71 (0.24 to 2.15)	-0.05 (-0.20 to 0.11)
Lithium v carbamazepine					
Placidi *et al.* (1986) (34)	27/29	13/27	12/29	1.16 (0.65 to 2.09)	0.07 (-0.19 to 0.33)
Lusznat *et al.* (1988) (12)	20/20	5/20	6/20	0.83 (0.30 to 2.29)	-0.05 (-0.33 to 0.23)
Coxhead *et al.* (1992) (12)	16/15	1/16	2/15	0.47 (0.05 to 4.65)	-0.07 (-0.28 to 0.14)
Lithium v lithium-divalproate combination					
Solomon *et al.* (1997) (12)	7/5	2/7	2/5	0.71 (0.15 to 3.50)	-0.11 (-0.66 to 0.43)

CI, confidence interval; RD, risk difference; RR, risk ratio

* $P < 0.05$

† $P < 0.01$

Table 5.10 Comparison of risk of side-effects with lithium and controls

Trial	No of patients (Lithium/Control)	Crude rate		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		Lithium	Control			
Lithium v imipramine						
Prien *et al.* (1984)	42/36	34/42	22/36	1.32 (0.98 to 1.79)	0.20§ (0.00 to 0.40)	5 (3 to ∝)
Lithium v lithium-imipramine combination						
Prien *et al.* (1984)	42/36	34/42	34/36	0.86 (0.73 to 1.01)	-0.13 (-0.28 to 0.01)	N/A
Lithium v carbamazepine						
Coxhead *et al.* (1992)	16/15	14/16	12/15	1.09 (0.80 to 1.50)	0.08 (-0.18 to 0.33)	N/A
Lithium v lithium-divalproate combination						
Solomon *et al.* (1997)	7/5	3/7	5/5	0.43 (0.18 to 1.01)	-0.57† (-0.94 to -0.20)	2 (2 to 5)

CI, confidence interval; N/A, not applicable; NNT, number needed to treat; RD, risk difference; RR, risk ratio
NNT may be reported by some authors as NNH (number needed to harm).
† $P < 0.01$
§ $P = 0.05$

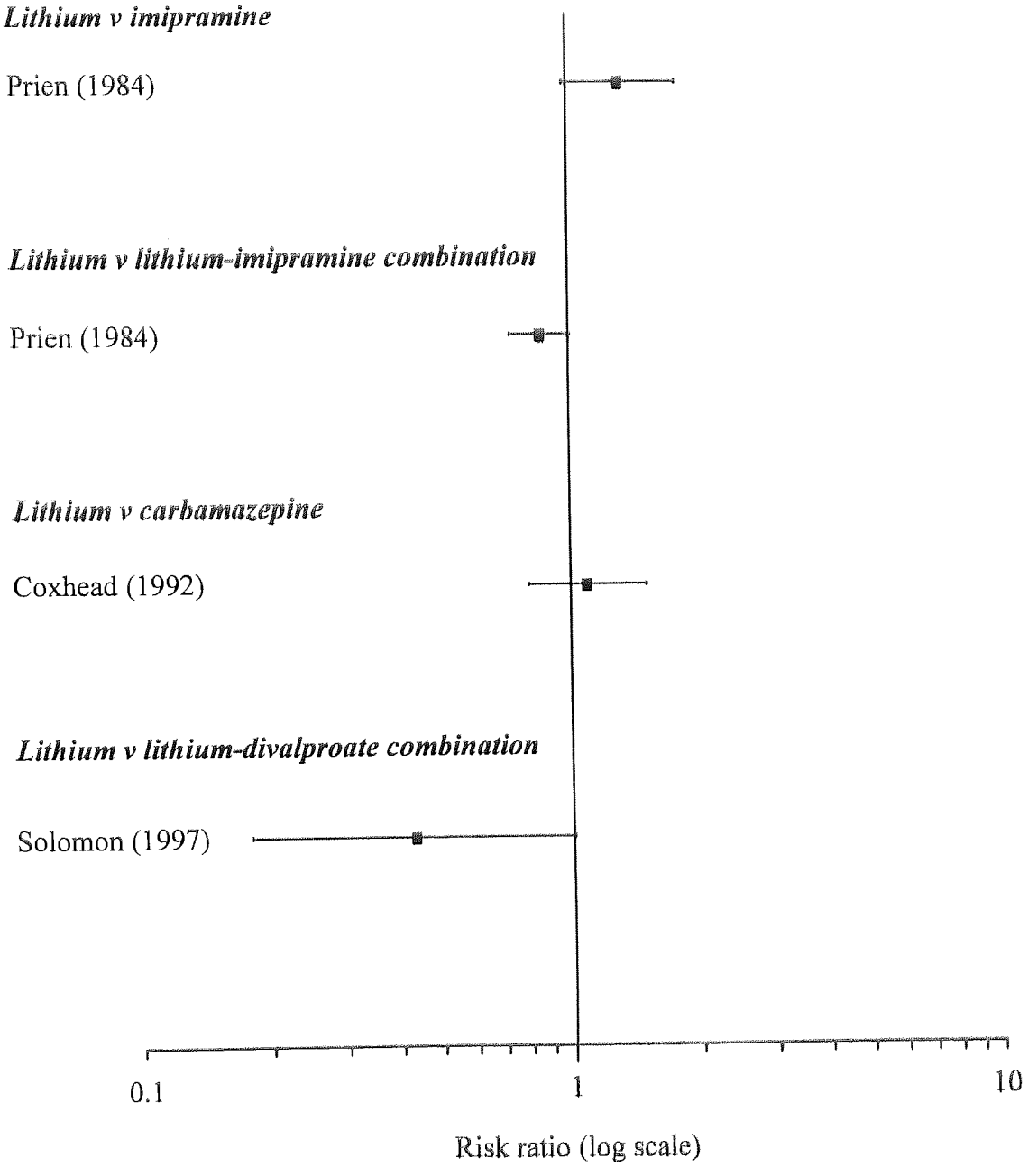

Figure 5.5 Risk ratios (95% confidence interval) for side-effects with lithium and controls.

Adverse effects were more frequently reported, but not significantly so, with the lithium-imipramine combination than with lithium alone. Polyuria and/or polydipsia, fine tremor, dry mouth and constipation were the most frequent problems associated with lithium. Those associated with imipramine and the lithium-imipramine combination included dry month, fine tremor, constipation and excessive sweating. The majority of reactions were of mild severity (Prien *et al.* 1984).

No significant difference in risk of side-effects was observed between lithium and carbamazepine. Drowsiness, dizziness, giddiness, nausea and indigestion were the most frequently reported side-effects associated with carbamazepine. These reactions were severe enough to require dosage reduction in some patients. Itchy and erythematous rash were reported to lead to carbamazepine withdrawal in two patients. Thirst and/or polyuria and weight gain were reported with lithium. Neither of these side-effects led to withdrawal from the study (Coxhead *et al.* 1992).

The combination of lithium and divalproate was associated with more adverse effects than lithium alone. The mean risk difference was -0.57 (95% CI -0.94 to -0.20). On average treating 2 patients with the lithium-divalproate combination will cause one more patient to report an adverse effect than if they were treated with lithium alone. Side-effects associated with the lithium-divalproate combination included gastrointestinal distress, tremor, cognitive impairment and alopoecia. These reactions were of moderate or severe intensity and led to some patients withdrawal from the trial (Solomon *et al.* 1997).

5.4 Discussion

The outcome measures for assessing the efficacy of lithium in the prophylaxis of bipolar disorder have been reported in various ways (Table 5.1) and there is a need for greater consistency in future trials. Even the definition of relapse differed somewhat from trial to trial, but generally referred to affective episodes requiring supplementary medications or hospital admission (Table 5.4). Using relapse, defined as such, the results of this meta-analysis support the conclusion arrived at by Goodwin & Jamison (1990) and Davis *et al.* (1999) that lithium is superior to placebo in the prophylaxis of bipolar disorder. Lithium's efficacy is also confirmed when using drop-out as a surrogate measure for lack of efficacy. The main reasons for early termination in placebo-treated patients were poor clinical response and the development of an acute episode.

In our statistical pooling we excluded a major 24-month long randomised trial (Prien *et al.* 1973a) because although both clinical assessor and patient were blinded, the responsible physician was not and therapy could be adjusted as necessary. The trial should therefore ideally be considered a single-blind trial. This led to Moncrieff (1995) arguing that the evidence for lithium's efficacy being invalid. Inclusion of this trial led to an estimated relapse risk ratio was 0.52 (95% CI 0.41 to 0.65) and the risk ratio for drop-out was 0.46 (95% CI 0.33 to 0.64). Sensitivity analysis by inclusion of this trial did not lead to any qualitative difference in results.

Although the available evidence indicates that tricyclic antidepressants are more effective than placebo for patients with bipolar depression (Souza & Goodwin 1991), their efficacy relative to lithium is less certain. Additionally, their efficacy when

combined with lithium has not yet been systematically compared with lithium alone (American Psychiatric Association 1994). Indeed, relatively few studies have compared lithium against imipramine in the prophylaxis of bipolar disorder. That lithium is more effective than imipramine may be partly explained by an association between the use of antidepressants and the emergence of mania (Prein *et al.*1973b, 1984).

Our results suggest that carbamazepine is no more effective than lithium. This is consistent with the conclusions drawn by Davis *et al.* (1999) and Dardennes *et al.* (1995), although in their meta-analysis, they included studies which dealt with patients with both bipolar and unipolar disorder as well as those who were schizoaffective, and schizophreniform (Dardennes *et al.* 1995). Although divalproate has been shown to be effective in the acute treatment of mania, its efficacy in the prophylaxis of bipolar disorder has not yet been firmly established and that compared to lithium needs further investigation.

Several methodological shortcomings in clinical trials of lithium in bipolar disorder can be highlighted. A bias in favour of lithium may be introduced in the trials employing a discontinuation design in which patients are stabilised on lithium for some time before randomisation (Moncrieff 1995, 1997). Such a design may select out good lithium responders. Moreover, the discontinuation of stable maintenance treatment with lithium may provoke the recurrence of episodes (Suppes *et al.* 1991). Further, in some studies (Prien *et al.* 1973b, 1984, Quitkin *et al.* 1981a, Placidi *et al.* 1986, Lusznat *et al.* 1988) patients were entered in a maintenance phase, after an acute episode had been stabilised with the study medication. Again selection bias in favour of individuals with demonstrated responsiveness to lithium may take place (King 1990b). It is for these

reasons that we adopted very stringent entry criteria for trials included in our pooling.

Since completion of our review, Davis *et al.* (1999) reported a meta-analysis of mood stabilizers, including lithium, in the prevention of recurrent affective disorders. Davis *et al.* (1999) used much more permissive entry criteria in their meta-analysis. In particular they included case-control matched-subject studies with double-blind randomised controlled trials and the diagnostic criteria were also looser. While there is a case for such a broad examination of the evidence relating to lithium's efficacy, their approach is not as widely accepted as our much more stringent approach. Given the strong current controversy about the role of lithium we opted for more specificity rather than more generalisability. Despite the different approaches, both meta-analyses suggest that lithium is an effective prophylactic in bipolar disorder. This conclusion is important because there are few drugs of proven efficacy for this indication.

5.5 Conclusion

The current evidence strongly supports the efficacy of lithium in the prophylaxis of bipolar disorder. Lithium is more effective than placebo and imipramine in bipolar disorder. Adding imipramine to lithium provides no advantage over lithium alone. Lithium causes more acute side-effects than placebo, and imipramine, but no more than its combination with imipramine, nor carbamazepine. The combination of lithium and divalproate may be more effective than lithium alone, but may also produce more adverse effects. Carbamazepine's superiority over lithium has yet to be demonstrated. It is our view that based on estimates of efficacy, lithium should remain the first line prophylactic treatment for bipolar disorder.

Chapter 6

Haloperidol plasma concentrations and clinical response in schizophrenia

6.1 Introduction

Antipsychotic or neuroleptic drugs were first used in the 1950s (Delay *et al.* 1952). Chlorpromazine which was developed as a pre-anaesthetic sedative was found to be a useful antipsychotic. Several related agents were then developed and also used successfully as antipsychotics (Jacobsen 1986). However, it became evident that their use was associated with a variety of adverse effects including a range of extrapyramidal disorders such as acute dystonia, Parkinsonism, akathesia and tardive dyskinesia (Deniker 1990). These adverse effects and poor response in some patients limited antipsychotic pharmacotherapy.

Despite the fact that antipsychotic drugs have been used for more than 40 years, there has been no general consensus on the most appropriate doses for the different agents. In clinical practice, the estimation of the optimal dose for individual patients relies on trial and error. Doses are generally titrated based on clinical efficacy and side-effects during the course of treatment (Volavka and Cooper 1987, Moller 1996). To achieve maximum benefit of antipsychotics whilst minimising their side-effects, doses are adjusted based on plasma drug levels. Hence the therapeutic drug monitoring of some antipsychotics including haloperidol (Balant-Gorgia *et al.* 1993, Eilers 1995).

Despite the widespread use of such dose titration, there is still no consensus about the relationship between plasma drug levels and clinical effects. Among the many antipsychotics, the relationship between haloperidol blood levels and therapeutic effect has been perhaps the most extensively investigated. Yet even in this case there remains a fierce debate about the relationship between blood concentrations and response. Several fixed-dose studies found no association (Itoh *et al.* 1984, Linkowski *et al.* 1984, Shostak *et al.* 1987, Doddi *et al.* 1994, Lane *et al.* 1997), while others reported a curvilinear relationship and putative therapeutic ranges (Magliozzi *et al.* 1981, Smith *et al.* 1984, Van Putten *et al.* 1985, 1992, Palao *et al.* 1996). A linear relationship has also been reported (Cohen & Baldessarini 1981, Wistedt *et al.* 1984).

The inconsistent findings may be attributed to a number of factors to include differences in dosage regimen (fixed/flexible dose), population sample heterogeneity and differences in sample size, severity of illness, duration of treatment, concomitant drug use, timing of blood sampling, and assay technique (Bernado *et al.* 1993, Oliveira *et al.* 1995). To systematically evaluate the conflicting data, we therefore undertook a systematic overview of haloperidol concentration-clinical response relationship in the treatment of schizophrenia.

6.2 Materials and methods

6.2.1 Identification of studies

The studies investigating the relationship between haloperidol blood concentrations and

clinical response were searched through MEDLINE database for the year 1966 to the end of August 1999, and BIDS database (Science Citation Index and EMBASE) from 1980 to the end of August 1999. "Haloperidol", "reduced haloperidol", "schizophrenia", and "dose-response relationship" were used as keywords for the computer search. Reference lists of all articles identified in the computerised literature search were also reviewed. The unpublished data on individual patients were also obtained from the authors, where applicable.

6.2.2 Inclusion and exclusion criteria

Studies included were those investigating the relationship between haloperidol blood concentrations and clinical response. The studies were excluded when they did not provide individual patients' data concerning blood concentrations and percentage improvement in symptom score. When more than one publication including individual patient data was available, the most recent one was used.

Only studies providing percentage improvement in psychotic symptoms assessed by the 18-item Brief Psychiatric Rating Scale (BPRS) were included in detailed statistical analysis. Those admitting patients with diagnoses other than schizophrenia, schizoaffective, and schizophreniform disorder were not included. Also excluded were the studies in which patients were treated with depot neuroleptics and those including chronic patients with stable psychotic disorder, or refractory to previous antipsychotic treatment.

6.2.3 Data extraction

The eligible studies were reviewed and details on dosage regimens (fixed/flexible), wash-out period, duration of treatment, assay method, and patients characteristics (diagnosis, age, sex, and duration of illness) were abstracted. Outcomes of interest were haloperidol blood levels and percentage improvement in psychotic symptoms which were drawn from tables or graphs. In case of graphs, the estimations were obtained by means of computerised method (Appendix). The coordinates were then translated into blood concentrations and percentage improvement.

If a study did not present these specific outcomes, the lead author of the study was contacted in an attempt to obtain more complete data. When subsequent studies by the same authors appeared to include some patients from the earlier studies, the authors were approached to confirm this. Only the data from the new patients were extracted.

6.2.4 Statistical analysis

The relationship between haloperidol plasma concentrations and therapeutic response was calculated using the Receiver Operating Characteristic (ROC) curves (Perry *et al.* 1994). To identify the lower limit for response, the individual drug levels were ordered from the highest level to the lowest level. Then the proportion of true responders and true nonresponders at a particular drug level were calculated. The ROC curve was constructed by plotting the percentage of true responders on the y-axis against the percentage of true nonresponders on the x-axis. The optimal predictive drug concentration is located at the point closest to y-axis and furthest from x-axis, i.e. the

point that has the largest difference when the x-value is subtracted from the y-value. The upper limit was identified by reordering the drug levels from the lowest level to the highest level. The sensitivity and specificity of therapeutic blood levels were determined by χ^2 analysis.

6.3 Results

6.3.1 Study characteristics

29 studies (Magliozzi *et al.* 1981, Mavroidis *et al.* 1983, 1985, Balant-Gorgia *et al.* 1984, Linkowski *et al.* 1984, Miller *et al.* 1984, Neborsky *et al.* 1984, Bigelow *et al.* 1985, Gerlach *et al.* 1985, Potkin *et al.* 1985, Smith *et al.* 1985, Van Putten *et al.* 1985, Shostak *et al.* 1987, Smith 1987, Altamura *et al.* 1988, Kirch *et al.* 1988, Louza-Neto *et al.* 1988, Ko *et al.* 1989. Santos *et al.* 1989a, b, c, Coryell *et al.* 1990, Kelly *et al.* 1990, Volavka *et al.* 1992, Jibiki *et al.* 1993, Palao *et al.* 1994, 1996, Odou *et al.* 1996, Ulrich *et al.* 1998a) presented individual patients' data with paired haloperidol and percentage improvement in psychotic symptom score. More complete data on the BPRS score than was available in two further reports were supplied by Volavka and coworkers (1995) and Lane *et al.* (1997).

Of these, four (Mavroidis *et al.* 1983, 1985, Potkin *et al.* 1985, Odou *et al.* 1996) evaluated therapeutic response using the New Haven Schizophrenia Indices (NHSI) (Mavroidis *et al.* 1983, 1985), the Clinical Global Impression (CGI) (Potkin *et al.* 1985), and the Positive and Negative Syndrome Scale for Schizophrenia (PANNS) (Odou *et al.*

1996). The further three studies (Smith *et al.* 1985, 1987, Van Putten *et al.* 1985) provided individual data on clinical improvement assessed by the BPRS psychosis factor score (Smith *et al.* 1985, 1987) or schizophrenia factor score (Van Putten *et al.* 1985). Various versions of the BPRS were used. The 16-item BPRS score was used in seven studies (Magliozzi *et al.* 1981, Balant-Gorgia *et al.* 1984, Linkowski *et al.* 1984, Neborsky *et al.* 1984, Geralch *et al.* 1985, Ko *et al.* 1989, Jibiki *et al.* 1993). A 17-item version was adopted by Shostak *et al.* (1987), and the 23-item version in four studies (Bigelow *et al.* 1985, Kirch *et al.* 1988, Coryell *et al.* 1990, Kelly *et al.* 1990). One study did not specify the BPRS used (Altamura *et al.* 1988). These studies were rejected from the further statistical analysis. Table 6.1 presents the characteristics of the 31 studies.

6.3.2 Identification of therapeutic range

Numerous clinical studies have reported putative therapeutic ranges for haloperidol in the treatment of schizophrenia (Figure 6.1). The study characteristics and statistical analyses are shown in Table 6.2.

In the studies included in the detailed dose-response analysis (Miller *et al.* 1984, Louza-Neto *et al.* 1988, Santos *et al.* 1989a, b, c, Volavka *et al.* 1992, 1995, Palao *et al.* 1994, 1996, Lane *et al.* 1997, Ulrich *et al.* 1998a), a total of 381 patients were treated for two to six weeks with a fixed daily dose ranging from 10 mg to 30 mg or with a flexible dose regimen. Characteristics of these studies are summarised in Table 6.3. In each study, therapeutic response was assessed by the 18-item BPRS. Response to treatment was defined as 30% or more reduction of BPRS total score. The ROC curve analysis

Table 6.1 Studies of haloperidol plasma level-clinical response relationship

Study	N	Diagnostic criteria	Diagnosis	Rating scale (no. of items)	Wash-out period	Dose (mg/d)	Treatment period (week)	Assay
Magliozzi (1981)	17	RDC	SCN/SCA	BPRS (16)	-	2-120	3-12	GLC
Mavriodis (1983, 1985)	14	DSM-III	SCN/SCP	NHSI	2 days	6, 12, or 24	2	GLC
Balant-Gorgia (1984)	18	ICD-9	SCN/SCA	BPRS (16)	-	flexible: 5-30	3	GLC
Linkowski (1984)	20	RDC	SCN	BPRS (16)	8 days	30	6	RIA
Miller (1984)	21	DSM-III	SCN/SCA/SCP	BPRS (18)	-	flexible: 5-80	3	GLC
Neborsky (1984)	18	DSM-III	SCN/SCP	BPRS (16)	-	flexible: after IM and po rapid neuroleptisation, assigned to high (39 ± 4) or low (12 ± 0.7) dose	1	RIA
Gerlach (1985)	14	Feighner	SCN	BPRS (16)	1-6 weeks	flexible: 3-24	12	HPLC
Potkin (1985)	44	DSM-III	SCN/SCP	CGI	1 week	0.15 or 0.4 mg/kg	6	RIA
Smith (1985)	33	RDC/DSM-III	SCN/SCA	BPRS, psychosis factor	1-3 weeks	7.5-40	3	GLC
Van Putten (1985)	34	N/R	SCN	BPRS, schizophrenia factor	few days-3weeks	5, 10, or 20	4	RIA
Shostak (1987)	13	RDC/DSM-III	SCN/SCA	BPRS (17)	1-4 days	10	4	RIA
Smith (1987)	24	RDC/DSM-III	SCN/SCA	BPRS, psychosis factor	1-2 weeks	8 or 40	3	GLC

Table 6.1 Studies of haloperidol plasma level-clinical response relationship (continued)

Study	N	Diagnostic criteria	Diagnosis	Rating scale (no. of items)	Wash-out period	Dose (mg/d)	Treatment period (week)	Assay
Altamura (1988)	18	DSM-III	SCN	BPRS (N/R)	-	flexible: 6-21	4	GLC
Bigelow (1985), Kirch (1988)	30	DSM-III	SCN	BPRS (23)	4 weeks	0.4 mg/kg	6	HPLC
Louza-Neto (1988)	16	RDC/DSM-III	SCN/SCA	BPRS (18)	-	0.15 or 0.4 mg/kg	6	RIA
Ko (1989)	15	DSM-III-R	SCN	BPRS (16)	6 weeks	0.4 mg/kg	6	HPLC
Santos (1989a,b)	30	DSM-III	SCN	BPRS (18)	-	15, 20, or 30	3	RIA
Santos (1989c)	20	DSM-III	SCN	BPRS (18)	10 days	15, 20, or 30	3	RRA
Coryell (1990)	25	RDC	SCN/SCA	BPRS (23)	-	fixed plasma ranges: 8-18 or 20-35 ng/ml	2	HPLC
Kelly (1990)	29	DSM-III-R	SCN	BPRS (23)	-	fixed plasma ranges: 8-18 or 25-35 ng/ml	2	HPLC
Volavka (1992)	103	RDC	SCN/SCA	BPRS (18)	6.9 ± 4.8 days	fixed plasma ranges: 2-13, 13.1-24, or 24.1-35 ng/ml	6	GLC
Jitoki (1993)	11	DSM-III-R	SCN	BPRS (16)	-	2, 3, or 4	2	EIA
Volavka (1995)	54	DSM-III-R	SCN/SCA	BPRS (18)	3 days -1week	fixed plasma levels: 2 or 10 ng/ml	3	GLC
Palao (1994, 1996)	32	DSM-III-R	SCN	BPRS (18)	1 week	10, 20, or 30	3	LC
Odou (1996)	19	DSM-III-R	SCN/SCA	PANSS	≥ 1 week	flexible: 6-40	3	RRA

Table 6.1 Studies of haloperidol plasma level-clinical response relationship (continued)

Study	N	Diagnostic criteria	Diagnosis	Rating scale (no. of items)	Wash-out period	Dose (mg/d)	Treatment period (week)	Assay
Lane (1997)	48	DSM-IV	SCN	BPRS (18)	1 week	10	2	HPLC
Ulrich (1998a)	57	ICD-10	SCN/SCA	BPRS (18)	-	flexible	3	GLC

IM, intramuscular; po, per oral; N/R, not reported
BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; DSM-III, Diagnostic and Statistical Manual, 3rd ed.; DSM-III-R, Diagnostic and Statistical Manual, 3rd ed. (revised); DSM-IV, Diagnostic and Statistical Manual, 4th ed.; EIA, enzyme-immuno assay; GLC, gas liquid chromatography; HPLC, high performance liquid chromatography; ICD-9, International Classification of Diseases, 9th ed.; ICD-10, International Classification of Diseases, 10th ed.; LC, liquid chromatography; NHSI, New Haven Schizophrenia Indices; PANSS, Positive and Negative Syndrome Scale for Schizophrenia; RIA, radioimmuno assay; RDC, Research Diagnostic Criteria; RRA, radioreceptor assay; SCA, schizoaffective disorder; SCN, schizophrenia; SCP, schizophreniform disorder

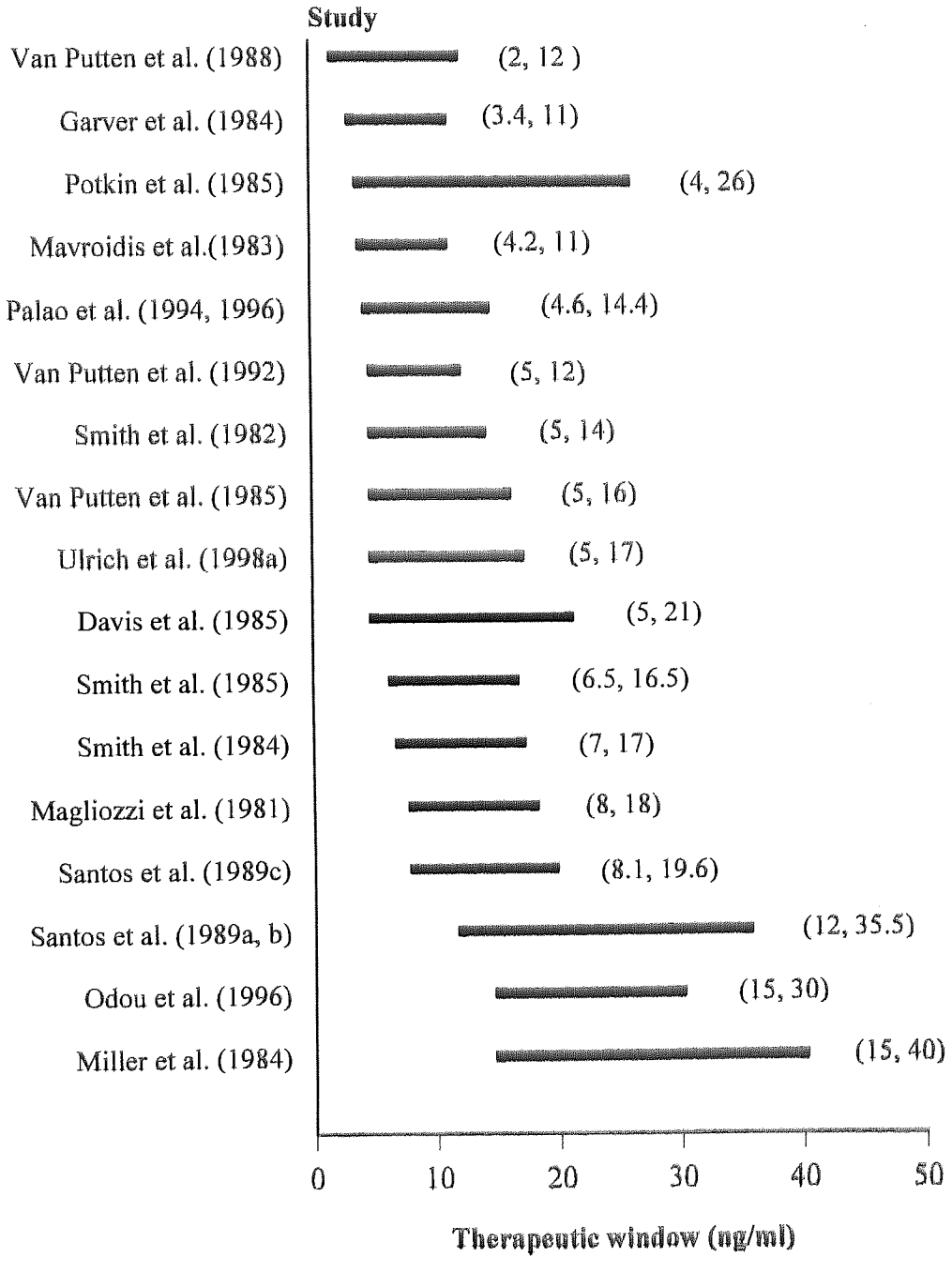

Figure 6.1 Comparison of published therapeutic windows for haloperidol

Table 6.2 Studies reporting therapeutic windows for haloperidol in the treatment of schizophrenia

Study	N	Dose (mg/day)	Duration (week)	Outcome measure	Therapeutic window (ng/ml)	Statistical analysis
Magliozzi *et al.* (1981)	17	fixed: 2-120	3-12	Improvement index	8-18	Improvement index, defined as baseline BPRS score divided by final score Therapeutic window defined as plasma range for which the Mann-Whitney U statistics was least
Smith *et al.* (1982)	26	10, 20, or 25	3	%BPRS Psy	5-14	Regression analysis Therapeutic window defined by examination of scatterplots
Mavroidis *et al.* (1983, 1985)	14	6, 12, or 24	2	%NHSI	4.2-11	Regression analysis Therapeutic window defined as plasma levels associated with at least 40% improvement
Garver *et al.* (1984)	17	6, 12, or 24	2	%NHSI	3.4-11	Regression analysis Therapeutic window defined as plasma levels associated with at least 40% improvement
Miller *et al.* (1984)	21	flexible: 5-80	3	%BPRS	15-40	Regression analysis Divided plasma levels into 3 ranges (<15, 15-40, >40 ng/ml) and tested for significance
Smith *et al.* (1984)	27	10, 20, or 25	3	%BPRS Psy	7-17	Regression analysis Therapeutic window defined as plasma levels on either side of the curve for which the estimated clinical response, plus the given confidence interval, does not contain the maximum predicted value of the entire curve
Davis *et al.* (1985)	35	60 (IM) then 15 (po) or 15*	3	Improvement rate on BPRS†	5-21	Regression analysis Divided plasma levels into 3 ranges (<5, 5-21, >21 ng/ml) and tested for significance

Table 6.2 Studies reporting therapeutic windows for haloperidol in the treatment of schizophrenia (continued)

Study	N	Dose (mg/day)	Duration (week)	Outcome measure	Therapeutic window (ng/ml)	Statistical analysis
Potkin *et al.* (1985)	44	0.4 or 0.15 mg/kg	6	%CGI	4-26	Regression analysis Divided plasma levels into 3 ranges (<1, 4-26, >26 ng/ml), and tested for significance
Smith *et al.* (1985)	33	7.5-40	3	%BPRS Psy	6.5-16.5	Regression analysis Therapeutic window defined as plasma levels on either side of the curve for which the estimated clinical response, plus the given confidence interval, did not contain the maximum predicted value of the entire curve
Van Putten *et al.* (1985)	47	5, 10, or 20	4	%BPRS Sch	5-16	Regression and examination of scatterplots
Van Putten *et al.* (1988)	76	5, 10, or 20	4	dBPRS Psy	2-12	Regression and examination of scatterplots
Santos *et al.* (1989a, b)	30	15, 20, or 30	3	%BPRS	12-35.5	Regression analysis Lower limit defined as plasma level corresponding to 40% improvement Upper limit defined as plasma level corresponding to the inflexion point of the regression curve
Santos *et al.* (1989c)	20	15, 20, or 30	3	%BPRS	8.1-19.6	Regression analysis Lower limit defined as plasma level corresponding to 40% improvement Upper limit defined as plasma level corresponding to the inflexion point of the regression curve

Table 6.2 Studies reporting therapeutic windows for haloperidol in the treatment of schizophrenia (continued)

Study	N	Dose (mg/day)	Duration (weeks)	Outcome measure	Therapeutic window (ng/ml)	Statistical analysis
Van Putten *et al.* (1992)	69	5, 10, or 20	4	dBPRS Psy	5-12	Fitted curve obtained from the theoretical model of two sigmoidal plasma level-effect curves Divided plasma levels into 4 ranges by examination of fitted curve, and tested for significance
Palao *et al.* (1994, 1996)	32	10, 20, or 30	3	%BPRS	4.6-14.4	Fitted curve obtained from the theoretical model of two sigmoidal plasma level-effect curves Therapeutic window defined by examination of fitted curve
Odou *et al.* (1996)	19	flexible: 6-40	3	%PANSS Pos	15-30	Regression analysis Therapeutic window defined as plasma range containing the maximum number of responders and no non-responders Responders defined as patients with more than 70% improvement
Ulrich *et al.* (1998a)	57	flexible	3	%BPRS	5-17	Fitted curve obtained from the theoretical model of two sigmoidal plasma level-effect curves Therapeutic window defined as plasma levels associated with at least 50% improvement

* high loading dose 60 mg (IM) for 5 days then progressively decrease to 15 mg/day (po) or standard dose 15 mg/day
† improvement rate not defined
%BPRS, percent change of BPRS total score; %BPRS Psy, percent change of BPRS psychosis factor; %BPRS Sch, percent change of BPRS schizophrenia factor; dBPRS, absolute change in BPRS total score; dBPRS Psy, absolute change in BPRS psychosis factor; %CGI, percent change of Clinical Global Impression; %NHSI, percent change of New Haven Schizophrenia Indices; %PANSS Pos, percent change of Positive and Negative Syndrome Scale for Schizophrenia, positive subscale

Table 6.3 Characteristics of haloperidol studies

Study	N	Age (year)	Sex (M/F)	Diagnosis	Duration of illness (year)	Dose (mg/d)	Treatment period (week)	Assay		
								Type	CV (%)	Sensitivity (ng/ml)
Miller (1984)	21	29.8± 9.7	11/10	SCN/SCA/SCP	3.2 ± 5.4	flexible: 5-80	3	GLC	3.6-13.6	0.5
Louza-Neto (1988)	16	N/R	N/R	SCN/SCA	N/R	0.15 or 0.4 mg/kg	4	RIA	10	N/R
Santos (1989a,b)	30	26.2± 5.5	30/0	SCN	5.1 ± 5.4	15, 20, or 30	3	RIA	6.7-7.1	0.05
Santos (1989c)	20	24.9± 4.9	20/0	SCN	4.2 ± 4.8	15, 20, or 30	3	RRA	9.3-14.7	0.2
Volavka (1992)	103	N/R	N/R	SCN/SCA	N/R	fixed plasma ranges: 2-13, 13.1-24, or 24.1-35 ng/ml	6	GLC	3.9-5.7	N/R
Volavka (1995)	54	34.2± 8.5	43/11	SCN/SCA	N/R	fixed plasma levels: 2 or 10 ng/ml	3	GLC	3.5-7.5	0.5
Palao (1994, 1996)	32	N/R	N/R	SCN	N/R	10, 20, or 30	3	LC	3.4-5.3	3.0
Lane (1997)	48	33.8± 8.0	21/27	SCN	8.7 ± 7.0	10	2	HPLC	4.0-12.0	0.1
Ulrich (1998a)	57	38.3± 10.2	26/31	SCN/SCA	N/R	flexible	3	GLC	N/R	N/R

Bold for studies where the data were extracted.
CV, coefficient of variation; F, female; M, male; N/R, not reported; SCN, schizophrenia; SCA, schizoaffective disorder; SCP, schizophreniform disorder; GLC, gas liquid chromatography; HPLC, high performance liquid chromatography; LC, liquid chromatography; RIA, radioimmunoassay; RRA, radioreceptor assay

suggested a threshold concentration for response at 11.20 ng/ml (Figure 6.2) and the upper limit at 30.30 ng/ml ($\chi^2 = 6.94$, $p < 0.01$) (Figure 6.3). Haloperidol concentrations between 11.20 ng/ml to 30.30 ng/ml predicted a group of 159 patients that included 112 patients (70%) who responded to the drug and predicted nonresponse in 43% (95 of 222) of patients.

Sensitivity analysis for the studies lasting at least 3 weeks produced similar results. The therapeutic window ranged between 11.20 ng/ml and 30.30 ng/ml ($\chi^2 = 5.35$, $p < 0.025$). The sensitivity and specificity were 70% and 42%, respectively.

ROC curve analysis restricted to fixed-dose/plasma levels studies (303 patients) yielded results similar to those obtained when both fixed-dose and flexible-dose regimens were pooled. They were treated with fixed doses varying from 10 mg to 30 mg per day or with fixed plasma haloperidol levels ranging from 2 ng/ml to 35 mg/ml for 2-6 weeks. A therapeutic range of 11.20-30.30 ng/ml was suggested ($\chi^2 = 5.84$, $p < 0.025$). The sensitivity and specificity were 64% and 50%, respectively.

6.4 Discussion and conclusion

Although numerous studies have attempted to establish the relationship between plasma haloperidol levels and clinical response, the results appear inconsistent. On the basis of our data, the ROC curve analysis suggested an optimal range of 11.20-30.30 ng/ml which lies within those previously reported (Table 6.2, Figure 6.1). A minimum of 2 weeks seems to be adequate before assessing clinical response, although a period of

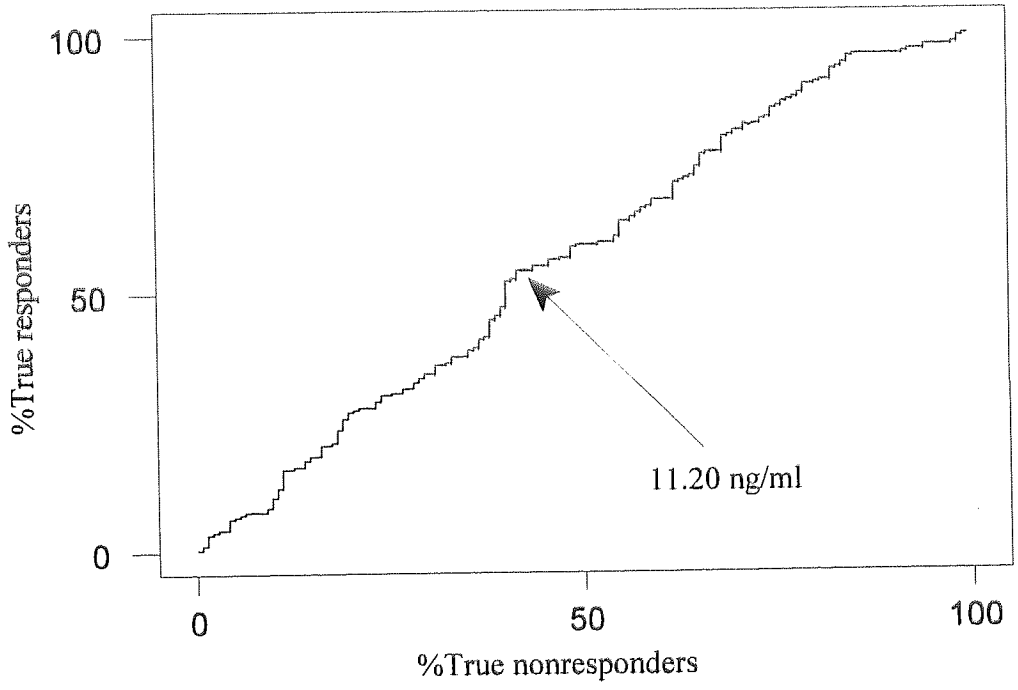

Figure 6.2 ROC curve for the relationship between haloperidol plasma concentrations and percent improvement in BPRS scores showing the lower limit for response at 11.20 ng/ml.

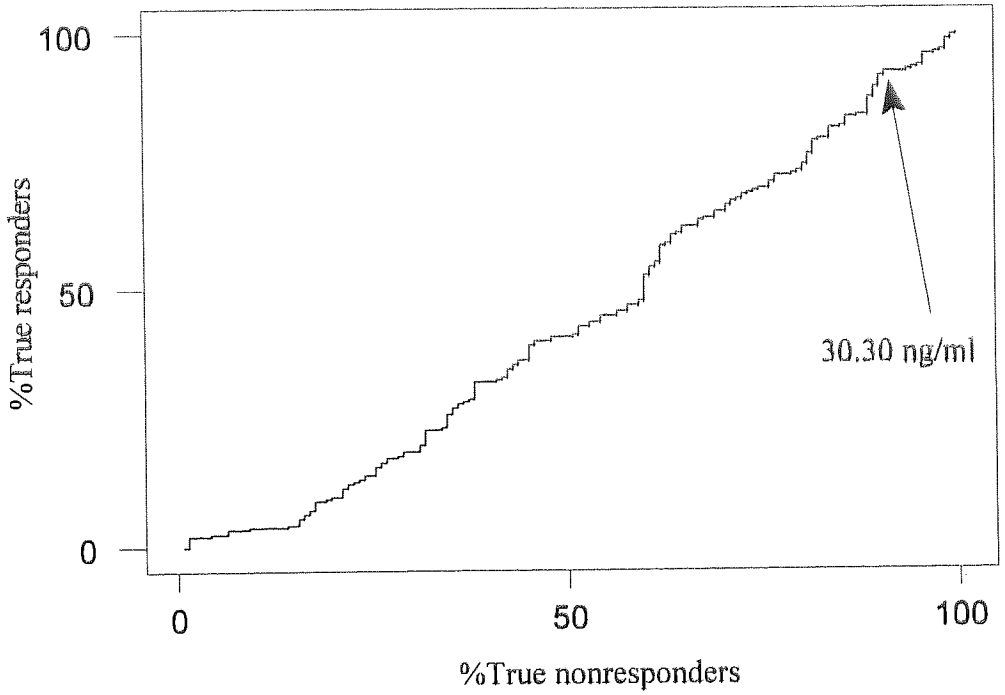

Figure 6.3 ROC curve for the relationship between haloperidol plasma concentrations and percent improvement in BPRS scores showing the upper limit for response at 30.30 ng/ml.

three to four weeks has been suggested (Sramek *et al.* 1988).

It has been suggested that only fixed dose/plasma levels studies are appropriate when investigating plasma drug levels-response relationships (Sramek *et al.* 1988, Bernardo *et al.* 1993). In flexible-dose regimens, the dose is clinically adjusted, nonresponding patients tend to receive higher doses and thereby achieve higher blood concentrations. This may suggest a spurious therapeutic window as responders usually improve at lower doses and nonresponders fail to improve even at higher doses (Sramek *et al.* 1988, Bernardo *et al.* 1993). We would argue that in clinical practice one would be interested in the plasma concentrations which produce desirable responses. Due to interindividual variability in pharmacokinetics, these concentrations may not be achieved in some patients given certain doses of haloperidol, or it is possible that an adequate amount of drug does not reach the central nervous system, hence the necessity for dose titration.

The therapeutic range suggested by our study differs slightly from those of meta-analyses reported by Oliveira *et al.* (1996) and Ulrich *et al.* (1998b) who suggested therapeutic windows of 4-26 ng/ml and of 5.6-16.9 ng/ml, respectively. In those meta-analyses (Oliveira *et al.* 1996, Ulrich *et al.* 1998b), individual studies which evaluated clinical response using various rating scales were combined. These scales included different versions of the Brief Psychiatric Rating Scale (BPRS) with different subscales, the Clinical Global Impression (CGI), the New Haven Schizophrenia Indices (NHSI), and the Amelioration scale. Although these ratings were standardised to take account of different scales when the results were pooled, some were used unchanged (Ulrich *et al.* 1998b). Additionally, different methods were used to obtain the cut-off points.

The clinical usefulness of routine monitoring of plasma haloperidol levels is unclear (Bernado *et al.* 1993). Haloperidol therapeutic plasma concentrations are still poorly defined (Van Putten & Marder 1995). If plasma drug levels are to be monitored at all, concentrations of 11.20-30.30 ng/ml may be appropriate.

Chapter 7

Pharmacogenetics and psychopharmacotherapy

7.1 Introduction

It is well recognised that the response to drugs often shows wide interindividual variability. A drug that proves to be inactive in some patients may be pharmacologically active or even toxic in others. These differences in drug response are influenced by many variable factors in the biological system, such as body weight, age, sex, general condition of health, and genetic make-up. Biological variability may influence the nature of drug response resulting in idiosyncratic effects such as allergic or hypersensitivity responses which are poorly understood. However, variability usually influences the intensities of drug responses. These result from interindividual variation in ability to absorb, distribute, metabolise or excrete compounds, i.e. the pharmacokinetic parameters which control the amount of drug reaching the site of action. The results of an altered drug response due to variation in pharmacokinetics can only be resolved by altering the dose, dosage form, and route of administration (Rowland 1994). Thus therapeutic drug monitoring (TDM) is especially important for drugs with narrow therapeutic windows.

In this review, the biological factors of age, gender and health condition which modify drug response are briefly considered. The genetic factor as a major determinant for variations in pharmacokinetics among individuals is explored in more detail. Particular attention is given to inter-ethnic variabilities in pharmacokinetics, and response to

psychotherapeutic drugs.

7.2 Biological factors modifying drug response

7.2.1 Age

Children and the elderly are often unusually sensitive to drugs. This is associated with changes in the rates of drug absorption, distribution, metabolism or excretion. In the elderly, the functions of organ systems involved in drug absorption and elimination usually decrease. Gastric pH is increased and gastric motility is decreased with increasing age (Tam 1993). Many elderly patients suffer from multiple illnesses and receive concurrent medications which may have potential to interact with each other. These could partly explain the increased incidence and severity of adverse effects noted in age group (Rowland 1994). In newborn infants, particularly premature infants, many of the enzyme systems responsible for normal metabolic conversion and drug metabolism are underdeveloped. The renal excretion of drug is also depressed (Van den Anker 1996). These all account for pharmacokinetic differences and drug response variabilities.

7.2.2 Gender

Gender appears to be a relatively minor factor contributing to differences in drug response. A number of drugs show sex-related differences in pharmacokinetics. For example, elimination half-life of ofloxacin was shown to be shorter and peak plasma concentration higher in women than men (Sowinski *et al.* 1999). Gender differences in

pharmacokinetics may be due to differences in body composition, weight, ratio of lean to fat body mass, hormonal status, gastric motility and secretion, and hepatic metabolism (Harris *et al.* 1995, Matthews 1995). Women generally have more adipose tissue, secrete less gastric acid and have slower gastric emptying than men. The greater blood pressure response to amlodipine in women may be explained by sex-related pharmacodynamic differences (Kloner *et al.* 1996). These differences may also explain the higher incidence of adverse effects observed in women compared to men (Harris *et al.* 1995).

7.2.3 Disease

Drugs are usually administered to people in whom a physiologic or biochemical process is altered by disease. For instance, hepatic blood flow and extraction are altered in patients with cirrhosis. Drug disposition is thereby influenced by concurrent disease, with hepatic and renal diseases being the major concern. Hepatic drug elimination and the conversion of prodrug, such as enalapril and perindopril, may be substantially reduced in chronic liver disease (Morgan & McLean 1995). Drug-plasma protein binding may be decreased or increased in inflammatory, renal, or liver diseases (Souich *et al.*1993). In patients with hepatic or renal insufficiency, drugs eliminated by those organs must be used with caution and dosage adjustment may be required in these patients.

7.2.4 Genetics

Interindividual variability in drug response is largely due to variability in metabolism in the liver, whose enzyme activity is influenced by both genetic and environmental factors

(Meyer 1994). Genetic polymorphism of drug metabolising enzymes plays an important part in this genetic variability (Meyer 1994). Genetics also contributes to variability in pharmacodynamics of drugs (Rowland 1994).

The study of genetically-controlled variations in response to drugs is referred to as pharmacogenetics (Eichelbaum & Evert 1996). Pharmacogenetic differences can be divided into 2 types: (i) those characterised by alteration in the way the body acts on the drug (altered drug metabolism), such as those due to differences in levels of N-acetyltransferase (NAT2), paraoxonase, butyryl cholinesterase or atypical pseudocholinesterase and (ii) those characterised by alteration in the way drugs act on the body (altered drug action), such as drug-induced haemolysis due to glucose-6-phosphate dehydrogenase deficiency or human dopamine D4 receptors with variable affinity for clozapine (Eichelbaum 1982, Eichelbaum & Evert 1996, Kalow 1993). Interindividual variation in therapeutic drug response and toxicity is most often due to variability of drug metabolism rather than variability of drug receptor responses (Meyer *et al.*1990, Kalow 1991).

The aims of pharmacogenetic research are: (1) identification of the genetic basis of abnormal drug responses, (2) understanding the molecular mechanisms causing these variations, (3) evaluation of their clinical significance, and (4) development of methods for predicting those individuals who will react unusually to drugs (Vesell 1984, Meyer *et al.* 1990).

The study dealing with interethnic or population differences in response to, or in disposition of, drugs and exogenous chemicals is termed pharmacoanthropology.

Pharmacogenetics is hence the component of pharmacoanthropology dealing with inborn differences in drug handling and response (Kalow 1984).

Interethnic differences in drug response have been observed since the rise of pharmacogenetics, in the 1950s (Kalow 1994). Primaquine haemolysis was first found in the US Army, mostly in Black soldiers, during the Second World War. Later studies led to the discovery of genetically-controlled glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, a condition that occurs in approximately 10 % of African-Americans and Mediterranean as well as Southeast Asian populations (Lin *et al.* 1996). Another finding was the discovery of cross-ethnic differences in isoniazid-induced peripheral neuritis and hepatitis (Hughes *et al.* 1954) and the perception that the frequency of slow and fast acetylators varied considerably among different populations (Wood & Zhou 1991). These differences in drug response were poorly understood. Thus different ethnic groups had usually been prescribed similar drug doses without consideration of cross-ethnic variability in pharmacokinetics and pharmacodynamics. With the recent rapid development in pharmacogenetics and molecular biology, mechanisms involved in interindividual variations in drug response are being elucidated. As a consequence, the concept of individualising drug dose to account for ethnic differences has emerged (Kalow 1990).

7.3 Other factors contributing to interethnic differences in drug response

In addition to differences in genetic factors, environmental factors, such as climate,

nutrition and lifestyle, health, and cultural factors contribute to observed cross-ethnic variability in drug disposition or response (Levy 1993, Rowland 1994, Matthews 1995) (Figure 7.1). Climatic differences indirectly affect the availability of different foods. The different pharmacological and toxicological responses to some drugs may be caused by the geographically determined differences in types of food or temperature. Nutrition and lifestyle could also lead to differences in drug disposition. Alteration of enzymatic functions caused by certain foods, drugs, or environmental chemicals can change drug metabolism. The remarkable interethnic variability in therapeutic and side effects profiles of psychotropic drugs could be explained largely by cultural factors such as patients' beliefs and expectation (Lin & Poland 1995). These may affect the nature, frequency and persistence of mental disorders, and attitudes towards diseases and cure. Cultural factors may also influence medication compliance, perception and report of side-effects (Lin & Poland 1995). Determining whether a given interethnic difference in drug response is due to environmental or genetic factors is usually difficult and there is no doubt that there are interactions between nature and nurture.

7.4 Polymorphic drug metabolism and cytochrome P450 monooxygenase

Genetic factors involved in drug metabolism can be classified as monogenic or polygenic. Genes which produce their own marked effects are said to be monogenic. On the contrary, genes which individually produce small differences but which together produce significant effects are referred to as polygenic (Smith & Lawlins 1976). Much pharmacogenetic research focuses on the monogenic control of drug-metabolising

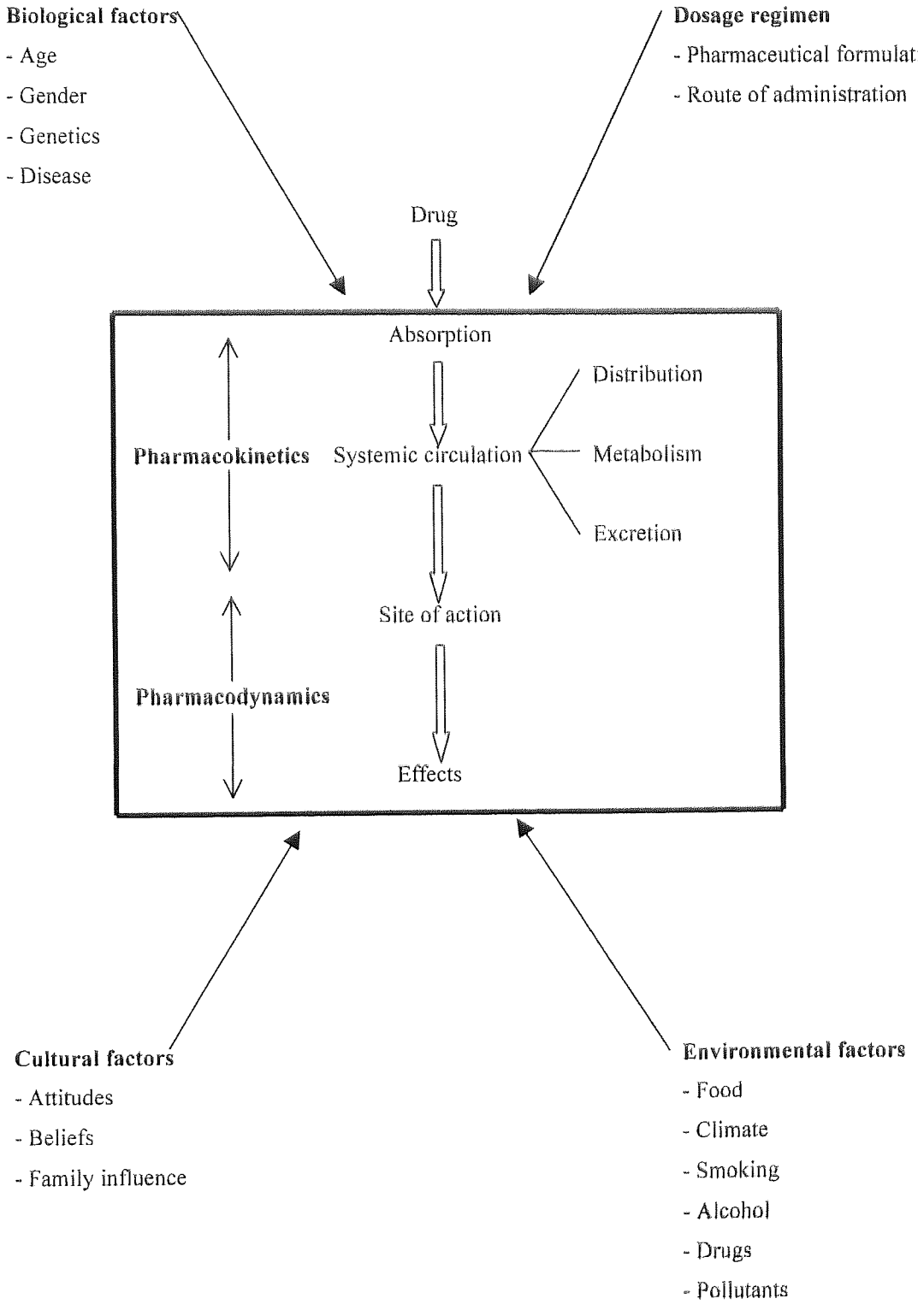

Figure 7.1 Schematic presentation of factors that contribute to variability in drug response.

enzymes (Inaba *et al.*1995). Their recognition enables one to discriminate different phenotypes in a population and therefore the existence of genetic polymorphism. This is a monogenic trait that exists in the population in at least two phenotypes and two genotypes with frequency of at least 1% (Meyer *et al.* 1990, Arias *et al.* 1991, Meyer 1994). Such genes generally affect drug biotransformation by altering the amount of particular enzymes such as glucuronyl transferase, N-acetyltransferase, alcohol dehydrogenase, debrisoquine hydroxylase, and mephenytoin hydroxylase. The population can be divided into two groups (or phenotypes) according to their abilities to metabolise specific probe drugs. Poor or slow metabolisers (PMs) have deficient metabolising ability when compared with persons with normal or extensive metabolic activity. In slow metabolisers, toxicity may occur due to drug or metabolites accumulating in tissues. Alternatively extensive metabolisers may need higher doses if the drug is metabolised much more quickly than usual, causing suboptimal or ineffective drug levels. A wide range of human drug-metabolising enzymes are involved in polymorphism (Table 7.1) (Kalow 1993, Gonzalez & Idle 1994).

Drug metabolism is generally divided into phase I and phase II reactions (Parkinson 1996). Phase I reactions, including oxidation, reduction and hydrolysis, introduce a polar group into the molecule, while phase II reactions conjugate an endogenous hydrophilic substance with a polar group in the molecule. These result in more water-soluble compounds. Of phase I reactions, oxidation is the most important (Blaauboer 1996). It is principally catalysed by the mixed-function oxidase (MFO) system which mainly comprises cytochrome P-450 (CYP) enzymes. Other major components include flavoprotein NADPH and NADP, and cytochrome b_5 (Blaauboer 1996). P-450 enzymes can be found in virtually all tissues, but the highest concentrations are in liver

Table 7.1 Polymorphic drug-metabolising enzymes

	Enzyme
Phase I reactions	
Oxidation	
Cytochrome P450 enzymes	CYP2C9
	CYP2C19
	CYP2D6
Non-cytochrome P450 enzymes	Alcohol dehydrogenase
	Aldehyde dehydrogenase
	Dihydropyrimidine dehydrogenase (DHD)
Hydrolysis	Butyrylcholinesterase
	Arylesterase/paraoxonase
Phase II reactions	
Acetylation	*N*-Acetyltranferase 2 (NAT2)
Glucuronidation	Uridine diphosphate-glucuronosyltransferase (UDPGT)
Methylation	Thiol methyltranferase
	Catechol-*O*-methyltranferase
	Thiopurine methyltransferase (TPMT)
Sulfation	Phenol sulfotransferase
Glutathione conjugation	Glutathione-*S*-transferase M1 (GSTM1)

endoplasmic reticulum (Spatzenegger & Jaeger 1995).

As part of the mixed function oxidase system, the cytochrome P450 enzyme system is responsible for the metabolism of many of drugs and other xenobiotics in man. The enzymes use oxygen to transform lipophilic compounds to more hydrophilic substances which are prone to phase II conjugation reaction (Spatzenegger & Jaeger 1995). The general reaction catalysed by cytochrome P450 has the following stoichiometry:

$$RH + NADPH + H^+ + O_2 \rightarrow ROH + NADP^+ + H_2O$$

The recommended nomenclature of cytochrome P450 isozymes is based upon grouping enzymes and genes into families and subfamilies with the prefix CYP denoting cytochrome P450 (Slaughter & Edwards 1995). Families are characterised by an Arabic number (e.g., CYP2), and subfamilies are indicated by a letter (e.g., CYP2D). The individual enzymes are denoted by an Arabic number; for example, CYP2D6. The members of the same family exhibit more than 40% identity in amino acid sequences, while a subfamily consists of those sharing greater than 55% sequence identity (Slaughter & Edwards 1995).

Several P450 isoenzymes are involved in human hepatic drug metabolism. These enzyme activities can be reduced or increased when exposed to a given drug with inhibiting or inducing properties. This may result in drug-drug interactions particularly when the enzyme inducer/inhibitor are co-administered with drug substrates of CYP isozymes (Tanaka 1998). Major human hepatic drug-metabolising P450 enzymes and their inducer/inhibitor are present in Table 7.2 (Nebert & McKinnon 1994, Slaughter &

Table 7.2 Human major hepatic drug-metabolising P450 enzymes, their substrates and enzyme inducers and inhibitors

P450	substrate	inhibitor	inducer
CYP1A2	caffeine, theophylline, phenacetin, imipramine, verapamil, lidocaine, proprafenone	fluvoxamine, enoxacin, erythromycin, ciprofloxacin, troleandomycin	omeprazole, phenobarbital, phenytoin, rifampicin, polycyclic aromatic hydrocarbons
CYP2C9*, CYP2C10	tolbutamide, phenytoin, s-warfarin	ketoconazole, metronidazole, itraconazole, fluvoxamine,	phenobarbital, rifampicin
CYP2C19*	S-mephenytoin, diazepam, omeprazole, citalopram, proguanil, moclobemide	fluoxetine, sertraline, omeprazole	phenobarbital, rifampicin
CYP2D6*	debrisoquine, sparteine, antiarrhythmics, beta-blockers, monoamine oxidase inhibitors, antipsychotics, tricyclic antidepressants, morphine, dextromethorphan	cimetidine, fluphenazine, quinidine, haloperidol, paroxetine, fluoxetine, sertraline, fluvoxamine, clomipramine, amitriptyline, perphenazine, thioridazine,	not known
CYP2E1	ethanol, chlorzoxazone, halothane, paracetamol, diethyl ether, ethosuximide	disulfiram	ethanol, isoniazid
CYP3A3, CYP3A4, CYP3A5	cyclosporin, dapsone, diltiazem, nifedipine, terfenadine, erythromycin, lidocaine, lovastatin, midazolam, triazolam, quinidine, ethinyl estradiol. imipramine, testosterone	cimetidine, erythromycin, diltiazem, gestodene, fluvoxamine, fluoxetine, paroxetine, ketoconazole, itraconazole, fluconazole, grapefruit juice	carbamazepine, dexamethazone, phenobarbital, phenytoin, rifampicin

* Indicates enzymes subject to genetic polymorphism

Edwards 1995, Spatzenegger & Jaeger 1995, Tanaka 1998).

The isoenzymes CYP2C9, CYP2C19 and CYP2D6 have been shown to be polymorphic in some individuals (Ingelman-Sundberg *et al.* 1999). The cytochrome P450 isozymes, CYP2D6 and CYP2C19 will be considered here in more detail since these are responsible for the metabolism of many psychotropic drugs. Both have been studied more extensively in Caucasian and Oriental populations than in the Black population (Bertilsson 1995, Smith & Mendoza 1996).

7.4.1 Debrisoquine/sparteine hydroxylation polymorphism: CYP2D6

The CYP2D6 has been the most well characterised P450 enzyme showing polymorphism in humans. Debrisoquine and sparteine were the first compounds shown to be subject to CYP2D6 polymorphism and are commonly used as probe drugs in phenotyping enzyme activity (Gonzalez & Idle 1994, Meyer 1994). A remarkable variation in the activity of CYP2D6 is caused by mutations in the CYP2D6 locus, resulting in no encoded enzyme, deficient enzyme, or enzyme with increased activity (Bertilsson 1995). Three phenotypes have been identified so far, i.e. slow/poor metabolisers, rapid/extensive metabolisers, and ultrarapid metabolisers (Coutts & Urichuk 1999). The poor metaboliser (PM) trait is inherited in an autosomal recessive pattern with gene encoding the CYP2D6 enzyme localised on chromosome 22. The extensive metabolisers (EMs) are either homozygous for the unmutated (wild-type) gene coding for this enzyme or heterozygous for one of those alleles with defective function. The amplification of functional CYP2D6 genes accounts for the very rapid metabolism seen in ultrarapid metabolisers.

A wide range of commonly used drugs including antiarrhythmics, beta-blockers, antihypertensives, antipsychotics, and tricyclic antidepressants are metabolised by CYP2D6 (Table 7.3) (Brosen & Gram 1989, Kalow & Bertilsson 1994, Bertilsson 1995). The genotype of each patient prescribed these drugs is potentially of clinical significance. Thus when treated with recommended doses of these drugs, PMs often produce significantly higher plasma drug concentrations and may be more susceptible to adverse effects, while EMs usually show subtherapeutic plasma concentrations. Thus dose adjustment of such compounds may be necessary for PMs to avoid adverse effects (Guttendorf & Wedlund 1992).

The incidence of PMs of debrisoquine varies greatly among various populations. With the exception of San Bushman in Southern Africa, the highest rate was found in Caucasians and lowest in Orientals (Table 7.4). The occurrence seems to be similar in different Caucasian populations, being about 7% in Swedish Caucasians, other European and American Caucasian populations. Likewise, a comparable low incidence of PMs, approximately 1%, has been shown in Chinese, Japanese, and Korean populations (Nakamura *et al.* 1985, Bertilsson *et al.* 1992, Roh *et al.* 1996). Metabolic capacity for debrisoquine hydroxylation appears to be lower in Chinese EMs compared with Caucasian EMs, but may be comparable with other Oriental populations (Lou 1990).

7.4.2 S-mephenytoin hydroxylation polymorphism: CYP2C19

Two phenotypic groups of individuals are identifiable according to their ability to 4'-hydroxylate the racemic drug S-mephenytoin. Mephenytoin, an obsolete anticonvulsant, is used mainly as a probe drug for CYP2C19. The S-enantiomer is rapidly hydroxylated

Table 7.3 CYP2D6 substrates

Cardiovascular agents

Antiarrhythmics	**Beta-blockers**	**Antihypertensives**
propafenone	propranolol	debrisoquine
encainide	timolol	guanoxan
flecainide	metoprolol	Indoramin
perhexiline	bufuralol	clonidine
sparteine	alprenolol	
N-propylajmaline	Labetalol	
quinidine	pindolol	
	oxprenolol	

Psychoactive agents

Antipsychotics	**Antidepressants**
haloperidol	nortriptyline
perphenazine	amitriptyline
thioridazine	clomipramine
fluphenazine	desipramine
clozapine	imipramine
trifluperidol	fluoxetine
zuclopenthixol	paroxetine
risperidone	maprotiline
chlorpromazine	mianserin

Miscellaneous agents

codeine	phenformin	methoxyamphetamine
dextromethorphan	nicotine	phenacetin

Table 7.4 Prevalence of CYP2D6 poor metabolisers (PMs) in various populations

Population	Probe drug	Cut-off point	%PMs	PMs/Total	Reference
African-American	DX	$MR_{DX} > 0.3$	1.9	2/106	Relling et al. 1991
American	DB	$MR_{DB} \approx 13$	7.0	11/156	Wedlund et al. 1984
	DX	$MR_{DX} > 0.3$	7.7	37/480	Relling et al. 1991
Australian	DB	$MR_{DB} > 12.6$	6.0	6/100	Peart et al. 1986
Belgian	DB	$MR_{DB} > 12.6$	7.2	12/167	Leclercq et al. 1987
British	DB	$MR_{DB} > 12.6$	8.9	23/258	Price-Evans et al. 1980
Canadian	SP	N/R	8.3	4/48	Vinks et al. 1982
	SP	N/R	7.2	6/83	Inaba et al. 1984
Chinese (China)	DB	$MR_{DB} > 12$	0.7	2/269	Lou et al. 1987
Chinese (China)	MT	$MR_{MT} > 12.6$	0	0/107	Sohn et al. 1991
Chinese (China)	DB	$MR_{DB} > 12.6$	1.0	7/695	Bertilsson et al. 1992
Chinese (Singapore)	DB	N/A	0	0/97	Lee et al. 1988
Cuna Amerindian (Panama)	SP	N/A	0	0/142	Arias et al. 1988
Danish	SP	N/R	7.3	22/301	Brosen et al. 1985
	SP	N/R	9.2	33/358	Drohse et al. 1989
Dutch	DX	$MR_{DX} > 0.3$	8.0	341/4252	Tamminga et al. 1999
Egyptian	DB	N/R	1.4	1/72	Mahgoub et al. 1979
Estonian	DB	$MR_{DB} > 12.6$	5.1	4/78	Kiivet et al. 1993
	DX	$MR_{DX} > 0.3$	3.8	3/78	Kiivet et al. 1993
	DB	$MR_{DB} > 12.6$	10.1	16/158	Marandi et al. 1996
	DX	$MR_{DX} > 0.3$	9.6	5/52	Marandi et al. 1996
Ethiopian	DB	$MR_{DB} \geq 12.6$	1.8	2/115	Aklillu et al. 1996
Filipino (Saudi Arabia)	DX	N/A	0	0/55	Price-Evans et al. 1995
French	DX	N/R	3.9	4/103	Larrey et al. 1987
	DX	$MR_{DX} > 0.3$	7.4	40/544	Vincent-Viry et al. 1992
	DX	$MR_{DX} > 1.0$	3.0	4/132	Jacqz et al. 1988
German	SP	$MR_{SP} > 20$	6.0	3/52	Ishizaki et al. 1987
Ghanaian	DB	$MR_{DB} > 12.6$	6.3	5/80	Woolhouse et al. 1979
	DB	$MR_{DB} > 12.6$	3.0	6/201	Griese et al. 1999
	SP	$MR_{SP} > 20$	0	0/154	Eichelbaum & Woolhouse 1985
	SP	$MR_{SP} > 20$	2.5	8/326	Griese et al. 1999
Greenlander (Denmark)	SP	$MR_{SP} > 20$	3.2	6/185	Brosen 1986
East Greenlander	SP	$MR_{SP} > 20$	3.3	10/300	Clasen et al. 1991

Table 7.4 Prevalence of CYP2D6 poor metabolisers (PMs) in various populations (continued)

Population	Probe drug	Cut-off point	%PMs	PMs/Total	Reference
West Greenlander	SP	$MR_{SP} > 20$	2.3	4/171	Clasen et al. 1991
Indonesian	MT	N/A	0	0/104	Setiabudy et al. 1994
Italian	DX	$MR_{DX} > 0.3$	4.5	11/246	Spina et al. 1994
Japanese	DB	$MR_{DB} > 13$	0	0/100	Nakamura et al. 1985
	SP	$MR_{SP} > 20$	2.4	2/84	Ishizaki et al. 1987
	MT	$MR_{MT} > 12.6$	0.7	2/295	Sohn et al. 1991
Jordanian	DB	$MR_{DB} > 12.6$	7.1	14/195	Hadidi et al. 1994
Korean	DB	$MR_{DB} > 12.6$	0	0/152	Roh et al. 1996
	MT	$MR_{MT} > 12.6$	0.5	1/218	Sohn et al. 1991
Malays	DB	$MR_{DB} > 10$	2.1	2/97	Lee et al. 1988
Maori (New Zealand)	DB	$MR_{DB} > 12.6$	5.0	5/101	Wanwimolruk et al. 1995
New Zealander	DB	$MR_{DB} > 12.6$	7.2	8/111	Wanwimolruk et al. 1992
Nigerian	DB	$MR_{DB} > 12.5$	8.1	10/123	Mbanefo et al. 1980
Polish	DB	$MR_{DB} > 12.6$	5.8	9/154	Kunicki et al. 1995
Russian (Estonia)	DB	$MR_{DB} \geq 12.6$	7.8	17/218	Marandi et al. 1997
Saudi Arabian	DB	$MR_{DB} > 12.6$	1.0	1/102	Islam et al. 1980
	DX	N/R	2.0	2/102	Price-Evans et al. 1995
Sinhalese	DB	N/A	0	0/111	Weerasuriya et al. 1994
San Bushman (South African)	DB	$MR_{DB} > 12.6$	18.8	18/96	Sommers et al. 1988
South Pacific Polynesian	DB	$MR_{DB} > 12.6$	0	0/100	Wanwimolruk et al. 1998
Spanish	DB	$MR_{DB} > 12.6$	6.6	25/377	Benitez et al. 1988
Swedish	DB	$MR_{DB} > 12.6$	5.4	41/757	Steiner et al. 1988
	DB	$MR_{DB} > 12.6$	8.8	18/205	Sanz et al. 1989
	DB	$MR_{DB} > 12.6$	6.8	69/1011	Bertilsson et al. 1992
Swiss	DB	$MR_{DB} > 12.6$	10.4	23/221	Küpfer & Preisig 1984
Tanzanian	SP	$MR_{SP} > 20$	0.5	1/216	Bathum et al. 1999
	DB	$MR_{DB} > 12.6$	7.5	8/106	Wennerholm et al. 1999
Thai	DB	$MR_{DB} > 12.6$	1.2	2/173	Wanwimolruk et al. 1990
Turkish	DB	$MR_{DB} > 12.6$	3.4	11/326	Bozkurt et al. 1994

DB, debrisoquine; DX, dextromethorphan; MT, metoprolol; SP, sparteine; N/A, not applicable; N/R, not reported

MR_{DB}, metabolic ratio defined as ratio between urinary recovery of debrisoquine and 4-hydroxydebrisoquine

MR_{SP}, metabolic ratio defined as ratio between urinary recovery of sparteine and dehydrosparteine

MR_{DX}, metabolic ratio defined as ratio between urinary recovery of dextromethorphan and dextrorphan

MR_{MT}, metabolic ratio defined as ratio between urinary metoprolol and α-hydroxymetoprolol

in the 4'-position while the R-enantiomer is eliminated slowly by N-demethylation. Those in whom the S-enantiomer is almost completely hydroxylated are extensive metabolisers (EMs). Those who have deficient ability to metabolise S-mephenytoin are poor metabolisers (PMs). Unlike CYP2D6 polymorphism, no ultrarapid metabolisers have been identified for this polymorphic enzyme (Daniel & Edeki 1996). Relatively few important drugs have been shown to be substrates of CYP2C19 (Table 7.5) (Bertilsson 1995, Daniel & Edeki 1996).

The PM phenotype is inherited in an autosomal recessive fashion on chromosome 10 and occurs independently of the debrisoquine/sparteine polymorphism (Meyer *et al.* 1990). The EM phenotype includes both the homozygous and heterozygous genotypes for the wild-type allele(s). This is likely to be one of the reasons for the variability of metabolic activities within the EM phenotype. Among Oriental EMs, there seems to be more heterozygotes than homozygotes, while the proportion of homozygous individuals is much higher in Caucasians compared to heterozygous individuals (Kalow & Bertilsson 1994, Inaba *et al.* 1995). The incidence of PM phenotype varies considerably among different ethnic groups (Table 7.6). Only a low incidence of PMs has been demonstrated in Caucasians (3-6%) and in African, African-American, Arab, and Western populations (2-4%). In contrast, 15 to 30% of the Asian populations have been shown to be poor metabolisers. Drugs metabolised by CYP2C19, in the absence of phenotyping or genotyping, should therefore be prescribed initially in lower doses in those populations. Among the substrates whose metabolism is catalysed by CYP2C19, diazepam and omeprazole show remarkable interethnic differences (Bertilsson 1995).

Table 7.5 Substrates of CYP2C19

S-mephenytoin	imipramine
diazepam and demethyldiazepam	propranolol
omeprazole	proguanil
citalopram	hexobarbital
moclobemide	mephobarbital
carisoprodol	amitriptyline
	clomipramine

Table 7.6 Prevalence of CYP2C19 poor metabolisers (PMs) in various populations

Population	Probe drug	Cut-off point	%PMs	PMs/Total	Reference
African -American	MP	S/R ratio ≥ 0.95	18.5	5/27	Pollock et al. 1991
American	MP	S/R ratio ≈ 1.0	2.6	4/156	Wedlund et al. 1984
	MP	S/R ratio ≥ 0.95	2.7	5/183	Nakamura et al. 1985
	MP	S/R ratio ≥ 0.95	4.1	5/123	Pollock et al. 1991
Canadian	MP	N/R	2.4	2/83	Inaba et al. 1984
	MP	%4-OHMP < 5.0	4.0	5/118	Jurima et al. 1985
Chinese (Canada)	MP	%4-OHMP < 5.0	5.1	2/39	Jurima et al. 1985
Chinese (China)	MP	%4-OHMP < 2.0	17.3	17/98	Horai et al. 1989
Chinese (China)	MP	S/R ratio > 1.0	14.6	20/137	Bertilsson et al. 1992
Danish	MP	S/R ratio ≥ 1.0	2.5	9/358	Drohse et al. 1989
Dutch	MP	S/R ratio ≥ 0.8	1.8	47/2613	Tamminga et al. 1999
Estonian	MP	N/R	3.8	6/156	Kiivet et al. 1993
	MP	S/R ratio > 0.9	1.0	2/210	Marandi et al. 1996
Filipino (Saudi Arabia)	MP	N/R	23.6	13/55	Price-Evans et al. 1995
French	MP	N/R	6.1	8/132	Jacqz et al. 1988
East Greenlander	MP	S/R ratio ≥ 0.9	9.3	28/300	Clasen et al. 1991
West Greenlander	MP	S/R ratio ≥ 0.9	2.9	5/171	Clasen et al. 1991
Indonesian	MP	%4-OHMP < 4.0	15.4	16/104	Setiabudy et al. 1994
Indian	MP	N/R	20.8	10/48	Doshi et al. 1990
Inuit	MP	S/R ratio ≥ 1.0	2.0	3/152	Jurima et al. 1996
Japanese	MP	%4-OHMP < 5.0	22.6	7/31	Jurima et al. 1985
	MP	%4-OHMP < 2.0	22.5	45/200	Horai et al. 1989
	MP	S/R ratio ≥ 0.95	18.0	18/100	Nakamura et al. 1985
Jordanian	MP	S/R ratio ≥ 0.95	4.6	9/194	Hadidi et al. 1995
Korean	MP	%4-OHMP < 2.0	12.6	26/206	Sohn et al. 1992
	MP	S/R ratio ≈ 1.0	15.8	24/152	Roh et al. 1996
Maori (New Zealand)	PG	PG/CG ratio ≥ 10	6.4	3/47	Wanwimolruk et al. 1995
Russian (Estonia)	MP	N/R	2.3	5/218	Marandi et al. 1997
Saudi Arabian	MP	N/R	1.96	2/102	Price-Evans et al. 1995
Sinhalese	MP	S/R ratio ≥ 0.90	14.4	16/111	Weerasuriya et al. 1994
South Pacific Polynesian	PG	PG/CG ratio ≥ 10	13.6	8/59	Wanwimolruk et al. 1998
Spanish	MP	S/R ratio > 1.0	1.3	5/373	Reviriego et al. 1993

Table 7.6 Prevalence of CYP2C19 poor metabolisers (PMs) in various populations (continued)

Population	Probe drug	Cut-off point	%PMs	PMs/Total	Reference
Swedish	MP	S/R ratio > 0.8	2.8	7/253	Sanz et al. 1989
	MP	S/R ratio ≥ 1.0	3.3	16/488	Bertilsson et al. 1992
Swiss	MP	HI > 5.6	5.4	12/221	Küpfer & Preisig 1984
Tanzanian	MP	S/R ratio > 0.9	3.6	7/216	Bathum et al. 1999
Zimbabwean	MP	S/R ratio > 0.9	4.0	4/103	Masimirembwa et al. 1995

MP, mephenytoin; PG, proguanil; CG, cycloguanil; N/R, not reported
PG/CG ratio, ratio of urinary proguanil and cycloguanil
S/R ratio, ratio of urinary S- and R-enantiomers of mephenytoin
%4-OHMP, percentage of dose excreted as 4-hydroxymephenytoin
HI, hydroxylation index for mephenytoin, defined as the amount of S-mephenytoin administered/the amount of urinary 4-hydroxymephenytoin

7.5 Ethnic differences in the metabolism of psychotropic drug substrates of CYP2D6

7.5.1 Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have a narrow therapeutic index. Expression in an individual of CYP2D6 can alter pharmacokinetic or pharmacodynamic characteristics of those TCAs making the dose-response relationship for these drugs unpredictable (Cohen & De Vane 1996).

An early study showing ethnic difference in drug response to antidepressants was conducted in Asians (Pakistani and Indian) and British Caucasians. Allen and co-workers (1977) and Lewis and colleagues (1980) compared plasma concentrations and effects after giving a single dose of clomipramine (25 mg or 50 mg) on two separate occasions. The plasma clomipramine concentrations were shown to be significantly higher in Asians than in British volunteers. Additionally, the incidence of drug-related side-effects was higher in Asians.

In healthy Chinese and Caucasians given a single oral dose of 100 mg desipramine, Rudorfer *et al.* (1984) showed that the mean total plasma clearance was significantly higher in Caucasians than in Chinese (123 L/hr vs 74 L/hr, $P < 0.05$). This difference remained significant after correcting for body weight. There was no significant difference in elimination half-life and plasma protein binding between the two groups. Pi *et al.* (1986) compared the pharmacokinetics of a single dose of 50 mg desipramine

in Asian (Chinese, Japanese, Korean) volunteers with 75 mg desipramine in Caucasian volunteers. The groups differed only in that Asians had an earlier time to peak plasma concentration (4.0 hr vs 6.9 hr, $P < 0.05$). Their subsequent study yielded a different conclusion (Pi *et al.* 1989). Significant differences were found in time to peak plasma concentration (5.0 hr for Asians vs 3.0 hr for Caucasians, $P < 0.05$), and in total clearances of desipramine and hydroxylated desipramine which became statistically nonsignificant when corrected for body weight. Both clearances appeared to follow tri-modal distribution; slow, intermediate, and rapid, with a tendency for more Caucasians to be in the rapid clearance group.

A study of single-dose kinetics of nortriptyline in Japanese and American volunteers revealed that Japanese individuals, while receiving only half as much nortriptyline (50 mg) as Americans, had significantly higher AUC (1150 ng.hr/ml) compared to American subjects (730 ng.hr/ml) (Kishimoto & Hollister 1984). The results, however, may be due to the difference in dosage form as Japanese received a powdered suspension while Caucasians received nortriptyline capsules. Similar results were reported in a subsequent study (Schneider *et al.* 1991). Asians were found to produce greater AUC for both nortriptyline (1509 ng.hr/ml vs 920 ng.hr/ml; $P = 0.07$) and its main metabolite 10-hydroxy-nortriptyline (2671 ng.hr/ml vs 2112 ng.hr/ml; $P = 0.13$) and have lesser clearance of nortriptyline (32 L/hr vs 54 L/hr; $P = 0.08$). These findings suggested relatively slower hepatic hydroxylation in Asians compared to Caucasians (Schneider *et al.* 1991). This could be due to lower metabolic capacity of CYP2D6 which also partly explains why Asians are generally treated with lower doses of antidepressants compared with Caucasians (Lou 1990, Bertilsson 1995).

Fewer studies investigating cross-ethnic differences in drug disposition and response to TCAs have been undertaken in African and Hispanic individuals. Pharmacokinetics study of a single dose nortriptyline in Hispanic (Mexican) and American healthy subjects showed no differences between the two groups (Gaviria *et al.* 1986). The authors suggested that purported hypersensitivity to antidepressant treatment in Hispanic patients may be due to receptor hypersensitivity. The differences between black and white patients in their response to TCAs may be explained by the higher plasma levels in black patients (Ziegler & Biggs 1977). Differences in pharmacokinetics of TCAs among various ethnic groups are summarised in Table 7.7.

7.5.2 Antipsychotic drugs

Asians are reported to require low doses of antipsychotic drugs and appear to develop toxicity at lower doses compared to Caucasians (Yamamoto *et al.* 1979, Lin & Finder 1983, Lin *et al.* 1989). These interethnic variations may be attributed to differences in pharmacokinetics.

Chinese patients were shown to produce 40% to 50% higher plasma haloperidol concentrations compared to non-Chinese patients (Caucasians and blacks) (Potkin *et al.* 1984), and were claimed to require significantly lower doses to achieve haloperidol plasma levels comparable to those in non-Chinese group (Jann *et al.* 1989, 1992). The higher haloperidol levels noted in Chinese may be explained by the lower clearance in this population (6.17 ml/min/kg) (Chang *et al.* 1992) compared with Caucasian reported in the literature (10.8 ml/min/kg) (Holley *et al.* 1983).

Table 7.7 Ethnic differences in response to tricyclic antidepressants

Reference	Subjects	Intervention	Results[†]
Allen *et al.* (1977) Lewis *et al.* (1980)	Male volunteers (19-33 yr) 6 Asians (Indian , Pakistani) 11 English	Clomipramine 25 mg and 50 mg	*25 mg dose* AUC; Asians 224 ± 91 ng.hr/ml English 183 ± 44 ng.hr/ml (P = 0.22) C_{max}; Aisans 20.6 ± 5.7 ng/ml English 13.9 ± 3.8 ng/ml (P = 0.011) *50 mg dose* AUC; Asians 572 ± 111 ng.hr/ml English 352 ± 102 ng.hr/ml (P = 0.0009) C_{max}; Asians 45.1 ± 13.1 ng/ml English 28.3 ± 10.8 ng/ml (P = 0.019) Higher incidence and severity of side-effects in Asians than in English
Kishimoto & Hollister (1984)	Male volunteers 10 Japanese (22-25 yr) 10 Americans (22-30 yr)	Nortriptyline 50 mg for Japanese 100 mg for Americans	AUC; Japanese 1150 ± 316 ng.hr/ml Americans 730 ± 445 ng.hr/ml (P < 0.05) No differences in C_{max}, T_{max}, $T_{1/2}$

Table 7.7 Ethnic differences in response to tricyclic antidepressants (continued)

Reference	Subjects	Intervention	Results†
Rudorfer *et al.* (1984)	Healthy volunteers 14 Chinese (38.4 ± 12.6 yr) 16 Caucasians (38.4 ± 11.2 yr)	Desipramine 100 mg	C_{max}; Chinese 45.4 ng/ml Caucasians 29.8 ng/ml ($P < 0.05$) CL_{DMI}; Chinese 1.27 ± 0.59 L/hr/kg Caucasians 1.78 ± 0.96 L/hr/kg ($P = 0.05$) No differences in $T_{1/2}$, plasma protein binding, and fraction metabolised to OH-DMI
Gaviria *et al.* (1986)	Healthy volunteers (20-30 yr) 10 Americans 10 Mexicans	Nortriptyline 75 mg	No differences in absorption rate constant, C_{max}, T_{max}, V_d, CL, AUC, and $T_{1/2}$
Pi *et al.* (1986)	Healthy volunteers 20 Asians (28.5 yr) (Chinese, Japanese, Korean) 20 Caucasians (38.7 yr)	Desipramine 50 mg for Asians 75 mg for Caucasians	T_{max}; Asians 4.0 ± 1.3 hr Caucasians 6.9 ± 2.6 hr ($P = 0.0001$) No differences in C_{max}, V_d, CL, and $T_{1/2}$
Pi *et al.* (1989)	Healthy volunteers 18 Asians 19 Caucasians	Desipramine 1 mg/kg	T_{max} (median); Asians 5 (3-7) hr Caucasians 3 (1-12) hr ($P < 0.05$) No differences in $C_{max, DMI}$, $C_{max, OH-DMI}$, CL_{DMI}, CL_{OH-DMI}, $T_{1/2, DMI}$, and fraction metabolised to OH-DMI

Table 7.7 Ethnic differences in response to tricyclic antidepressants (continued)

Reference	Subjects	Intervention	Results†
Schneider *et al.* (1991)	Healthy volunteers 6 Asians (24.5 ± 2 yr) 8 Caucasians (28 ± 2.9 yr)	Nortriptyline 40 mg	AUC_{NT}; Asians 1509 ± 738 ng.hr/ml Caucasians 920 ± 529 ng.hr/ml (P = 0.07) $AUC_{10\text{-}OHNT}$; Asians 2671 ± 756 ng.hr/ml Caucasians 2112 ± 569 ng.hr/ml (P = 0.13) CL_{NT}; Asians 32 ± 16 L/hr Caucasians 54 ± 24 L/hr (P = 0.08)

† mean ± SD
AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; CL, clearance; DMI, desipramine; NT, nortriptyline; OH-DMI, hydroxydesipramine; OH-NT, hydroxynortriptyline; T_{max}, time to reach maximum concentration; $T_{1/2}$, half-life; V_d, volume of distribution; yr, years,

Lin and co-workers (1988) studied the pharmacokinetics of haloperidol in Caucasian, American-born Asian, and foreign-born Asian volunteers. The single dose of haloperidol was administered orally and intramuscularly on 2 separate occasions. Asian groups were found to achieve higher serum haloperidol concentrations than did Caucasian group following both oral and intramuscular administrations. The differences were greater following oral than intramuscular administration. There was no difference between foreign-born Asians and American-born Asians. The results suggested interethnic variability in first-pass metabolism or oral absorption.

Cross-ethnic variations in kinetic profiles of haloperidol could also be partially explained by the differences in the occurrence of PMs of CYP2D6. A number of studies have demonstrated interethnic differences in plasma reduced haloperidol (RH) concentrations and reduced haloperidol/haloperidol (RH/HL) ratios. Chinese subjects were found to have remarkably lower reduced haloperidol levels and RH/HL ratios than non-Chinese (Blacks, Caucasians, and Hispanic) subjects (Jann *et al.* 1989, 1992). The higher haloperidol plasma concentrations and lower reduced haloperidol levels and RH/HL ratios observed in Chinese may be explained by the lower metabolic capacity of Chinese EMs compared to Caucasian EMs (Lou 1990). Other metabolic pathways which include N-dealkylation of haloperidol and back oxidation of reduced haloperidol to haloperidol may also be responsible for interindividual and interethnic variability in haloperidol metabolism (Jann *et al.* 1993).

Ethnic variations in pharmacokinetics of clozapine have been suggested by studies in Korean-Americans (Matsuda *et al.* 1996) and Chinese (Chang *et al.* 1997). Preliminary findings indicated that Korean-American patients achieved significantly lower clozapine

concentrations than Caucasians, even after controlling for the differences in daily doses (Matsuda *et al* 1996). In contrast to Korean-American patients, Chinese patients were reported to have 30% to 50% higher concentrations than those reported for Caucasians in the literature. The results suggested a slower rate of clozapine metabolism in Chinese (Chang *et al.* 1997). These studies, however, were not always aimed at investigating pharmacokinetics and were probably confounded by other variables known to affect drug pharmacokinetics such as diet and enzyme inducers/inhibitors. More rigorous and carefully designed studies are necessary to confirm any observed differences across ethnic groups.

There have been comparatively few studies examining the mechanisms responsible for the difference in clinical response of antipsychotics in black patients (Masimirembwa & Hasler 1997). Midha and co-workers (1988a) studied pharmacokinetics of trifluoperazine in black and white healthy male subjects. Although there was wide intersubject variation in pharmacokinetic parameters, no significant difference was detected between the two groups. Nor was there any ethnic difference in the pharmacokinetics of fluphenazine (Midha *et al.* 1988b). Ethnic variations in response to antipsychotic drugs are summarised in Table 7.8.

Table 7.8 Ethnic differences in response to antipsychotic drugs

Reference	Subjects	Intervention	Results[†]
Potkin *et al.* (1984)	Schizophrenic patients 18 Han Chinese (25.5 ± 4.8 yr) 18 Americans (32.9 yr) (15 whites, 3 blacks)	Haloperidol 0.4 mg/kg/d for 6 weeks	52% higher mean plasma haloperidol level in Chinese than in Americans (P = 0.024)
Lin *et al.* (1988)	Male volunteers 12 Caucasians (26.8 ± 5.7 yr) 11 ABA (24.4 ± 5.1 yr) 11 FBA (30.2 ± 3.8 yr) (Filipino, Chinese, Japanese, Korean)	Haloperidol 0.5 mg IM and 1 mg p.o.	No differences in frequency or severity of sedative side effects *Oral administration* C_{max}; Caucasians 0.71 ± 0.33 ng/ml ABA 1.41 ± 0.84 ng/ml (P < 0.01 vs Caucasians) FBA 1.67 ± 0.52 ng/ml (P < 0.01 vs Caucasians) Shorter T_{max} for ABA and FBA than for Caucasians (P < 0.025) No differences in serum prolactin concentrations *Intramuscular administration* C_{max}; Caucasians 1.18 ± 0.58 ng/ml ABA 1.61 ± 0.75 ng/ml FBA 1.98 ± 0.81 ng/ml (P < 0.05 vs Caucasians) No differences in T_{max} Serum prolactin concentration; Caucasians 6.19 ± 3.35 ng/ml ABA 9.51 ± 3.77 ng/ml (P < 0.05 vs Caucasians) FBA 11.08 ± 4.52 ng/ml (P < 0.01 vs Caucasians)

Table 7.8 Ethnic differences in response to antipsychotic drugs (continued)

Reference	Subjects	Intervention	Results[†]
Midha *et al.* (1988a)	Male volunteers (18-40 yr) 32 whites 25 blacks	Trifluoperazine 5 mg	No differences in C_{max}, T_{max}, AUC, V_d, CL, $T_{1/2}$
Midha *et al.* (1988b)	Male psychiatric patients (20-41 yr) 9 whites 12 blacks	Fluphenazine 10 mg	No differences in C_{max}, T_{max}, AUC, $T_{1/2}$
Jann *et al.* (1989)	Schizophrenic patients 32 Chinese (34.8 ± 11.7 yr) 32 non-Chinese (36.7 ± 11.6 yr) (Hispanic, black, white)	*Chinese*: fixed dose of haloperidol 10 or 20 mg/d for 2weeks, and clinically adjusted dose for 4 weeks *Non-Chinese*: Clinically adjusted dose of haloperidol	*Haloperidol dose*; Chinese 18.8 ± 7.1 mg/d Non-Chinese 31.6 ± 13.7 mg/d (P = 0.001) *Reduced haloperidol plasma levels*; Chinese 5.3 ± 4.3 ng/ml Non-Chinese 16.3 ± 18.5 ng/ml (P = 0.003) No differences in haloperidol plasma levels Higher incidence of extrapyramidal side effects in Chinese than in non-Chinese (P = 0.043)
Lin *et al.* (1989)	Schizophrenic patients 13 Caucasians (34.1 ± 8.4 yr) 16 Asians (33.8 ± 12.6 yr) (Chinese, Japanese, Filipino, Korean, Vietnamese)	Haloperidol 0.15 mg/kg/d for 2 weeks, then clinically adjusted dose for 10 weeks	*Fixed dose phase;* No differences in haloperidol plasma levels *Variable dose phase;* Lower haloperidol dose at neuroleptic threshold (P < 0.005) and at optimal dose (P < 0.001) in Asians than in Caucasians Lower haloperidol plasma levels at neuroleptic threshold (P < 0.02) and at optimal response (P < 0.05) in Asians than in Caucasians

Table 7.8 Ethnic differences in response to antipsychotic drugs (continued)

Reference	Subjects	Intervention	Results[†]
Jann *et al.* (1992)	Schizophrenic patients 156 Chinese (29.9 ± 9.4 yr) 37 Caucasians (45.1 ± 14.6 yr) 51 Hispanics (40.1 ± 10.4 yr) 23 Blacks (39.8 ± 15.1 yr)	Clinically adjusted dose of haloperidol	*Haloperidol dose*; Chinese 21.1 ± 12.9 mg/d Caucasians 33.1 ± 25.1 mg/d (P < 0.01 vs Chinese, P < 0.05 vs Hispanics) Hispanics 47.1 ± 22.0 mg/d (P < 0.01 vs Chinese) Blacks 35.5 ± 26.5 mg/d (P < 0.01 vs Chinese, P < 0.05 vs Hispanics) *Haloperidol plasma levels*; Chinese 18.3 ± 13.4 ng/ml Caucasians 17.2 ± 15.9 ng/ml (P < 0.05 vs Hispanic) Hispanics 28.4 ± 22.5 ng/ml (P < 0.01 vs Chinese) Blacks 16.4 ± 15.8 ng/ml (P < 0.05 vs Hispanics) *Reduced haloperidol plasma levels*; Chinese 11.4 ± 18.9 ng/ml Caucasians 19.6 ± 24.5 ng/ml (P < 0.01 vs Chinese) Hispanics 33.4 ± 46.1 ng/ml (P < 0.01 vs Chinese) Blacks 20.5 ± 26.3 ng/ml (P < 0.01 vs Chinese)

Table 7.8 Ethnic differences in response to antipsychotic drugs (continued)

Reference	Subjects	Intervention	Results†
Matsuda *et al.* (1996)	Schizophrenic patients 17 Korean-Americans 7 Caucasians	Clinically adjusted dose of clozapine	*Clozapine dose*; Korean-Americans 366 ± 196 mg/d Caucasians 532 ± 194 mg/d ($P < 0.025$) *Clozapine plasma levels*; Korean-Americans 212 ± 148 ng/ml Caucasians 376 ± 170 ng/ml ($P < 0.05$) *Percent change in BPRS* Korean-Americans 48 ± 12.6 Caucasians 37.1 ± 15.3 ($P < 0.05$) Significantly higher rate of anticholinergic side-effects in Korean-Americans ($P < 0.05$)

† mean ± SD
ABA, American-born Asians; FBA, foreign-born Asians; AUC, area under the plasma concentration-time curve; BPRS, Brief Psychiatric Rating Scale; CL, clearance; IM, intramuscular; p.o., per oral; C_{max}, maximum concentration; T_{max}, time to reach maximum concentration; $T_{1/2}$, half-life; V_d, volume of distribution; yr, years

7.6 Ethnic differences in the metabolism of psychotropic drug substrates of CYP2C19

7.6.1 Diazepam

There have been relatively few studies concerning ethnic differences in response to benzodiazepines. Ghoneim *et al.* (1981) investigated ethnic differences in kinetic and dynamic effects of diazepam in healthy Caucasians and Orientals. Oriental subjects were found to have lower total body clearance (mean ± SE; 0.29 ± 0.03 vs 0.40 ± 0.03 ml/min/kg, $P < 0.01$). The volume of distribution was 20% to 30% higher in Caucasians, but no difference was seen when corrected for body weight. The serum protein binding was almost identical. A slower metabolism of diazepam in Oriental subjects may be due to the higher percentage of CYP2C19 deficiency among this group. There were no differences in mental and psychomotor effects between the two groups (Ghoneim *et al.* 1981). It is possible that the relatively high dose of diazepam (0.2 mg/kg) used may have been too sedating to differentiate any ethnic differences in mental or behavioural responses. In addition, the subjects also came from mixed ethnic backgrounds. For example, Caucasians included German, Scandinavians, Dutch, Irish, Scotch, Russian, and Spanish. Chinese, Japanese, Japanese-American, and Chinese-American were defined as Orientals.

It has been noted that Hong Kong physicians normally prescribe smaller doses of diazepam for Chinese than for white Caucasians (Kumana *et al.* 1987). In their pharmacokinetic study, Kumana *et al.* (1987) reported results which contrast to those

previously shown (Ghoneim *et al.* 1981). Differential responses to diazepam found in Chinese and Caucasian subjects were primarily due to the differences in body fat which was greater among the latter group (Kumana *et al.* 1987). This factor is likely to be the reason for the higher doses required by Caucasian patients.

7.7 Ethnic differences in pharmacodynamics

Cross-ethnic differences in response to drugs cannot always be explained solely by pharmacokinetic factors. Ethnic variations such as those in the effects of beta-adrenoceptor antagonists and those in the therapeutic concentrations of several psychotropic drugs have led to the concept of ethnic differences in pharmacodynamics. Unlike genetic polymorphism of drug-metabolising enzymes, little is known about ethnic variations in the structure and functions of receptors (Lin *et al.* 1993).

7.7.1 Antipsychotic drugs

The majority of the studies of ethnicity and antipsychotic drug response has been conducted in Asian and Caucasian populations, with fewer studies being undertaken in Hispanic and African-Americans. Although a number of studies have suggested ethnic differences in dose requirement and adverse reactions, the data are inconsistent.

Asians are reported to require lower doses of antipsychotic drugs compared to Caucasians (Lin & Finder 1983, Rosenblat & Tang 1987, Lin *et al.* 1989, Collazo *et al.* 1996). But this was not confirmed by other studies which show that both populations optimal doses were comparable (Sramek *et al.* 1986, Zhang-Wong *et al.*1998). Two

further studies (Pearlman 1984, Strickland *et al.* 1991) reported that while black patients (Africans and African-Americans) required substantially higher doses of antipsychotics, Hispanics required smaller doses compared to Caucasians (Collazo *et al.* 1996). Still other studies reported different results. There were no differences in the dosage of antipsychotics required by Hispanics, Anglos, and blacks (Adams *et al.* 1984, Sramek *et al.* 1991). However, ethnic differences in dosing may well be due to variability in attitudes or habits affecting assessment and prescribing practices rather than from actual differences in antipsychotic drug response (Frackiewicz *et al.* 1997).

Interethnic differences in pharmacodynamics of antipsychotic drugs has been suggested by the marked differences in prolactin response to haloperidol administration (Lin *et al.* 1988). Asian subjects were reported to produce greater serum prolactin levels than Caucasian subjects. This remained statistically significant after controlling for difference in haloperidol concentrations, suggesting that the two groups differ in their dopamine receptor-mediated response (Lin *et al.* 1988). That Asian schizophrenic patients responded optimally to significantly lower plasma haloperidol concentrations compared to Caucasians has been attributed to ethnic variation in receptor sensitivity (Lin *et al.* 1989).

A greater degree of improvement at significantly lower clozapine doses and plasma levels, and a significantly higher incidence of anticholinergic and other side-effects in Korean-American patients compared to Caucasian patients also suggest ethnic differences in clozapine pharmacodynamics (Matsuda *et al.* 1996). It has been hypothesised that interindividual differences in response to clozapine may be attributed to polymorphism of the dopamine D4 receptor, the major binding site of clozapine. At

least 5 alleles have been identified, each differs in their binding affinity with clozapine *in vitro* (Van Tol *et al.* 1992). Thus far, therapeutic response to and side-effects of clozapine have been reported not to be associated with genetic variants of the dopamine D4 receptor (Rao *et al.* 1994, Rietschel *et al.* 1996). Receptor polymorphism therefore does not seem to explain the interethnic variation in clozapine response.

Ethnic differences in adverse responses to clozapine were suggested by the observation of an association between Jewish ethnic background and the development of agranulocytosis (Lieberman *et al.* 1990). An increased risk of clozapine-induced agranulocytosis was found to be related to human lymphocyte antigen (HLA) -B38, DR4 and DQw3 haplotypes which are prevalent in the Jewish population (10%-12%) (Lieberman *et al.* 1990). In the white population in general, the corresponding figure is 0.4%-0.8% (Lieberman *et al.* 1990).

While some studies reported that extrapyramidal side-effects were found more frequently in Asian patients than Caucasian patients (Binder & Levy 1981, Lin *et al.* 1989), others observed no difference between the two populations (Lin & Finder 1983, Sramek 1986). Early studies reported no differences in the incidence of tardive dyskinesia among Caucasians, Hispanics and African-Americans (Sramek *et al.* 1991). However, others found that the incidence rate was 1.83 times (95% CI 1.08 to 3.10, P = 0.025) greater in non-white (mostly black) than in whites (Glazer *et al.* 1994). The results of those studies appear to be controversial and be confounded by variables such as mixed ethnic groups, limited sample sizes, different diagnostic criteria for both psychiatric disorders and tardive dyskinesia, examination techniques, and uncertain inter-rater reliability among research groups (Pi *et al.* 1993). The differences in rates of

adverse reactions, however, may be explained either by differences in sensitivity to antipsychotic-induced adverse effects (pharmacodynamic factor), or by metabolic impairment in Asian patients (pharmacokinetic factor) leading to higher plasma drug concentrations and greater likelihood of developing side-effects.

7.7.2 Tricyclic antidepressants

Generally, the evidence suggesting ethnic differences in psychotropic pharmacodynamics has been primarily based on indirect assessments and inferences (Lin & Poland 1995). Although ethnic differences in pharmacodynamics of TCAs have not been directly examined, there is evidence that differences in therapeutic plasma concentrations and sensitivity to adverse effects of these drugs exist among different ethnic backgrounds (Silver *et al.* 1993, Sramek & Pi 1996).

Dosages of TCAs prescribed for Asian patients were significantly lower than for Caucasian patients (Kinzie & Manson 1983, Rosenblat & Tang 1987). Two studies in Asians (Yamashita & Asano 1979, Hu *et al.* 1983) indicated that severely depressed hospitalised Asian patients responded clinically to lower combined concentrations of imipramine and desipramine (130 ng/ml) compared to levels of 225 ng/ml or higher previously reported in Caucasians (Glassman *et al.* 1977). It was suggested that differential brain receptor responsiveness may partly be responsible for ethnic differences in dose requirement of TCAs (Lin *et al.* 1991).

Hispanic patients have been reported to require lower doses of antidepressants and experience more side-effects at lower doses compared to Caucasians (Escobar & Tauson

1980, Lawson 1986). Marcos and Cancro (1982) compared antidepressant response to TCAs between Hispanics and Caucasians and reported that Hispanic (predominantly Puerto Rican) patients required less than half of the doses of TCAs and complained of more side-effects than Caucasian patients. No pharmacokinetic data were collected. It is therefore not possible to ascertain whether the observed differences were due to pharmacokinetic or pharmacodynamic factors. Further study of nortriptyline indicated no kinetic variations between Hispanic and Caucasian populations (Gaviria *et al.* 1986). Taken together, it is likely that more favourable response by Hispanics to lower doses of TCAs compared with Caucasians may be due to pharmacodynamic differences.

Black American patients were reported to respond faster and better to TCAs while developing more toxic side-effects than Caucasians (Strickland *et al.* 1991). These responses may be due to higher plasma TCAs levels shown in African-Americans than in Caucasians (Ziegler & Biggs 1977). Interpretation of data on cross-ethnic differences in pharmacokinetics and pharmacodynamics of TCAs is made difficult by poor study designs. Whether these differences are truly due to ethnicity remains to be clarified (Pi 1998).

Data from pharmacodynamic and pharmacokinetic studies indicate that both factors which appear largely to be genetically determined contribute to ethnic variations in response to psychopharmacotherapy. Those studies, however, have been limited by their small and often inadequately characterised samples of subjects. Moreover, these variations can also be influenced by environmental and psychosocial factors such as physicians prescribing habits and attitude towards psychopharmacotherapy, patients attitude, and availability of medication and facilities (Pi 1998). Despite the existing

evidence to suggest that various ethnic groups differ pharmacokinetically and pharmacodynamically in their response to psychotropic drugs, carefully designed and well controlled studies are needed before any firm conclusions can be made.

7.8 Clinical implications of pharmacogenetics

It has been well recognised that interindividual variability in drug response is caused mainly by drug metabolism. Recent advances in molecular biology and pharmacogenetics have helped clarify observed differences in dynamics and kinetics of many drugs. The impact of pharmacogenetics on clinical practice can be highlighted (Edeki 1996). PMs generally produce higher plasma drug concentrations and are more likely to be prone to side-effects and toxicity when the parent compound is metabolised exclusively by polymorphic enzymes. EMs usually show subtherapeutic plasma levels. On the other hand, defective drug metabolism may also cause therapeutic failure in PMs or impose higher risk to develop toxicity in EMs if the enzyme deficiency is responsible for the formation of an active metabolite. For instance, PMs taking codeine may not benefit from its analgesic effect due to a failure in achieving adequate therapeutic plasma levels of morphine which is formed by *O*-demethylation of codeine by CYP2D6. Pharmacokinetics of the substrates of polymorphic P450 enzymes may be altered by drug interactions with certain drugs with high affinity to the enzymes. For example, the reduction of oral clearance of TCAs by fluoxetine can be explained by its inhibition of CYP2D6 (Otton *et al.* 1993). The consequences are noticeably greater in EMs than in PMs. The higher plasma haloperidol concentrations (Lin *et al.* 1988, Jann *et al.* 1989), lower does of antipsychotic drugs used (Lin *et al.* 1989), and higher concentrations of

nortriptyline (Schneider *et al.* 1991) in Asian populations including Chinese compared to Caucasian populations are examples of clinical consequences of population differences in the distribution of CYP2D6 defective alleles.

The major clinical implications of polymorphism of drug metabolising enzymes are obviously related to drug toxicity and therapeutic failure. Its clinical relevance, however, is strongly dependent on the therapeutic class of compounds involved and on the concentration-effect relationships of the desired and unwanted effects (Tucker 1994, Inaba *et al.* 1995). For example, beta-adrenoceptor antagonists are metabolised by CYP2D6. Deficiency in this pathway would result in higher bioavailability of parent drugs with an increased risk of cardiovascular side-effects. Because these drugs have a large therapeutic margin and adverse effects are clinically mild, plasma-drug concentration monitoring is not necessary. In contrast, tricyclic antidepressants and some antipsychotics require monitoring of plasma drug levels in order to prevent untoward effects in poor metabolisers and therapeutic failure in ultrarapid metabolisers (Tucker 1994, Inaba *et al.* 1995).

The CYP450 polymorphism, particularly CYP2D6, is of clinical importance principally in psychopharmacotherapy. For example, antidepressants and antipsychotics can be either substrates or inhibitors of CYP2D6. Yet no consensus has emerged as to the usefulness of screening psychiatric patients for their enzyme activity or gene expression (Chen *et al.* 1996). Moreover, the application of pharmacogenetics is limited by inability to determine individual phenotypes in general clinical settings and the process is time- and cost-consuming (Cohen & De Vane 1996, Zuhlsdorf 1998). Despite several advantages over phenotyping, genotyping can be performed only when mutant alleles

have already been identified. Phenotyping of specific ethnic groups may be informative when individual phenotypes or genotypes are not available (Chen *et al.* 1996). An awareness of pharmacogenetics will help explain interindividual and interethnic variations in response to drugs, especially those used in psychiatry, and help clinicians better manage their patients'pharmacotherapy.

The role of pharmacogenetics is increasingly recognised by the pharmaceutical industry as shown by its consideration during programmes directed at drug discovery and development (Lichter & Kurth 1997, Zuhlsdorf 1998). Candidate drugs whose metabolism may involve polymorphic pathways can be screened out. Pharmacogenetic data will be used either to design better compounds or to help plan clinical studies. Screening volunteers and patients included in clinical trials may become necessary to minimise adverse events and optimise efficacy. Clinical investigations in various populations will help clarify interethnic differences in drug disposition and response to a given drug. Knowledge of pharmacogenetics should help reduce the time and costs associated with drug development.

7.9 Conclusion

Clinical responses to drugs vary widely between populations. With the rapid developments in molecular biology, elucidation of the mechanisms leading to individual variations in drug response will become easier. Information crucial to the understanding of intra- and inter-ethnic differences in response to drugs will become more generally available. A large number of drug metabolising enzymes have been shown to be

polymorphic. Of the P450 enzymes, the debrisoquine/sparteine hydroxylase (CYP2D6) and the S-mephenytoin hydroxylase (CYP2C19) have been the most extensively studied. The two isozymes may be of particular importance in psychopharmacotherapy as they are responsible for the metabolism of many commonly used psychotropic drugs including antipsychotics, antidepressants and benzodiazepines. In contrast to increasing insights into genetic polymorphism in drug metabolism, knowledge about interindividual and interethnic variations in drug pharmacodynamics is more sparse and more research on this aspect is required.

Studying ethnic differences in psychopharmacology is often difficult and results of published studies are sometimes contradictory. Problems with published studies include ill-defined study samples, small sample sizes, poor study design, variable diagnostic criteria, lack of control of factors affecting pharmacokinetic parameters, and insufficient emphasis on pharmacodynamics (Pi 1998). Broad classifications of ethnicity have been used in the majority of studies instead of precisely defined ethnic groups. For example, the term Asians is commonly used to encompass various ethnic groups such as Chinese, Vietnamese, Korean, and Filipino. Caucasians or whites may include several populations of European and Americans who may differ genetically and culturally. Pharmacogenetic studies in homogeneous ethnic groups would help to identify true differences in intra- and inter-ethnic variations in response to drugs.

Chapter 8

General discussion

Bipolar disorder or manic-depressive illness is a recurrent mental illness characterised by clinically marked mood swings between mania and depression. A manic episode involves a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Additional symptoms include inflated self-esteem, flight of ideas, expansive sociability, distractibility, pressure of speech, and decreased need for sleep. Signs and symptoms of depression include persistent feelings of sadness, anxiety, guilt, or hopelessness, loss of interest or pleasure in all or most activities, disturbances in appetite and sleep, loss of energy, difficulty in thinking, concentrating, or making decision, and suicidal ideation or attempts. These symptoms represent a change from the patients' previous functioning and cause clinically significant distress or impairment in social and occupational functioning.

Evidence from epidemiology and family studies suggests that bipolar disorder is an heritable illness (McGuffin & Katz 1989, Grof *et al.* 1994). The severity of the disease is incredibly diverse. For example, some patients suffer mild, infrequent episodes, while others have more severe, protracted courses. Moreover, patients with bipolar disorder may be affected by other mental illnesses, such as anxiety disorder and alcoholism, at the same time. Pharmacological treatments are a crucial component of the management of bipolar disorder and may be used in the acute treatment of manic and depressive episodes and/or in the prophylaxis of recurrence of further episodes.

Since the principal treatment of bipolar disorder often involves medication, evaluation of the patients and rational use of an appropriate psychopharmacological agent is necessary. A number of measures have been used to assess the severity of illness and its response to treatment. Eight symptom-rating scales were systematically identified through reports of clinical trials of mania and their qualities were critically appraised. The Mania Rating Scale (MRS) was the most commonly used for assessing treatment response. Two more recently developed scales are the Manchester Nurse Rating Scale for Mania (MNRS-M) and the Clinician-Administered Rating Scale for Mania (CARS-M). The latter appears well validated. But its in-use reliability needs to be further explored. The translation of observed changes in instrumental ratings into clinically meaningful change has to be further established. In particular, the relative weighting to be attached to the individual items needs further study. The advantage of the MRS is that there is a relatively extensive database of studies based on it and this will no doubt ensure that it remains a gold standard for the foreseeable future.

Lithium has long been considered as effective treatment for acute mania (Licht 1998). This is confirmed by our results. On the basis of antimanic efficacy and short-term safety profiles, lithium should remain the first line treatment for acute mania. Principally, patients treated with lithium were twice as likely to obtain remission than when they were given placebo or chlorpromazine. Neither carbamazepine nor valproate was more effective than lithium when improvement rate or the reduction in symptom severity score was used as efficacy measures. Haloperidol was no better than lithium on the basis of improvement based on assessment of global severity. Symptom and global severity was at least as well

controlled with lithium as with verapamil. Short-term side-effects of lithium were as well tolerated as those of carbamazepine or valproate.

Given that outcome measures in clinical trials of mania are diverse and the identified mania rating scales are generally poorly validated, there is a need to develop a standardised outcome measure for evaluating treatment efficacy. Categorical outcomes may be more clinically useful than rating scale scores. But they need to be precisely defined and universally agreed on so that the results of future trials can be directly compared.

The efficacy of lithium in the prophylaxis of bipolar disorder has been recently questioned (Moncrieff 1997). Based on available evidence, our results strongly support the efficacy of lithium in the prophylaxis of bipolar disorder showing that patients receiving placebo or imipramine were twice as likely to relapse than when they were on maintenance treatment with lithium. Adding imipramine to lithium provided no additional benefit than lithium alone. The risk of relapse was greater with lithium alone than with the lithium-divalproate combination, but was comparable to that with carbamazepine. Side-effects with lithium appear to be tolerable either in the short-term or in maintenance treatment and were no more than those caused by carbamazepine nor valproate. Similarly, outcome measures in prophylaxis of bipolar disorder need standardisation. Relapse or time in remission may be useful, but again precise definitions are essential.

Based on individual data concerning plasma haloperidol concentrations and percent improvement in psychotic symptoms, our results suggest an optimal concentration

range of 11.20-30.30 ng/ml. At the cut-off point the predicted percentage responding is 70% and the predicted percentage nonresponding is 43%. A minimum of 2 weeks should be allowed before evaluating therapeutic response. Monitoring of drug plasma levels seems not to be necessary unless behavioural toxicity or noncompliance is suspected.

It is generally recognised that different individuals may show widely different pharmacological responses to the same drugs. Four principal types of factors account for this variability: biological factors, environmental factors, cultural factors and factors related to administration. Genetic differences make up one of the most important biological factors contributing to variability in drug response. Differences in receptor sensitivity may have a genetic basis but it is with respect to metabolism that genetic differences have been most clearly demonstrated. Genetic polymorphism often enables division of individuals within a given population into two groups, poor metabolisers (PMs) and extensive metabolisers (EMs) of certain drugs.

The two most extensively studied genetic polymorphisms are those involving debrisoquine/sparteine hydroxylase (CYP2D6) and S-mephenytoin hydroxylase (CYP2C19). To greater and lesser extents, both enzymes are responsible for the metabolism of clinically important psychotropic drugs including antidepressants and antipsychotics. About 7% of Caucasians and 1% of Orientals are PMs of debrisoquine, while the incidence of PMs of S-mephenytoin is much higher in Asians (15-30%) than in Caucasians (3-6%). Variability in pharmacokinetics of a number of psychotropic drugs is associated with oxidation polymorphism. Ethnic differences

in responses to antipsychotic and antidepressant drugs may be explained, at least in part, by ethnic variations in polymorphic isoenzymes. Ethnic variations in pharmacodynamics are suggested by observed ethnic differences in therapeutic concentrations and adverse drug responses. However, differences in response to psychotropic drugs cannot be explained solely by genetic make-up in pharmacokinetics and pharmacodynamics. Psychosocial factors also play an important part in the observed differences. This makes it difficult to study the effect of ethnicity on psychopharmacological responses. This may account for apparently conflicting results.

Appendix

Extracting data for meta-analyses when only graphical results are presented: method description and validation

Background

Authors often present data in graphical form only. When undertaking a meta-analysis, an objective is to be comprehensive about the inclusion of valid data. Discarding graphical data is inappropriate. Therefore, reliable methods for abstracting such information from research reports are important but do not appear to have been explored in detail in the literature. In this report we describe a computerised method which we believe has wide applicability and is amenable to rigorous cross-validation and quality assurance and control. We illustrate application of the method with a critical appraisal of published studies investigating the relationship between plasma drug concentration and clinical response using amitriptyline as an exemplar. We use only reports where both graphical and tabular data are provided to enable us to validate our proposed method.

Method

A systematic method for literature retrieval was adopted, starting with a search of the MEDLINE database and using amitriptyline combined with one of, blood level, plasma level, therapeutic drug monitoring, pharmacokinetics, and pharmacodynamics as key

words. The computerised search covered the period 1966-end of 1999. A historical search was then undertaken through the reference lists of the publications retrieved.

Reports which included both graphical and tabular data were identified from the set retrieved and the graphs electronically scanned using a Logitek Freescan scanner and Adobe PhotoDeluxe V1 software. The images were saved as pcx files. Each graph was then analysed using PhotoFinish version 3.0 (Zsoft corporation). A typical graph would include a series of points on a graph with drug blood level on the X axis and clinical outcome, notably the Hamilton Depression Score, on the Y axis. The coordinates of each point which represents the blood level - clinical score pair are read automatically using the cross-hair facility of PhotoFinish. Once a point has been identified, its coordinates were read by blowing it up to 1600% magnification. Four readings were taken: two extreme x values and two extreme y values. The coordinates of the point were taken as the average of the two x and the two y values. Each graph was read independently by two abstractors, on two occasions at least half an hour apart. The coordinates of each point are fed into the database of a statistical analysis package (Minitab version 10.5).

To convert the X coordinates for the various points into concentration units we constructed a calibration line using the arbitrary values given by PhotoFinish and the corresponding concentration values given on the graph. The X coordinate for each point was then converted to concentration unit by interpolation onto the calibration line which takes the form Concentration = aX + b where a and b are the coefficients of the equation estimated using least-squares. Similarly, the Y coordinates were converted to Hamilton score by constructing a calibration line for the arbitrary Y values and the values given

on the graph and then interpolating the Y coordinates onto the line (Hamilton score = cY + d, where c and d are again the least squares coefficients). Each calibration line used five data pairs as equally spaced as possible along the axes and including the extreme X and Y labeled values on the graphs (see results section for detailed example).

Results

We identified six studies (Robinson *et al.* 1979, Jungkunz & Ku 1980, Breyer-Pfaff *et al.* 1982a, b, 1989, Miljković *et al.* 1996) which included both graphical and tabular data for amitriptyline plasma level and clinical response. These form the data set for this study. The paper published by Breyer-Pfaff et al. (1982a) was used as an exemplar for illustrative purposes.

Figure 1 is a scanned reproduction of Breyer-Pfaff et al.'s (1982a). In this particular case, the plasma concentrations used for constructing the X calibration curve were 100, 150, 200, 300, and 400. The Hamilton Depression Scores used for the Y calibration line were 0, 6, 12, 18, and 24. These values were chosen to ensure even spread across the entire calibration range. Table 1 and Figure 2 show a set of values obtained by our approach and the actual values reported by the authors. The results suggest that both the graphical values and the reported values were concordant.

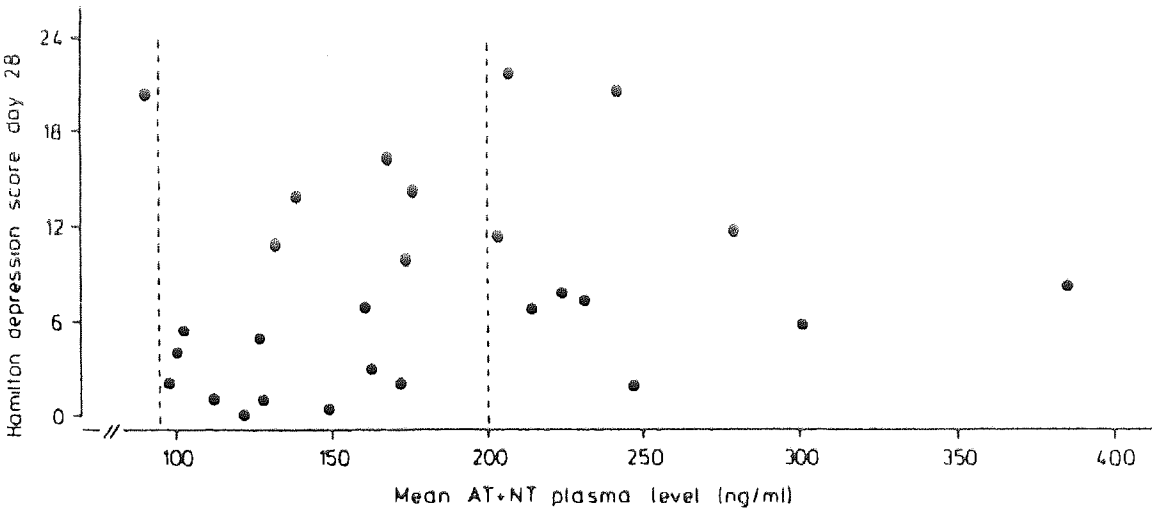

Figure 1 Plasma drug levels and Hamilton Depression Score

Table 1 Comparison of data obtained by the present method and actual results reported by the authors

Actual Hamilton Depression Score at week 4	Estimated Hamilton Depression Score at week 4	Actual amitriptyline plus nortriptyline plasma levels (ng/ml)	Estimated amitriptyline plus nortriptyline plasma levels (ng/ml)
11.5	11.4	202.7	202.6
1.0	1.1	111.7	112.2
4.0	4.1	100.7	100.5
5.5	5.5	103.5	102.5
0.0	0.1	121.7	121.7
22.0	21.8	207	206.2
7.0	6.8	214.7	213.4
8.0	7.8	223.3	223.1
8.5	8.3	385.5	384.3
1.0	1.0	128.0	128.0
10.0	9.9	174.0	173.3
5.0	5.0	127.0	126.7
7.0	6.9	161.3	160.3
6.0	5.9	300.3	300.2
12.0	11.8	279.3	278.1
0.5	0.5	149.0	148.8
14.0	13.9	139.3	138.5
16.5	16.4	167.3	167.4
2.0	2.0	172.3	171.7
21.0	20.7	242.3	240.8
11.0	10.8	132.7	131.9
14.5	14.3	176.7	175.5
3.0	3.0	163.0	162.4
7.5	7.4	230.7	230.3
2.0	1.9	247.0	246.2
2.0	2.1	98.7	97.9
20.5	20.5	91.0	90.5

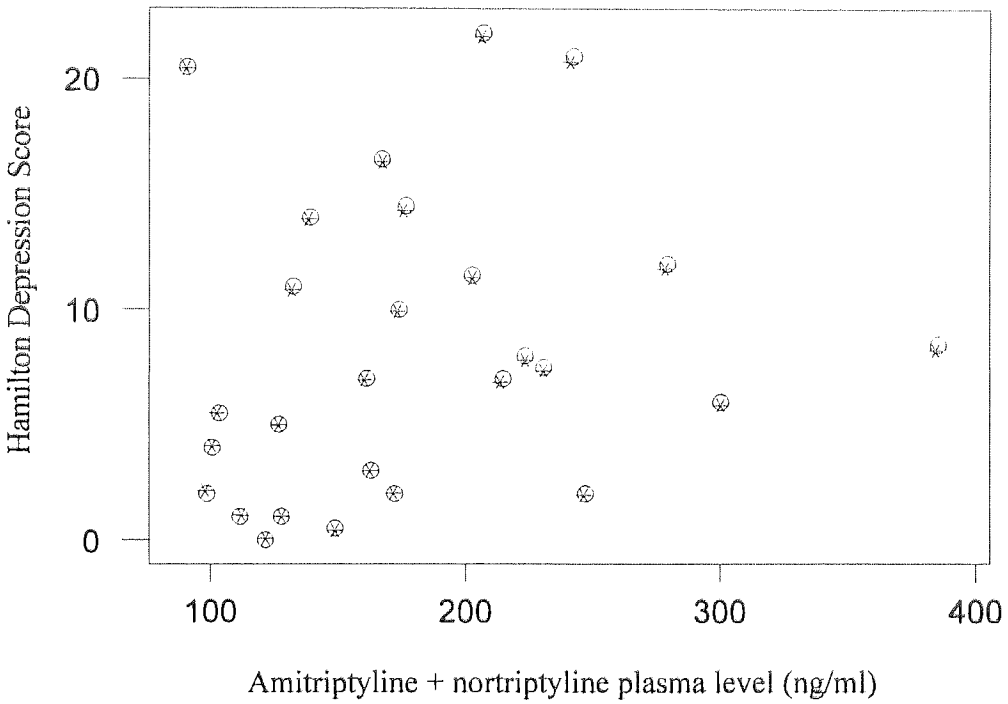

Figure 2 Plot of plasma amitriptyline and nortriptyline levels and clinical response comparing estimated values (*) and actual values (o).

Discussion and conclusion

We believe that the proposed method has wide applicability in the area of meta-analysis of published data. When data are given at the individual patient level, such data can be incorporated in individual patient meta-analysis which is widely regarded as being more powerful than meta-analysis of summary statistics. The method also helps identify inconsistencies in reported data and may help identify patients in duplicate reports of the same studies.

Based on our experience of abstracting quantitative data from graphs, the following observations may be worth considering by both reporters of such data and those abstracting such data. Firstly, we would encourage the reporting of data in graphical form when appropriate. Graphs show patterns in data which summary statistics often fails to convey. Secondly, we were conscious of the possibility of two or more data points being superimposable on each other. To ensure that the reader is aware of such points when they occur, we recommend labeling those points with a number to indicate how many such points are being superimposed under one single symbol. In one of Robinson *et al.*'s graphs (1979) there was one fewer patient than were reported in the text. We cannot be sure whether it was missed out by mistake or whether there were some patients who had superimposable data. However since the tabular data reported by the authors do not show any superimposable coordinates, the former explanation looks more plausible.

In the analysis of the blood level-clinical response studies, we would like to make several recommendations too. Firstly, when doing the correlation studies it seems most

logical to plot mean plasma concentrations during the treatment periods and clinical response data at the end of treatment. Robinson *et al.*(1979), with treatment period of 6 weeks, used blood level data at week four and response data at week six. Secondly, it seems inappropriate to report drug concentration as the mean of two chemical species. Both Robinson *et al.* (1979) and Breyer-Pfaff *et al.*(1982a), for example, used the mean of amitriptyline and nortriptyline concentrations. Mathematical modelling of such data is more easily undertaken using amitriptyline and nortriptyline as separate, though not necessarily independent predictors. Likewise, some authors (Jungkunz & Ku 1980) used the ratio of amitriptyline and nortriptyline concentrations as the independent predictor. Again, reporting of the separate concentrations would facilitate the task of those who wish to make use of the data in subsequent meta-analyses. Thirdly, the precision of the chemical analytical methods used in the study should also be reported so that these can be taken into account whenever the reported data are subsequently meta-analysed.

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