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Combination antipsychotic and mood stabilizers in maintenance treatment of bipolar patients in community practice

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Chapter 1: Literature Review

1.1 Introduction Bipolar Disorder: General Overview

Bipolar disorder is a complex illness, characterised by disparate phases and multiple patterns of presentation. It is a life long, episodic disorder, with periods of attenuated symptoms or symptom free periods between episodes.

The disorder has a lifetime prevalence of 1.6% (Australian and New Zealand guidelines for treatment of Bipolar Disorder 2004) but studies using criteria that include subsyndromal manic or hypomanic symptoms indicate a lifetime prevalence of 6.4% (Judd LL 2003). However, it is often undetected. A third of patients seek help after more than a decade since onset of the illness, and even then 70% are repeatedly misdiagnosed (most commonly because of a misdiagnosis of unipolar depression) (Berk M 2004).

For the diagnosis of bipolar disorder to be considered, a patient must experience at least one episode of mania or a mixed episode during the course of their illness.

The disease includes a diversity of clinical manifestations and the clinician must take into account whether the patient has classic mania (bipolar I), hypomania with episodes of depression (bipolar II), mixed episodes, or rapid cycling.

The diagnostic criteria for manic and depressed episodes appear in the Appendix of the text.

1.1.1 Signs and Symptoms of the Manic Phase

A manic episode may be characterised by euphoria, elation or irritability and mood lability. The thoughts of manic patients are overly positive, optimistic and expansive. Racing thoughts, flight of ideas, looseness of associations, grandiosity and distractibility represents the most frequent cognitive symptoms of mania.

Lack of insight and denial are well documented in manic patients and leads them to engage in activities that harm themselves and love ones, delay in initiating the treatment and poor compliance.

The behaviour manifestations of mania are impulsivity, psychomotor agitation, disinhibition, pressure of speech, hypersexuality, extravagant behaviour, violence, religiosity and catatonia.

All type of psychotic symptoms may occur in the severely manic patient. Hallucinations and delusions are usually mood congruent (Kaplan and Sadock 2004).

Differential diagnoses of mania include medical conditions, substances /medication induced mania, schizophrenia, schizoaffective disorder, personality disorder.

1.1.2 Signs and Symptoms of the Depressive Phase

Depression is the most frequent type of presentation. On average, people with bipolar disorder spend 3 times as much time depressed as manic (Post RM 2003, Swann AC 2005).

Bipolar depression is associated with a wide range of affective, behavioural, cognitive, perceptual, physical and neurobiological symptoms.

Co-morbidity with anxiety disorders, substances abuse, eating disorders and ADHD is a common finding (McElroy SL 2001).

Bipolar depression is associated with higher rates of dysfunction, more morbidity and mortality than bipolar mania (Post RM 2005).

Bipolar depression imposes a greater burden on patients and their families than unipolar depression, due to earlier age of onset, more frequent episodes, a greater proportion of time spent ill, and a relative acute onset and offset of symptoms (Bowden CL 2001, Post RM 2005). Suicide risk is much higher in bipolar depression (almost 80%) than in bipolar mania (2%) (Disalver SC 1997).

Unfortunately, bipolar disorder is often undiagnosed or misdiagnosed as unipolar depression, leading to incorrect or inadequate treatment and continuing disability (Suppes T 2005).

Repeated episodes lead to progressively deteriorating levels of functioning, (social, occupational, interpersonal) and poor response to treatment.

In bipolar patients suicide attempts and completed suicide has been a frequent complication (Strakowsky 1996, Angst 2002, Cipriani 2005, Goldberg 2005)**.**

Substance abuse is higher than in any other psychiatric condition, and early-onset bipolar disorder may be a risk factor for substance use disorder (Australian and New Zealand guidelines) (Bowden CL 2001).

People with bipolar disorder have a higher prevalence of cardiovascular diseases and diabetes compared with general population. One possible explanation for this higher prevalence is that, bipolar patients don't take as good care of themselves as do the general population (Goodwin FK 2002).

1.2 Bipolar disorder: Treatment

Prevention is a very important goal of long –term management because mood episodes have consequences that surpass their own duration (Swann AC 2005).

The treatment of bipolar disorder is a challenge and the objectives of treatment are not fully met by currently available pharmacotherapies. The management involves a complex combination of biological, psychological and social strategies. Each treatment protocol must address the individual needs of the patient.

In acute mania, for patients with less severe illness, mood stabilizers alone may be sufficient. Short-term adjunctive treatment with benzodiazepines can be helpful.

The first line of treatment for acute severe mania is combination of mood stabilizer and/or an antipsychotic (preferably an atypical antipsychotic). If first line treatment at optimal doses fails to control the symptoms, the guidelines of treatment (American Psychiatric Association 2002) recommended addition of another first –line medication, or adding an antipsychotic if not already prescribed, or changing one antipsychotic to another. In severe cases Electroconvulsive Therapy (ECT) may also be considered.

The first line of treatment for an acute depressive episode is a mood stabilizer in combination with an antidepressant. All the guidelines advise caution and discourage the use of monotherapy with antidepressants as monotherapy increases the risk for a switch to hypomania or mania and rapid cycling. There is controversy regarding the duration of antidepressant treatment in bipolar patients. The British Association for Psychopharmacology recommends short-term use (1-6 months) and tapering after that. The American Psychiatric Association suggests tapering and discontinuation of antidepressants but does not mention a

specific time limit. According to Ghaemi (2003) depressive symptoms reappear in15% to 20% of the patients after discontinuation of antidepressants.

The use of antipsychotics is recommended in the presence of psychotic symptoms.

ECT may be considered in severe depression, during pregnancy, life threatening inanition, psychosis and suicidality (Perlis RH 2005, APA, BAP, Bowden CL 2005, Suppes T 2005, Grunze H 2005, Calabrese JR 2005, International Consensus 2004, Muzina DJ 2005).

The long- term management of bipolar disorder includes a number of important goals, such as prevention of relapse and recurrence, suicide prevention, increase compliance, improvement of level of function. (Keck PE 2002) (American, Australian and New Zealand practice guidelines).

Most guidelines recommend continuation of medication that helped to achieve remission at the lowest effective therapeutic doses. The use of antipsychotics in maintenance therapy is controversial. American and British guidelines do not recommend their use unless they are required for control of persistent psychosis; however recent data support the use of atypical antipsychotics because of a more benign side effect profile and good prophylactic efficacy (Perlis RH 2005).

In the acute-phase, treatments are routinely continued following an episode, medication review and changes are common in outpatient care and often made during long-term follow-up (Texas implementation 2005).

Numerous therapeutic drug trials have been conducted in order to establish the most effective agents for maintenance treatment of bipolar disorder. Monotherapy, with one mood stabilizer may be effective, however a significant proportion of patients fail to respond to monotherapy. Combination therapy has become the standard of care, in an attempt to achieve more rapid

stabilization and improved rates of remission, especially in treatment refractory cases. According to Muzina D (2005) the patient on monotherapy, if followed for sufficiently long periods, will eventually require combination treatment to maintain the full remission. Concern regarding drug interactions, and side effects of their long-term administration is growing. Polypharmacy has the risk of increased side effects. If side effects do occur with combination therapy it is difficult to know which drug or drug interaction is responsible (Freeman MP 1998).

The problems of prescribing include unclear diagnostic and treatment plan, use of inadequate or excessive dosages, inadequate monitoring of treatment and inadequate documentation for use of particular treatment.

Although the development of mood stabilizers has largely centred on antiepileptic drugs, resources have also been invested in the development of atypical antipsychotics.

There is no ideal mood stabilizer available within the current range of treatment of bipolar mood disorder. Such an agent will be effective in each phase of the disease and could be used as monotherapy for maintenance treatment.

It would have acute onset of action (within hours of administration), low rates of drug discontinuation due to side effects, no side effects requiring additional treatment and would be safe in overdose (Calabrese J 2001).

The need to free up beds for new admissions creates the pressure to discharge the patients quickly. This might encourage rapid escalation of doses, or premature addition of antipsychotics. Other reasons to add antipsychotics may be that a single drug failed to control the symptoms.

The management of bipolar disorder patients in community clinics is difficult.

This is due to the: - Complexity of the illness

- Possible premature discharge from hospital, due to pressure for beds
- Co morbidity with substances abuse especially alcohol and cannabis
- Co morbidity with medical or other psychiatric conditions
- Risk of noncompliance

Noncompliance is a major contributing factor to a poor clinical course. Studies of outpatients with bipolar disorder have reported rates of noncompliance ranging from 51% to 64%, regardless of the drug/drugs administered (Perlis RH 2005).

The reasons for noncompliance are multifaceted and complex. The drug tolerability influences patients' compliance and resistance to taking medication for the rest of one's life (Goodwin FK 2002, Byrne MK 2004).

Individual treatment goals should keep the balance between quality of life and patient acceptance of side effect burden. Even a patient who was initially compliant and achieved long-term symptom relief may become noncompliant later on.

If a patient does not respond quickly to the treatment, he may stop the treatment (Sachs GS 2003, Gianfrancesco FD 2006).

Some patients who responded well to the treatment may yearn for the euphoria and productiveness of the manic episode and may discontinue therapy for that reason (Sachs GS 2003). A patient who was well controlled on medication for years may start thinking that he was cured and stops the treatment.

Other factors associated with poor compliance are complexity of the treatment, a perceived disruption of normal routine by the dosing regimen, and a lack of education of the patient and

his family (Australian and New Zealand clinical practice guidelines 2004).

Mood stabilizers are recommended as a first line of treatment for bipolar patients. In the USA antipsychotic medication is used only as an adjunct for agitation, dangerous behaviour, or psychosis. In Europe antipsychotics are the main line of treatment.

However, in general, antipsychotic agents are often prescribed routinely. The effectiveness of these agents in mania have been established. Newer atypical compounds demonstrate antimanic efficacy with reduced incidence of neurological side effects (Hirschfeld RMA 2003, Yatham LN 2002).

The complexity and difficulties involved in treating this mental condition are well recognised. The wide variety of pharmacological options includes mood stabilizers (lithium, valproic acid, Carbamazepine); newer anticonvulsants (lamotrigine, topiramate); antipsychotics, antidepressants; benzodiazepines and ECT.

1.2.1 Mood stabilizers

a) Lithium

Lithium is first line treatment in bipolar disorder. It is effective in both the short-term treatment and in prophylaxis of bipolar disorder (Jefferson JW 1990, Gershen S 1997, Bowden CL 1998, Nemeroff CB 2000, American Psychiatric Association 2002).

Lithium is an alkali metal, similar to sodium and potassium. It is completely absorbed by the gastrointestinal tract; does not bind to plasma proteins and is not metabolised. It is distributed non-uniformly throughout body water and does not cross the blood –brain barrier rapidly.

The kidneys excrete more than 95% of lithium and its excretion is related to glomerular filtration rate. In healthy adults its elimination half- life is approximative 24 hours. If the glomerular filtration rate is decreased (e.g. in patients with renal failure, the elderly) the elimination half- life is prolonged. Equilibrium is reached after 5 –7 days of regular intake. The mechanism of action may involve various neurotransmitter systems and the membrane structure. One theory is that lithium blocks inositol phosphatases within the neurons with the decrease in cellular responses to neurotransmitters that are linked to the phosphatidylinositol second –messenger system. Chronic lithium treatment also increases the expression of the neuroprotective protein, raising the possibility that some of lithium's effects are mediated through neurotrophic/ neuroprotective effects (Kaplan and Sadock 2004, Ikonomov OC 1999, Manji H.2001, El-Mallakh 2001).

The most common side effects of lithium are on thyroid, kidneys, heart, and haematopoietic system. Lithium impedes the release of thyroid hormone from the thyroid gland and can result in hypothyroidism or goiter. The most common side effect on the renal system is polyuria with secondary polydipsia. Lithium decreases the ability of the kidneys to concentrate urine; the effect is not always reversible after lithium was stopped. Severe but rare renal complications are glomerulo-nephritis, interstitial nephritis and renal failure. Lithium interferes with sinus node function, which can result in heart block in susceptible persons. On the haematopoietic system, lithium can produce leukocytosis.

Less severe side effects include weight gain, gastrointestinal problems, dermatological effects (acne, psoriasis), and nervous system effects (tremor, memory loss, dysphoria) (Dunner DL 2003).

The plasma levels of lithium should be periodically monitored because lithium may be toxic

at twice the therapeutic dose. Lithium toxicity is a medical emergency. It is more common in elderly patients, physical illness with vomiting and diarrhoea, pregnancy or at higher serum concentrations. Levels higher than 2.0 mEq/L can result in coma and death (Dunner DL 2003). The use of lithium in the elderly is complicated by the presence of other illnesses, other medication, special diet, age related decreases in glomerular filtration rate and increased sensitivity to side effects. Patients should be started in lower than usual doses, changing the doses should be done less frequently as the time required to reach steady state is much longer in the elderly. If lithium is stopped, serum levels decrease more slowly and longer time is required for side effects to subside (Kaplan and Sadock).

In pregnancy, in the first trimester, lithium can cause cardiac malformations (Ebstein's Syndrome); during late pregnancy, lithium can cause 'floppy baby 'syndrome, Hypothyroidism and nephrogenic diabetes insipidus (Yonkers KA 2004, Barnes C 2005).

Lithium should be used with caution in patients receiving diuretics (angiotensin-converting enzyme inhibitors, distal tubule diuretics, potassium-sparing diuretics) and non steroidal anti-inflammatory drugs can increase lithium levels. Other diuretics (carbonic anhydrase inhibitors, acetazolamide, osmotic diuretics) increase lithium excretion (Dunner DL 2003, Kaplan and Sadock 2004).

Co administration of lithium and antipsychotics or lithium and anticonvulsants may increase risk of neurological side effects. However these combinations can be beneficial for some patients but treatment should be started at lower doses and slowly increased (American Psychiatric Association 2002).

80% of manic patients respond to lithium; however the effect of lithium in mania is delayed, the response can take 1-3 weeks of treatment at therapeutic concentrations and adjunctive

treatment with benzodiazepines and/or antipsychotics is necessary (Kaplan and Sadock 2004, Hyman SA 1995, Bowden CL 1996).

20-24% of the patients can't tolerate or don't respond to lithium (Muzina DJ 2005). Predictors of poor response include rapid cycling, mixed or dysphoric mania, co morbidity with medical, psychiatric or substance abuse, history of poor response to lithium, negative family history of mood disorder, severe mania, more lifetime episodes, poor interepisode functioning and an episode sequence of depression-mania-euthymia. (Jefferson J W 1990, Keck PE 1996).

In bipolar depression about 80% of patients respond to lithium alone, decreasing the need for antidepressants and eliminating the risk of antidepressant inducing mania and rapid cycling. If depression is severe and antidepressants are needed they must be withdrawn gradually, soon after remission to decrease risk of inducing mania or rapid cycling. However, in practice patients seem to require and tolerate long-term use of combination.

If depression occurs during maintenance therapy with lithium one should consider the possibility of:

- lithium induced hypothyroidism
- substance abuse
- noncompliance

Possible treatments include increasing lithium concentration up to 1.2 mEq per L, augmentation with thyroid hormone, combination with other mood stabilizers, judicious use of antidepressants and ECT. (If ECT is used, lithium must be stopped to avoid cognitive impairment) (Fawcett JA 2003, Sachs GS 2003, Academic Highlights 2004).

Augmentation of lithium with thyroxin, combination of lithium with valproate or

carbamazepine may have beneficial antidepressant effect without the risk of inducing rapid cycling or mania.

The risk of suicide or suicide attempts is lower for patients treated with lithium compared with those not treated with lithium. The risk increases when treatment is stopped (Nilsson A 1999, Goodwin FK 2002, Baldessarini RJ 2003, Swann AC 2005).

Lithium is more effective in treating mania compared with depression (Maj M 1998).

Most of the guidelines recommend the initiation of maintenance lithium therapy after the second episode of mania, but many individual factors must be considered (abruptness, severity, frequency of episodes, and presence of risk factors) (Goodwin FK 2002).

Sometimes the response to lithium monotherapy is delayed, or incomplete and other pharmaco-interventions are necessary on an intermittent or continuous basis (Moller HJ 2003).

Maintenance treatment with lithium decreases the duration, the severity and the frequency of episodes. However, bipolar episodes can occur but they become less frequent and less severe.

After few years of successful treatment with lithium some of the patients seem to develop tolerance to treatment and the addition of anticonvulsants, antipsychotics or benzodiazepines is necessary (Keck PE 1996, Maj M 1998, Moller HJ 2003).

If treatment is discontinued the risk of relapse is increased, 50% of the patients relapse within 5 months (Australian and New Zealand clinical practice guidelines).

Some of the patients who responded well to treatment may not respond again when lithium is reintroduced or response is incomplete (Post RM 1992, Goodwin FK 2002).

b) Sodium Valproate

Sodium valproate is considered safe and effective in the treatment of bipolar disorder, both as monotherapy and in combination with lithium and /or other mood stabilizers (Dunner DL 2003, Bowden C.2004).

In the stomach, sodium valproate is converted into valproic acid; absorption of the drug is delayed by food ingestion.

Therapeutic effects of valproate may be mediated by:

- the effects of the drug on gama-aminobutyric acid (GABA), the inhibitory neurotransmitter, which may act directly or may regulate the activities of other neurotransmitters
- the inhibition of neuronal excitation
- the antikindling properties (El –Mallakh 2001, Xiaohua Li 2002, Salloum IM 2005)

The principal effects of valproate are on the central nervous system. Haematopoietic and gastrointestinal systems are also affected. The most common adverse effects involving the nervous system are sedation, tremor, headache, ataxia, dysarthria and they require lowering the doses of valproate or use of extended release formulation. The gastrointestinal common adverse effects are nausea and diarrhoea and they are more frequent in the first month of treatment. Persistent elevation of liver transaminases, hepatotoxicity, and pancreatitis are serious side effects of valproate (Dunner DL 2003). Weight gain is a frequent side effect and physical exercise and diet is recommended (Swann AC 2001, Aronne LJ 2003).

Platelet dysfunction and thrombocytopenia are rare side effects occurring at high dosages of

valproate (Kaplan and Sadock 2004).

Dermatological reactions to valproate include erythema multiforme, transient alopecia, petechiae, photosensitivity and pruritus (Herbert A 2001).

Sodium valproate can cause toxicity at about 3 times the average dose (Goodwin FK 2003). Overdoses of valproate can lead to coma and death (Kaplan and Sadock 2004).

Administration of valproate in the first trimester of pregnancy has been associated with neural tube defects (e.g. spina bifida) and mental retardation (Yonkers KA 2004). Valproate is excreted in breast milk and liver enzymes, bilirubin and white cell count should be monitored in the baby (Burt VK 2001). The prevalence of polycystic ovary syndrome is controversial. Several studies have found increased prevalence of polycystic ovaries in women receiving valproate (8-10%) (Isojarvi JI 1993, Ragson NL 2000, O'Donovan C 2002); however more trials are needed to assess the risk of polycystic ovarian syndrome in bipolar patients treated with valproate (Ketter TA 2004).

Valproate can increase the levels of other anticonvulsants by displacing them from plasma proteins or inhibiting their metabolism (Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder 2004).

Bowden found that valproate patients have lower premature termination rates due to mood episodes when they are compared with placebo, however patients receiving valproate experienced more side effects than placebo patients but the difference wasn't statistically significant. Lithium patients had three-fold termination rates compared with placebo group, due to non-compliance or side effects of the drug. Valproate patients continued treatment significantly longer than patients on lithium; relapse times were longer in valproate patients compared with lithium or placebo patients (Bowden CL 2000).

The response rates of the patients treated with valproate are generally considered to be comparable to those of lithium (Freeman TW 1992, Bowden CL 1994).

Valproate has some advantages over lithium:

- oral loading at doses of 20 mg/kg/day rapidly yields therapeutic blood concentrations (Keck PE 1993)
- anti-manic effects can be achieved in the first week of treatment (Vasudev K 2000, Bowden CL 2006)
- in mania associated with psychotic symptoms, valproate appears to be as effective as haloperidol, but without extrapyramidal side effects (McElroy SL 1996)

Valproate is well tolerated, safe and effective in acute and prophylactic treatment of mania, dysphoric or mixed mania, rapid cycling, and co-morbidity with substances abuse, secondary mania and in patients with poor response to lithium (Swann AC 1997, Bowden C 2004).

In a small, randomised clinical trial of divalproex in bipolar depression Davis LL, reported that patients receiving valproate showed improvement of their depression and anxiety symptoms. He concluded, “If these findings are replicated in larger studies divalproex may prove a pattern of clinical efficacy for both manic and depressive phases of bipolar disorder” (Davis LL 2005).

Valproate inhibits the enzyme histone deacetylase 1.This enzyme is needed for HIV to remain in infected cells. A study published in The Lancet in August 2005 (Lehrman G 2005, Routy JP 2005) showed that patients treated with valproic acid in combination with antiretroviral medication had a 75% reduction in latent HIV infection. “This may one day lead to a cure for HIV and AIDS” (Gadd C 2005).

c) Carbamazepine

Carbamazepine is effective in the treatment of acute mania and in prophylaxis of manic and depressive episodes. In acute mania the response rates are comparable with lithium (Small JG 1991, Licht RW 1998).

Carbamazepine is absorbed slowly and erratically from gastrointestinal tract. The absorption of the drug is enhanced by food ingestion (Kaplan and Sadock 2004). The mechanism of its mood –stabilizing effects is unknown. Therapeutic effects of carbamazepine may be mediated by:

- decreasing calcium fluxes
- stabilization of sodium and potassium channels
- upregulating gama-aminobutyric acid (GABA) receptors
- antagonizing peripheral-type benzodiazepine receptor (De Leon 2001, El- Mallakh 2001, Xiaohua Li 2002)

The principal effects of carbamazepine are on the central nervous system. Cutaneous, haematopoietic and gastrointestinal systems are also affected. The most common adverse effects involving the nervous system are headache, dizziness, drowsiness, ataxia, diplopia and sedation (McIntyre RS 2002). Cutaneous reactions include pruritic rash, oral ulcerations, bruises, and life -threatening exfoliative dermatitis and Stevens-Johnson syndrome. If the rash develops carbamazepine should be stopped.

The common gastrointestinal adverse effects are nausea and vomiting, constipation, diarrhoea, anorexia and liver function abnormalities (hypersensitivity hepatitis and cholestasis) (Swann AC 2001). Weight gain is less in patients treated with carbamazepine, compared with those treated with lithium or valproate (Ketter TA 2004). Hematologic side effects of

carbamazepine include anemia, agranulocytosis and thrombocytopenia (Swann AC 2001, Dunner D 2003).

Carbamazepine decreases atrio-ventricular conduction and should be used with caution in cardiac patients (Ketter TA 2004).

Most of the early side effects can be managed by starting treatment at low doses and progressively increasing the doses. However due to rare and life-threatening side- effects patients require careful ongoing monitoring (McIntyre RS 2002, Ketter TA 2004).

Carbamazepine has been associated with fetal abnormalities (craniofacial malformations, spina bifida, finger-nail hypoplasia) (Ketter TA 2004).

The factors associated with carbamazepine response are negative family history of mood disorder, mixed mania and rapid cycling (Post RM 1990).

Post RM (1990) and Tohen M (1990) suggest that carbamazepine, in time, may lose some prophylactic efficacy. Carbamazepine induces the metabolism of many drugs, including its own.

Use of carbamazepine is declining because of multiple drug interactions and its side effect profile (Ketter TA 2002).

d) <u>Newer anticonvulsants</u>

New anticonvulsants are a heterogeneous group with regard to target symptoms, the efficacy and adverse effects (Calabrese JR 2002).

They are used only for refractory cases; they are not studied enough in patients with bipolar disorders.

Lamotrigine

Lamotrigine is indicated for the treatment of partial seizures, absence seizures and generalized seizures. Lamotrigine has multi-channel (sodium, N-type calcium, potassium) blocking effects, suggesting its involvement in modulation of intracellular signal transduction mechanism (Xiaohua Li 2002). It decreases brain glutamate concentration or release, hence has neuroprotective effects (Ketter TA.2003). Lamotrigine has acute and prophylactic antidepressant effect in bipolar I disorder and prophylactic antidepressant effect in rapid cycling bipolar disorder. The efficacy of lamotrigine in mania remains unclear (Calabrese JR 2002)**.**

In depressed patients with poor response to lithium, antidepressants and/or antipsychotics, augmentation therapy with lamotrigine is warranted. Antidepressants increase the risk of inducing mania. However, in one review mood stability increased when lamotrigine was added to the treatment (Calabrese JR.2004).

Side effects include insomnia, sedation, nausea, ataxia, headache and all type of rashes (including life threatening Stevens-Johnson Syndrome). It is important that the patients are aware of the risks of developing skin reactions and that they are assessed by their physician immediately should it occur (Calabrese JR, 2003). Females have a greater risk of developing rash, as well as patients receiving a combination of lamotrigine and valproate. To minimize the risk of rash, lamotrigine must be started at lower doses and slowly increased (Hebert AA 2001).

Lamotrigine has significant drug interactions: carbamazepine induces lamotrigine metabolism, requiring higher lamotrigine doses; valproate inhibits lamotrigine metabolism, requiring lower lamotrigine doses and slower dose increases; valproate levels will be lowered (Calabrese JR

2004). Long –term treatment with lamotrigine may be associated with weight loss (Bowden CL 2004).

Other advantages of lamotrigine include lack of impact on cognition, and on sexual function, and no requirement for blood monitoring (Calabrese JR 2003).

Topiramate

Topiramate is a sulphamate monosaccharide.

Topiramate has multiple mechanisms of action, including regulation of GABA-ergic neurotransmission, modulation of sodium and calcium conductance, and blocking of excitatory amino acid neurotransmission. It is also a KA/AMPA glutamate receptor antagonist and inhibits carbonic anhydrase (Xiaohua Li 2002, White HS 2003, Stefan H. 2006).

Topiramate is indicated for the treatment of partial seizures, generalized tonic- clonic seizures and Lennox-Gastaut syndrome. Topiramate may have a role in treating both manic and depressive bipolar patients as add-on medication to other mood stabilizers especially if weight gain is a concern, as well as in patients with comorbid alcohol abuse, eating disorder or migraine (Calabrese JR 2002, Suppes T 2002, Yatham LN 2004). Topiramate side effects include sedation, dizziness, anxiety, tremor, confusion, cognitive impairment, weight loss, renal calculi, acute angle closure glaucoma and teratogenicity (Yatham LN 2004).

Topiramate decreases serum levels of valproate, carbamazepine, digoxin, estrogens and increases phenytoin levels.

Gabapentin

Gabapentin is indicated for the treatment of both simple and complex partial seizures.

Gabapentin is a GABA analogue; its mechanisms of action remain unclear.

Gabapentin increases the concentration of GABA, decreases the formation of glutamate, and reduces postsynaptic sensitivity to glutamate (Calabresi P.1999, Evins AE 2003).
Gabapentin does not induce microsomal hepatic enzymes, and thus does not interfere with the metabolism of other anticonvulsants (Ghaemi SN 2000, Stefan H. 2006).
The most common side effects of gabapentin are somnolence, fatigue, dizziness and weight gain. It should be used with care and at a lower dosage in patients with impaired renal function (Stefan H. 2006).
The role of gabapentin in bipolar disorder is unclear and more studies are needed.
Gabapentin may be used as add-on treatment in bipolar patients and for treating comorbid anxiety and substance abuse (Yatham LN, 2004).

Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazapine. It is metabolised by conjugation rather than by oxidation and the formation of the epoxide which is the metabolite that is thought to be responsible for much of the toxicity of carbamazepine is avoided.
Oxcarbazepine is not metabolised by the cytochrome P450 oxidase system, hence it has less tendency to induce oxidative enzymes and a reduced potential for drug–drug interactions. This metabolic profile makes oxcarbazepine an attractive drug to be used as an add-on medication.
Oxcarbazepine inhibits voltage-dependent fast sodium channels. However, its mechanisms of action remains unclear (White HS 2003, Stefan H. 2006).
Side effects includes CNS effects (dizziness, headache, diplopia, nystagmus, ataxia, poor coordination, slurred speech) nausea, diarrhoea, vomiting, anorexia, upper respiratory tract infection. Hyponatraemia via an antidiuretic effect on the kidneys is a potentially severe

complication, and caution is necessary in patients with severe renal impairment (Dunner DL 2003, Stefan H. 2006).

Oxcarbazepine has shown efficacy in treating acute mania, however its role in affective disorders remain to be clarified (Grunze H 2002).

1.2.2 Antipsychotics

The use of antipsychotics in the management of bipolar patients continues to be a topic of debate.

Antipsychotic medications are the most commonly used adjunctive agents in the treatment of affective disorders in the United States. In Europe, antipsychotic monotherapy is the first –line treatment for severely ill patients (Moller H J 2003).

These agents have a rapid onset of action. This observation has led to the practice of using combined treatment with antipsychotic and antimanic drugs during the acute stage of mania to control the psychotic symptoms, agitation and aggression before antimanic treatment becomes effective.

In the maintenance phase of the disease antipsychotics should be slowly tapered and stopped unless they are used to treat the psychotic symptoms associated with mania, or for patients with poor response to mood stabilizer treatment, or patients noncompliant with the mood stabilizer medication (American Psychiatric Association 2002, Saksa JR 2004).

Tohen M (1998) found that antipsychotics were used in 90 % of bipolar patients at some time during their illness. The use of typical antipsychotics may be necessary to stabilize the bipolar patients who are non-responsive to mood stabilizers and/or are intolerant to their side effects.

In noncompliant patients, depot preparations of antipsychotics are advantageous because they provide a reliable and sustainable delivery of a drug (Kane JM, 1998).
It is not clear whether neuroleptics protect against recurrences of the disease or whether their use influences the compliance with other antimanic drugs (Kane JM, 1998).
Many studies found that, once instituted, antipsychotics continued to be used chronically, despite ongoing concerns about their side effects. (Bipolar patients exposed to the neuroleptic treatments have an increased risk for akathisia, parkinsonian symptoms, tardive dyskinesia, neuroleptic malignant syndrome and cognitive impairment especially if they are used in combination with lithium). (Cookson J, 2001; Zarate C, 2004, Saksa JR 2004).

a) Typical Antipsychotics

Typical antipsychotics block the dopamine D_2 receptors. The steady-state levels for most of the dopamine receptor antagonists are reached in about 3 to 5 days. Their half-lives are about 24 hours. The bio availability increases—as much as 10-fold—when dopamine receptor antagonists are administered parenterally. This difference may reflect incomplete absorption of the drug in the gastrointestinal tract and extensive metabolism of oral drugs during the first pass through liver and gut. Most dopamine receptor antagonists are highly protein bound. They are metabolised by the cytochrome P450 (CYP) 2D6 and CYP 3A isoenzymes (Kaplan and Sadock 2004).
Adverse effects include:

- Neurological side effects
    - Akathisia (Feelings of restlessness may result in irritability or anxiety, and patients may appear hostile or belligerent. This could lead to an increase in the antipsychotic

medication, which in turn could worsen the extrapyramidal effect).

- Acute dystonia
- Parkinsonism
- Neuroleptic malignant syndrome (it is more common with the high-potency neuroleptics, at high dosages and when the dosage is increased rapidly).
- Tardive dyskinesia
- Perioral tremor
- Neuroleptics lower the seizure threshold and increase the risk of seizures in patients with a prior history of epilepsy. The high-potency dopamine receptor antagonists may be preferable for seizure-prone individuals.

- Cardiovascular effects
  - Decrease in the cardiac contractility, prolongation of the atrial and ventricular conduction time and refractory period and sudden death. The high-potency antipsychotics such as haloperidol appear to be safer in patients with a history of cardiac disease and thioridazine may be the worst.
  - Orthostatic hypotension is more likely with the low-potency antipsychotics (Bouman WP 2002)
- Gastrointestinal (dry mouth, constipation, occasional diarrhoea)
- Kidney and urinary function (urinary retention)
- Endocrine Effects
  - Hyperprolactinemia can lead to breast enlargement, galactorrhea, and irregular menses including anovulatory cycles and infertility.
  - High-potency drugs appear to be safe in pregnancy. (Barnes C 2005)

- Skin
    - Patients receiving low-potency dopamine receptor antagonists (chlorpromazine) may develop photosensitivity reactions and they should avoid direct sunlight and use sunscreens.
    - Low-potency dopamine receptor antagonists (chlorpromazine) are associated with blue-grey, metallic discoloration of the skin. Changing to another drug usually yields gradual improvement in the condition.
- Eye Effects
    - Patients receiving long-term treatment with chlorpromazine may develop granular deposits in the anterior lens and posterior cornea. Changing to another drug usually yields gradual improvement in the condition.
- Overdosage
    - Antipsychotics appear to be safe in overdose. However, when they are taken in combination with CNS depressants (alcohol, barbiturates, and benzodiazepines) the outcome may be unfavourable.
- Drug interactions
    - Plasma concentration of the dopamine receptor antagonist is increased by the serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, tetracyclic drugs, and β-adrenergic receptor antagonists.
    - Phenytoin, carbamazapine, and barbiturates decrease the antipsychotic plasma concentrations by increasing the metabolism of the dopamine receptor antagonist.
    - Antacids, cimetidine, and pectin can decrease the absorption of

antipsychotics from the gut.

- Increased absorption may occur with drugs that decrease gastrointestinal motility such as digoxin and steroids.
- Dopamine receptor antagonists may also enhance the effects of CNS depressants (analgesics, anxiolytics, and hypnotics) and the oral hypoglycaemic.

Typical antipsychotics are used in the acute and maintenance treatment of bipolar disorder. Gao K (2005) examining the use antipsychotics in bipolar depression, found that typical antipsychotics do not worsen the symptoms of depression; however more studies are necessary.

Haloperidol

Haloperidol is a member of butyrophenone class. It is the most prescribed typical antipsychotic drug in mania. It has a more pronounced antimanic effect comparing with chlorpromazine and is less sedating (Cookson J 2001). It has high affinity for the D2 and D3 receptor and moderate affinity for the D4 receptor. It blocks noradrenalin α_1 receptors and has a low affinity for the serotonergic receptors. Haloperidol has a half -life of 13-35 hours. Adverse effects include EPS, increase of plasma prolactin levels. Haloperidol has little effect on weight gain (McIntyre RS 2005).

Depot Antipsychotics

Depot antipsychotics have some advantages over oral medication:

- For patients who are not responding to the mood stabilizers, and for those noncompliant with the oral medication, depot formulations of antipsychotic drugs

have the advantage of providing a sustained and reliable delivery of a drug for periods of weeks (Cookson J 2001).

- Depot formulations allow for a more stable serum concentration of the active drug than oral formulations. The blood levels remain in the therapeutic range over longer periods and the daily oscillations of the blood levels related to the repeated doses of oral medication are avoided. However, a few days after receiving their depot antipsychotic, patients often complain of an increase in the side effects (e.g. sedation) (Patel MX 2005).
- Overdose with the antipsychotic medication is avoided by the depot preparations.

- Another advantage of the depot preparations is the regular staff–patient contact and better supervision of the patient. However patients' geographic location and access to transportation may affect the compliance with a depot regimen.
- Convenience seems to be the main reason for patient preference of depot preparations Wistedt B (1995) (cited in Walburn J, 2001) report that 67% of his sample found it easier to have an injection than taking tablets once or twice daily. Another study by Hoencam E et al (1995) (cited in Walburn J 2001), show that 42% of their sample found it more convenient to have an injection than taking tablets few times per day. The parenteral route of administration can be associated with coercion. More studies are necessary to address the issues of patient autonomy, coercion and stigma (Patel MX 2005).

b) Atypical Antipsychotics

There is an increasing interest in the use of atypical antipsychotic agents for the treatment of bipolar disorder. Several of these have been studied with evidence of anti-manic

properties-clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

Atypical antipsychotics appear to be effective in all phases of bipolar disorder, but with less extrapyramidal side effects, depression and cognitive impairment (Keck PE 2005, Suppes 2005). Higher tolerability profile of the atypical antipsychotics may increase the compliance especially in the maintenance phase of treatment (Vieta E 2005, Dolder CR 2002).

Mechanism of action of atypical antipsychotics involves multiple neurotransmitters. The second-generation antipsychotics have a higher ratio of serotonin type 2 ($5\text{-}HT_2$) to dopamine type 2 (D_2) receptor blockade, a more rapid dissociation from the dopamine D_2 receptor, and a greater specificity for the mesolimbic than the striatal dopamine system. (Kapur S 2001, Remington G 2003). Maintaining regionally selective balance between serotonin and dopamine systems appear to be needed to stabilize the mood (Yatham LN 2005).

The most common side effects of atypical antipsychotics are neurological (extrapyramidal symptoms, seizures, neuroleptics malignant syndrome, sedation), psychiatric (precipitation or exacerbation of mood switches), metabolic (weight gain, dyslipidemia, glucose intolerance), cardiovascular and hyperprolactinemia.

Atypical antipsychotics are associated with a lower risk for seizures (except clozapine and olanzapine, which have a dose –dependent risk of seizures). Neuroleptic malignant syndrome is less frequent with the atypical antipsychotics. Sedation can be useful in the acute phase of severe mania, however in the maintenance phase may decrease patient's level of function, and lead to noncompliance and relapse.

Atypical antipsychotics are not consistently associated with precipitation or exacerbation of mood switches (Altamura AC 2003, Tohen M 2003, McIntyre RS 2002, 2005).

Metabolic side effects (weight gain, dyslipidemia, glucose disturbances) are disturbing for

patients and contribute to non-compliance and relapse (Wirshing DA 2002, Nemeroff CB 2003, Guo JJ 2006)

Parenteral formulations of antipsychotics (risperidone, olanzapine and ziprasidone) are used in patients who are unable or unwilling to take oral medication (Perlis RH 2005).

Clozapine

Clozapine is the prototype of atypical antipsychotic agent. It has a relatively low affinity for the dopaminergic D_2 receptors and a high affinity for the dopaminergic D_1 and D_4 receptors and the serotonergic 5-HT_2 receptors. It is a potent antagonist at the adrenergic, histaminergic and cholinergic receptors (Bouman WP 2002, Kapur S 2001, Kaplan and Sadock 2004)**.**

It has serotonergic 5-HT_{1A} agonist properties, which may explain it's antianxiety and antidepressant effects. Clozapine is effective in mania, depression and mixed episodes. However, due to the severe side effects (agranulocytosis, sedation, weight gain and seizures) it should be used with caution for refractory cases (Ketter TA 2004).

Clozapine appears to be associated with increased risk of diabetes mellitus, myocarditis, cardiomyopathy and postural hypotension. Tolerance to the hypotensive effects of clozapine often develops over time (McIntyre RS 2005). It has few extrapyramidal adverse effects and a dose –dependent risk of seizures. It is metabolised by the cytochrome P450 system. Inhibition of CYP 1A2 and 2D6 isoenzymes by drugs (risperidone, cimetidine, SSRIs, tricyclic drugs, and valproate) decrease clearance of clozapine. Phenytoin and carbamazepine induces CYP 2C and 3A4 hepatic isoenzymes and decreases concentrations of clozapine (Kaplan and Sadock 2004).

Olanzapine (OLZ)

Olanzapine is a thienobenzodiazepine. It has a very weak affinity for the hepatic P450 cytochromes hence it has little drug interactions (Kaplan and Sadock 2004). Olanzapine predominantly blocks the serotonergic and dopaminergic receptors, and additionally blocks muscarinic, histaminergic and alpha adrenergic receptors. (Bouman.WP 2002, Kapur S 2001).

Few extrapyramidal effects have been reported (Kaplan and Sadock 2004). It is approved for the treatment of acute mania, mixed episodes and maintenance therapy. It appears to be effective in prevention of depression or mania relapse /recurrence. However more studies are needed to confirm these results (Tohen M 2003, 2004, 2005, Keck PE 2005).

The issue of efficacy of OLZ in patients with resistant bipolar disorder is controversial. Goldberg JF (2002) reported that, in patients with poor response to mood stabilizers, OLZ may be effective. Tohen M (2003, 2004) reported that patients who are resistant to the treatment with a mood stabilizer as monotherapy appear to have poor response to antipsychotic medication.

Olanzapine's adverse effects include headache, dizziness, somnolence, nervousness, nausea, constipation and orthostatic hypotension. Olanzapine is associated with hyperglycaemia and diabetes mellitus (Dunlop BW 2003*)*. It is also associated with the most significant increases in weight. Weight gain is disturbing for the patients. It leads to noncompliance and an increase risk of relapse (McIntyre RS 2005, Keck PE 2005). Problems with the weight gain become more difficult when OLZ is used in combination with other mood stabilizers, (especially valproate and lithium (Nemeroff CB 2003).

Olanzapine induce EPS at higher doses. It has a dose –dependent risk of seizures.

Ethanol increases olanzapine absorption, which may lead to increased somnolence and orthostatic hypotension. Carbamazepine and phenytoin decrease olanzapine concentration by inducing CYP 3A.

Risperidone

Risperidone is a benzisoxazol derivative. The mechanism of action involves predominantly antagonism of the serotonin (particularly 5-HT2A) and dopamine D2 receptors. It has high affinity for the α 1- and α 2-receptors but low affinity for the β-receptors and the muscarinic receptors (Leysen JE 1994, Kapur S 2001). It was approved for the treatment of manic and mixed episodes as monotherapy and in combination with mood stabilizers (Hirschfeld RMA 2004). Risperidone appears to improve bipolar depression (Vieta E 2001).

Side effects include diabetes, headache, dizziness, somnolence and nausea. Risperidone induces EPS at the higher doses; it has been associated with hyperprolactinemia which may result in galactorrhea, sexual disturbances and osteoporosis (Keck PE 2005).

Carbamazepine decreases the serum level of risperidone (Ketter TA 2004).

Ziprasidone

Ziprasidone is a benzisothiazolyl piperazine. It has antagonist effects at the serotonergic 5-HT_2 A and dopaminergic D_2 receptors, moderate affinity for the α1 receptor and low affinity for the histaminergic (H_1) receptor (Kaplan and Sadock 2004).

Ziprasidone has been approved for the treatment of manic and mixed episodes. Ziprasidone is related to a decrease in triglycerides level, no significant weight gain and low rate of EPS (McIntyre RS 2005). Somnolence is the most common adverse effect. Carbamazepine

decreases the serum level of ziprasidone (Ketter TA 2004). Combination ziprasidone and antiarrhythmic medication should be avoided due to the potential for QT interval prolongation (Ketter TA 2004).

Quetiapine

Quetiapine is a dibenzothiazepine with more potent serotonergic 5-HT_2 than dopaminergic D_2 receptor-blocking properties. It has a high affinity for histamine, α_1, and α_2 receptors, a moderate affinity for sigma receptors. It has very low affinity for the muscarinic and cholinergic receptors (Altamura AC.2003, Kaplan and Sadock). Quetiapine is approved for monotherapy and adjunctive therapy in bipolar mania. Quetiapine appears to be effective as monotherapy in bipolar depression. It has a rapid onset of action (1week) (Calabrese JR 2005). Side effects are postural hypotension, somnolence and dry mouth (Keck PE 2005). Carbamazepine decreases the serum level of quetiapine (Ketter TA 2004). Combination quetiapine and antiarrhythmic medication should be avoided due to the potential for conduction prolongation (Ketter TA 2004). The dosage should be lower in elderly and in patients with impaired hepatic and renal function.

Aripiprazole

This is a quinolinone derivative with a unique mechanism of action. It is a dopamine-serotonin system stabilizer. It is a partial agonist at dopamine D_2 receptors and serotonin (5-HT) $_{1A}$ receptors and antagonist activity at 5-HT_{2A} receptors and adrenergic (α_1) receptors (Burris KD 2002, Rosack J 2003). Aripiprazole is approved for the treatment of mania and mixed episodes. Aripiprazole is associated with minimal weight gain, prolactin elevation, QTc

prolongation and EPS (McIntyre RS 2005, Keck PE Jr 2003).

Common side effects are somnolence, headache, agitation, anxiety, nausea and constipation.

Serum aripiprazole is decreased by carbamazepine (Ketter TA 2004).

1.2.3 Antidepressants

The diagnosis and treatment of bipolar depression is a challenge, due to incorrect diagnosis as unipolar depression, co-morbidity with anxiety disorder and substance abuse, and the variability of responses to antidepressants (Suppes T 2005, Kupfer DJ, Marangell LB 2006). The guidelines recommend discontinuation of antidepressants within 3-6 months after remission of depressive episode (American Psychiatric Association 2002, Grunze H 2002). However some studies found that antidepressant discontinuation increased the risk of relapse into depression (Altshuler L 2003); other studies showed that they might induce a switch to mania or hypomania at a rate two or three times the spontaneous rate, induce rapid cycling and increase the number of both manic and depressed episodes (El- Mallakh RS 2002, Leverich GS 2006). Some patients (female gender, history of antidepressant induced mania, bipolar I) are more at risk to switch into mania or cycle acceleration (Schaffer A 2006). When antidepressants are used to treat bipolar depression, a combination with a mood stabilizer is recommended (American Psychiatric Association 2002, Grunze H 2002). However the risks still remain and this approach is controversial (Grunze H 2005).

The treatment of a chronic co-morbid anxiety disorder, is more problematic and antidepressant medication may be needed for the treatment of anxiety symptoms (Schaffer A 2006).

The role of antidepressants in bipolar disorder remains controversial. Antidepressants should be used with caution in the treatment of bipolar depression (El- Mallakh RS 2002).

1.2.4 Drug combinations

Bipolar disorder is a complex illness. The complexity and difficulties involved in treating this mental condition is well recognized. 40% of the patients have poor response to monotherapy and combination therapy is often necessary (Bowden CL 2004). Antipsychotics are introduced concomitant with mood stabilizer or as add-on medication to the mood stabilizer. The clinician should have a clear rationale supported by reliable evidence for using the drug combination (Bowden CL 2004).

Before adding another agent, the doses of the first drug should be titrated to a therapeutic level (American Psychiatric Association 2002). The need for each drug of combination, their adverse effects and pharmacokinetic should be continuously assessed (Bowden CL 2004).

The issue of discontinuation of the antipsychotics when patients become apsychotic is controversial. Practice guidelines recommend discontinuation of antipsychotics when patients improve (American Psychiatric Association 2002). Tohen (2002) suggest that if in the acute phase patients improve on combination treatment, this treatment should be continued in the maintenance phase as well.

In the treatment of acute mania combining a mood stabilizer with an antipsychotic appears to be more efficacious and has a more rapid onset of action than monotherapy (Sajatovic M 2001, Vieta E 2001, Sachs GS 2002, Schatzberg AF 2004). In bipolar depressed patients with psychotic features, and in patients who are not responding to the treatment with mood stabilizers and /or antidepressants, adding an atypical antipsychotic appears to be effective (Hirschfeld RMA 2003). However more studies are necessary.

When combining mood stabilizers with antipsychotics, antipsychotics doses are lower than

they are used alone, thus their risk and severity of side effects is decreased (Schatzberg AF 2004).

Problems with drug combination:

- The contribution of each type of medication used in combination is not clear (Saksa JR 2004, Perlis RH 2005)
- Combination therapy can induce symptoms difficult to differentiate from manifestations of bipolar disorder (Bowden CL 2004).
- Drug–drug interactions are concerns when considering any combination therapy. Bowden recommends that carbamazepine should be avoided in combined regimens due to multiple drug interactions (carbamazepine decreases atypical antipsychotics blood levels (Ketter TA 2004, Bowden CL 2006). Antipsychotic drugs can increase intracellular lithium levels (Cookson J 2001).
- Combination therapy may decrease compliance due to complicated regimen, more medication errors or unacceptable side effects (Yatham LN, 2003; Freeman MP, 1998).
- Side effects of medication should be at an acceptable level otherwise patients will stop a treatment they cannot tolerate (mood stabilizers in combination with antipsychotics may lead to weight gain and extrapyramidal symptoms) (Yatham LN 2002, Bowden C 2004). High levels of lithium in combination with high doses of antipsychotics, have been associated with severe neurological symptoms (Cookson J 2001).
- Drug combination can increase the costs of the treatment and lead to noncompliance. However in assessing the cost-effectiveness of a treatment the costs of inadequate therapy should also be considered (Bowden CL 2004).

Drug combinations yield a more rapid stabilization and decrease the rate of relapses of the bipolar patients (Hirschfeld RMA 2005). However some questions remain unanswered (Which combination is more effective? What are the most effective doses? What combination has the least side effects and is better tolerated?) More research is needed (Keck PE 2002).

1.2.5 Benzodiazepines

Benzodiazepines in combination with mood stabilizers and/or antipsychotics are useful in early treatment of acute mania. Because of their rapid onset of action, benzodiazepines allow for rapid control of dangerous symptoms, and decrease the dose of neuroleptics, with an associated lower incidence of extrapyramidal side effects and risk of tardive dyskinesia (American Psychiatric Association 2002, Freeman MA 2002).

Concern about the use of benzodiazepines include their side effects (ataxia, sedation, dizziness and disinhibition which may be difficult to differentiate from mania) and their potential for addiction and withdrawal. In maintenance phase of treatment they may be used as adjunctive agents (Kaplan and Sadock 2004).

1.2.6 Electroconvulsive Therapy (ECT)

ECT is used for the treatment of acute episodes of mania and depression and in maintenance treatment of bipolar disorder, if oral medication is not effective and for patients who are pregnant (Dunner DL.2003, Perlis RH 2005). However, Sackeim HA found that response rates and long-term effectiveness are decreased in treatment resistant patients (Sackeim HA

2000).

It has a rapid onset of action and this is beneficial for severely depressed patients with high suicide risk (Grunze H 2005). Bilateral ECT appears to be more effective than unilateral ECT (Grunze H 2005). Seizure activity is inhibited by anticonvulsants. ECT in combination with lithium increases the risk of neurotoxicity and/or delirium (Dunner DL 2003).

Some patients complain of memory loss, however future studies are needed to clarify this issue (Grunze H 2005).

Chapter 2 The Study

2.2 Study aim

The aim of this research is to investigate in a population of patients with bipolar disorder who are having treatment with a combination of a mood stabilizer and antipsychotics:

1) The number of prescriptions of antipsychotics, in bipolar patients in a community clinic

2) The rationale of such combination

3) Whether correlates exist between variables such as substance abuse and noncompliance and the prescription of antipsychotics

2.3 Rationale

Bipolar disorder is a complex illness. It is a life long episodic disorder, and can be very disruptive for the patient and family. Repeated episodes lead to progressively deteriorating level of functioning and poor response to treatment. Suicide attempts and completed suicide has been a frequent complication. The complexity and difficulties involved in treating this mental condition are well recognised .The pharmacological options include lithium, valproate, carbamazepine, lamotrigine, topiramate, and benzodiazepines.

The use of neuroleptics in bipolar disorder remain controversial because of the increased susceptibility of this group of patients to side effects of neuroleptics especially if they are used in combination with lithium. In the maintenance phase of the disease antipsychotics should be slowly tapered and stopped unless they are used to treat the psychotic symptoms associated with mania, or for patients with poor response to mood stabilizer treatment, or

patients noncompliant with the mood stabilizer medication (American Psychiatric Association 2002).

Tohen (2002) suggests that, if in the acute phase patients improve on combination treatment, this treatment should be continued in the maintenance phase as well.

This study investigates antipsychotics prescribing practices in a community clinic in bipolar patients hoping to improve and encourage judicious prescribing patterns.
The hypothesis is that in the community, patients are maintained on antipsychotic treatment for longer than is clinically warranted (i.e. in the absence of psychotic or behavioural symptoms).

Ethic committee approval was obtained prior to conducting the study from the Research Committee on Human Subjects of University of the Witwatersrand .The protocol number is M 060243

2.3 Study design and Methods

This retrospective, descriptive, analytic study was conducted at Voslooros Psychiatric Clinic, which is situated in the South East of Johannesburg. The clinical records of all patients with an initial diagnosis of bipolar disorder as at December 2004 were examined

Inclusion criteria:

All the patients aged between 18 and 65 years with the initial and final diagnosis of bipolar disorder.

Exclusion criteria: The files with incomplete data.

Particular note was taken of the following: demographic data, diagnosis, age of onset of psychiatric illness, duration of illness, treatment prescribed, reasons for prescribing this medication, response to the treatment, social circumstances of each patient, and compliance (as reflected by the patient, the nurse, and the doctors report).

The use of substances was assessed by using self-reported data (for alcohol and cannabis use) and toxicological screening (detection of cannabis in the urine).

Evaluation of the side effects associated with antipsychotics included extra-pyramidal symptoms and weight gain.

2.4 Statistical analysis

Descriptive Statistics was used in the processing of data. The proportion of bipolar patients on treatment with a combination of mood stabilizer and antipsychotic was expressed as a percentage along with its 95% confidence interval. Due to the categorical / discrete nature of the variables measured, frequency tables and cross-tabulation was used to summarize and analyse the data.

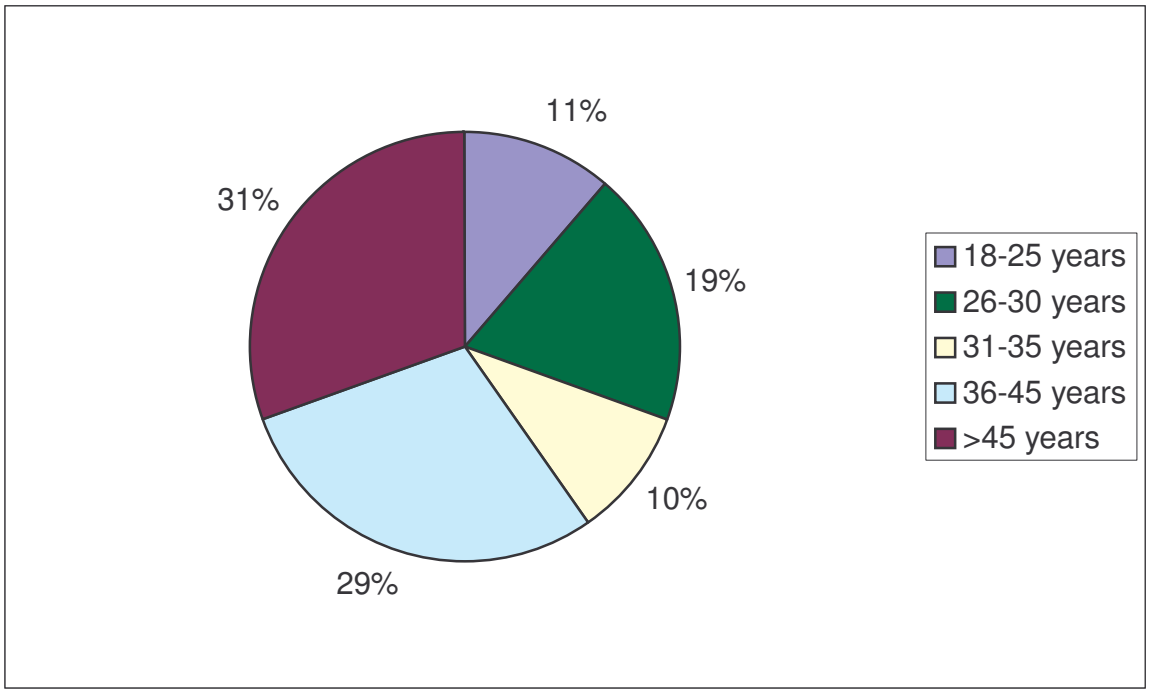
Chapter 3 Study Results

The sample consisted of 62 subjects. Of these 23 (37.1%) were males and 39 (62.9%) were females.

The age of the patients ranged between 18 and 58 years. The majority of the patients were 36 years or older (59.65%), 6 patients (9.7%) were between 31-35 years, 12 patients between 26-30 years (19.35%) and 7 patients (11.3%) were 25 years or younger.

These data are represented in Figure 1.

Figure 1: AGE DISTRIBUTION



The demographic data are presented in Table 1

Table 1: DEMOGRAPHIC DATA

PARAMETER	FREQUENCY	PERCENT
AGE (years)		
18-25	7	11.3
26-30	12	19.35
31-35	6	9.7
36-45	18	29.00
>45	19	30.65
SEX		
Female	39	62.9
Male	23	37.1
MARITAL STATUS		
Single	28	45.2
Married	28	45.2
Divorced	4	6.45
Widowed	2	3.2

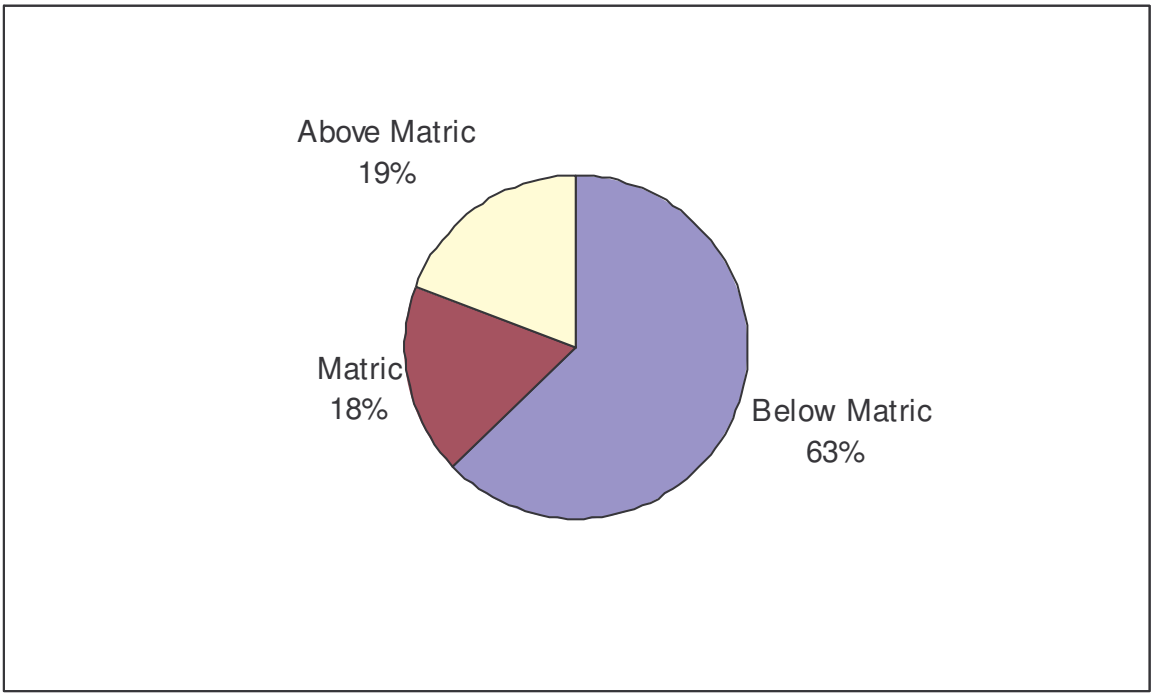
LEVEL OF EDUCATION

39 patients (62.9%) had level of education less than Matric, 12 (19.4%) studied above Matric, and 11 (17.7%) completed their Matric. These data are represented in Table 2 and Figure 2**.**

Table 2: LEVEL OF EDUCATION

LEVEL OF EDUCATION	FREQUENCY	PERCENT
< Matric	39	62.9
Matric	11	17.7
> Matric	12	19.4

Figure 2: LEVEL OF EDUCATION



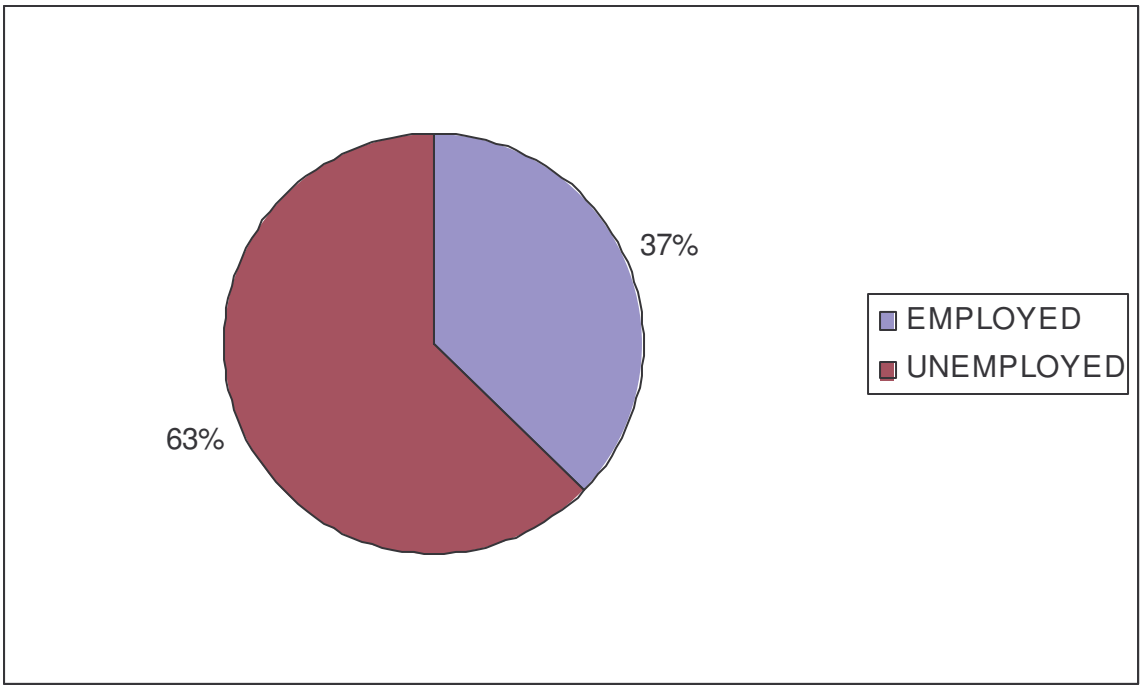
EMPLOYMENT

39 patients (62.9%) were unemployed and 23 (37.1%) worked. These data are represented in Table 3 and Figure 3.

Table 3: EMPLOYMENT

EMPLOYMENT	FREQUENCY	PERCENT
Yes	23	37.1
No	39	62.9

Figure 3: EMPLOYMENT



DURATION OF ILLNESS

Regarding the duration of illness, 46 patients (74.2%) were ill for 5 years or longer, and 7 patients (11.3%) were diagnosed in 2004. These data are represented in Table 4.

Table 4: DURATION OF ILLNESS

YEARS	FREQUENCY	PERCENT
1	7	11.3
2	4	6.45
3	2	3.2
4	3	4.8
5	6	9.7
More than 5 years	11	17.7
More than 10 years	13	21.0
More than 15 years	7	11.3
More than 20 years	9	14.5

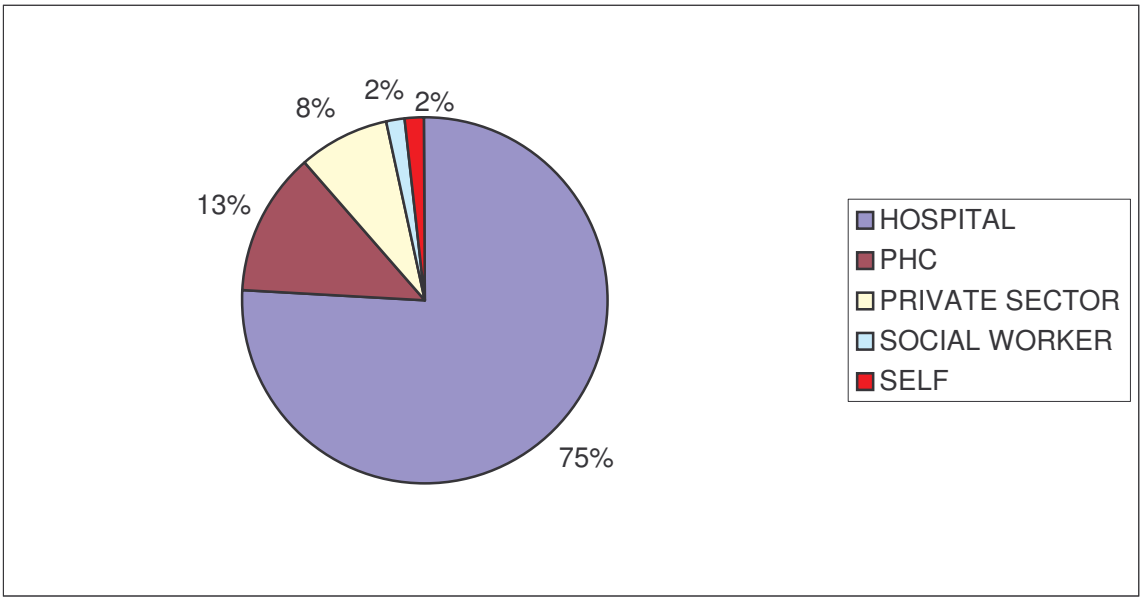
PATIENT REFERRAL

47 patients (75.8%) were referred by hospital, 8 (12.9%) were referred from primary health care clinic (PHC), 5 (8.1%) were referred by private sector. One patient (1.6%) referred himself and another was referred by a social worker. Table 5 and Figure 4 reflect these data.

Table 5: PATIENT REFERRAL

REFERRAL	FREQUENCY	PERCENT
HOSPITAL	47	75.8
PHC	8	12.9
PRIVATE SECTOR	5	8.1
SOCIAL WORKER	1	1.6
SELF	1	1.6

Figure 4: **PATIENT REFERRAL**



TYPE OF TREATMENT

53 patients (85.5%) were referred to the clinic on antipsychotics.

9 patients (14.5%) were referred to the clinic on other medication (mood stabilizers and / or antidepressants).

THE REASONS TO START ANTIPSYCHOTICS

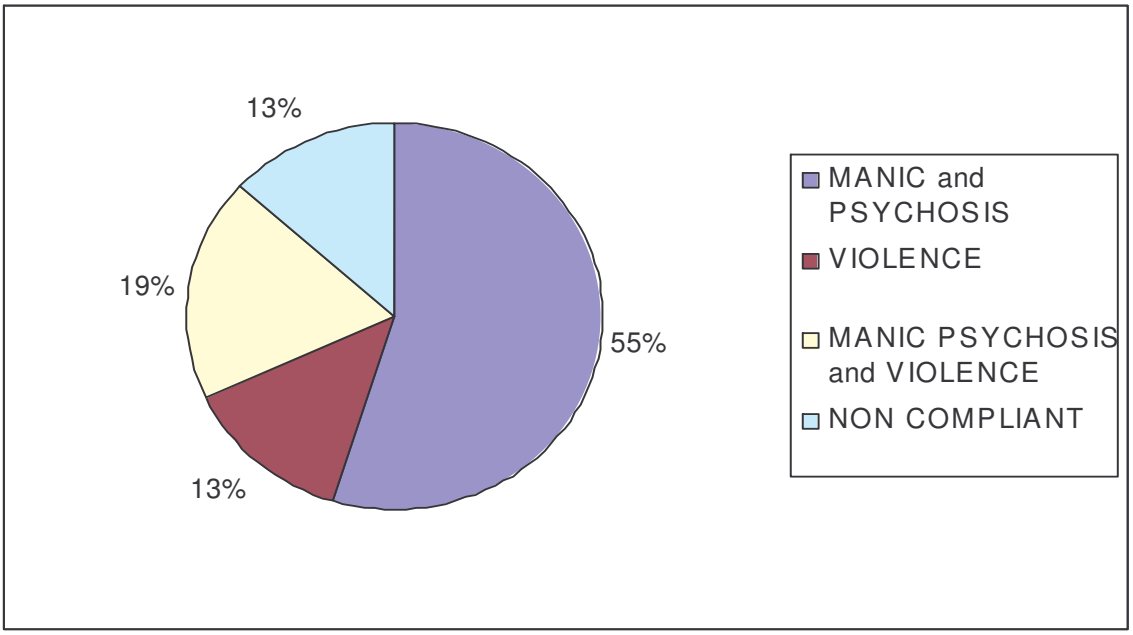
The data reflect that the reasons for commencing antipsychotic treatment were the presence of manic and psychotic symptoms (54.7% patients), violent behaviour (13.2% patients), manic and psychotic symptoms as well as violence (18.9 % patients). 13.2% patients were noncompliant with previous treatment.

These data are represented in Table 6 and Figure 5.

Table 6: THE REASONS TO START ANTIPSYCHOTICS

PARAMETER	FREQUENCY	PERCENT
MANIA+PSYCHOSIS	29	54.7
VIOLENCE	7	13.2
MANIC+PSYCHOSIS+VIOLENCE	10	18.9
NONCOMPLIANT	7	13.2

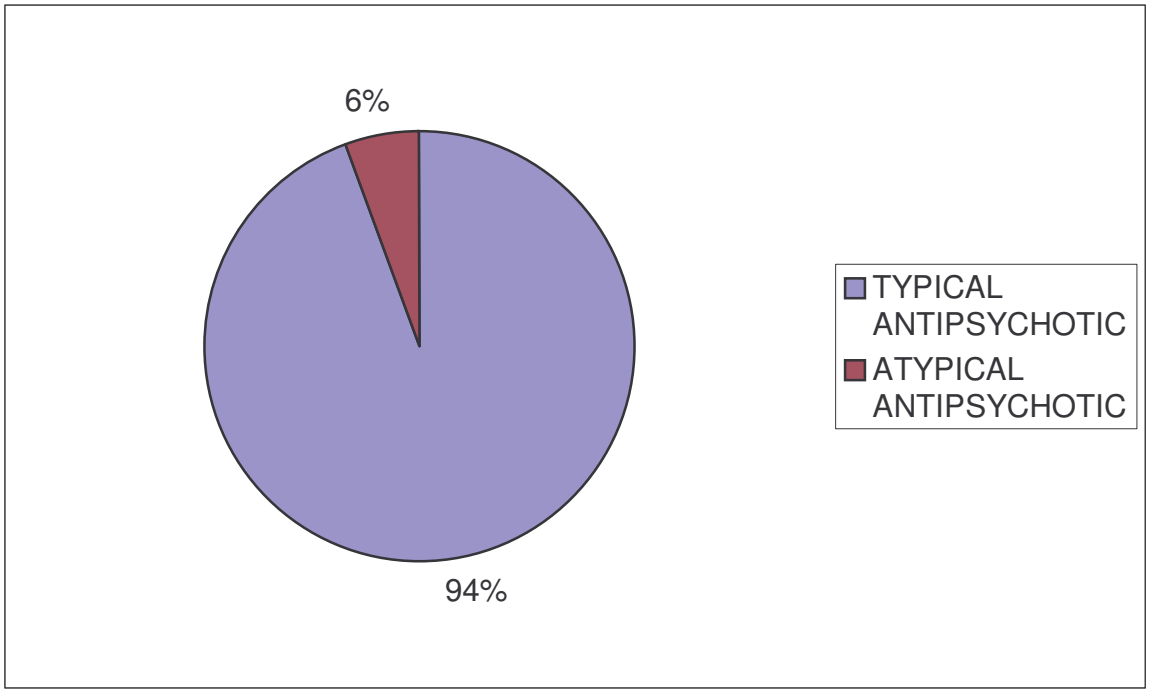
Figure 5: THE REASONS TO START ANTIPSYCHOTICS



TYPE OF ANTYPSYCHOTIC

Of the 53 patients referred on antipsychotics, 50 patients (94.3%) were prescribed a typical agent and 3 patients (5.7%) had an atypical antipsychotic added to the mood stabilizer (Figure 6).

Figure 6: TYPE OF ANTYPSYCHOTIC



THE MAINTENANCE TREATMENT

At the last recorded clinic visit, 12 patients (19.4%) out of 62 were on monotherapy with mood stabilizers.

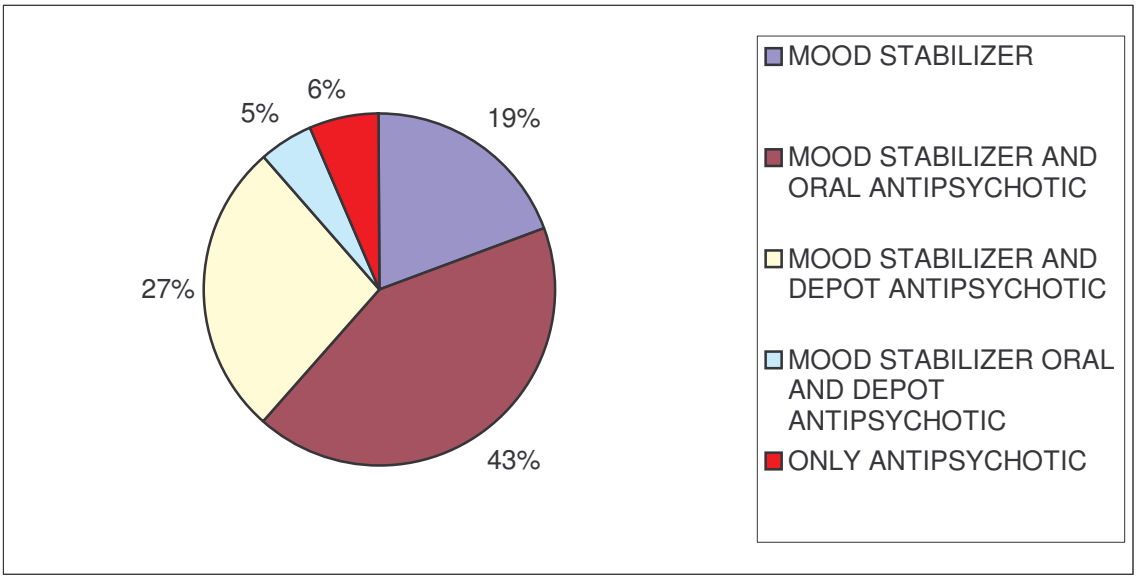
26 patients (41.9%) were on oral antipsychotics in combination with mood stabilizer, and 17 patients (27.4%) on depot antipsychotic and mood stabilizer, 3 patients (4.8%) were on combination mood stabilizer plus oral and depot antipsychotic and 4 patients (6.5%) were on antipsychotic only due to poor compliance (Table 7, Figure 7).

In 8 patients (12.9%), benzodiazepines were added to mood stabilizers and antipsychotics.

Table 7: THE MAINTENANCE TREATMENT

TREATMENT	FREQUENCY	PERCENT
MOOD STABILIZER	12	19.4
MOOD STABILIZER AND ORAL ANTIPSYCHOTIC	26	41.9
MOOD STABILIZER AND DEPOT ANTIPSYCHOTIC	17	27.4
MOOD STABILIZER ORAL AND DEPOT ANTIPSYCHOTIC	3	4.8
ONLY ANTIPSYCHOTIC	4	6.5

Figure 7: THE MAINTENANCE TREATMENT

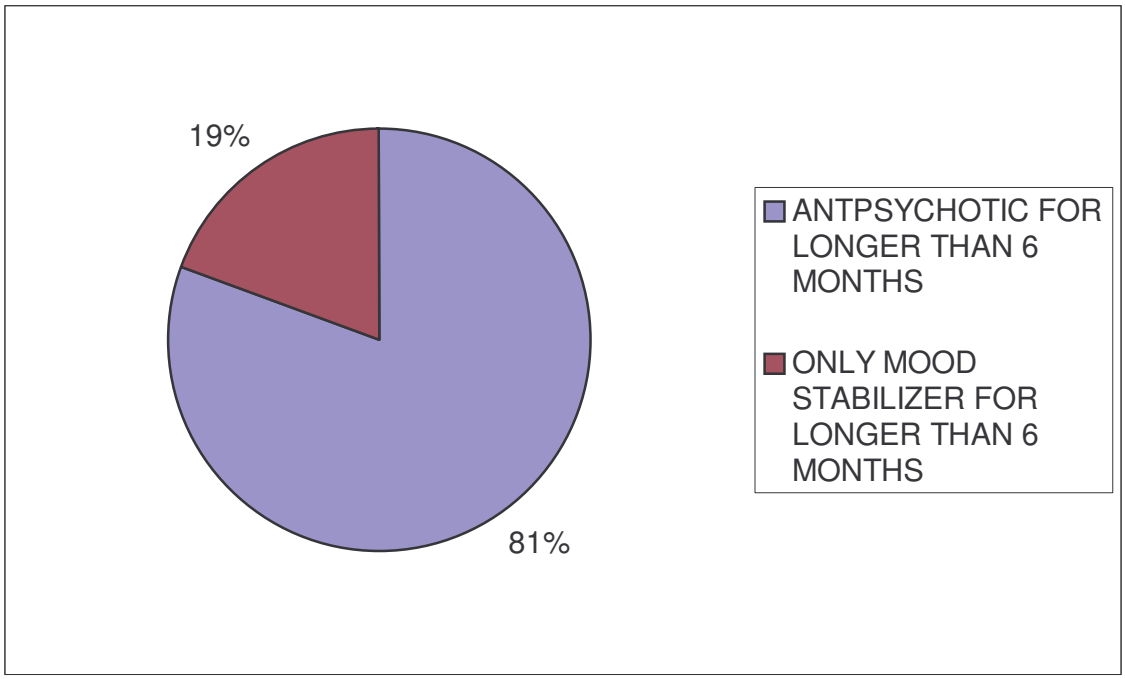


DURATION OF EXPOSURE TO ANTIPSYCHOTIC

Due to insufficient information in the files, it was difficult to determine with precision for how long bipolar patients had been exposed to antipsychotics.

In 12 patients (19.35%) the data reflect that mood stabilizers were the sole treatment for at least 6 months (Figure 8).

Figure 8: DURATION OF EXPOSURE TO ANTIPSYCHOTIC



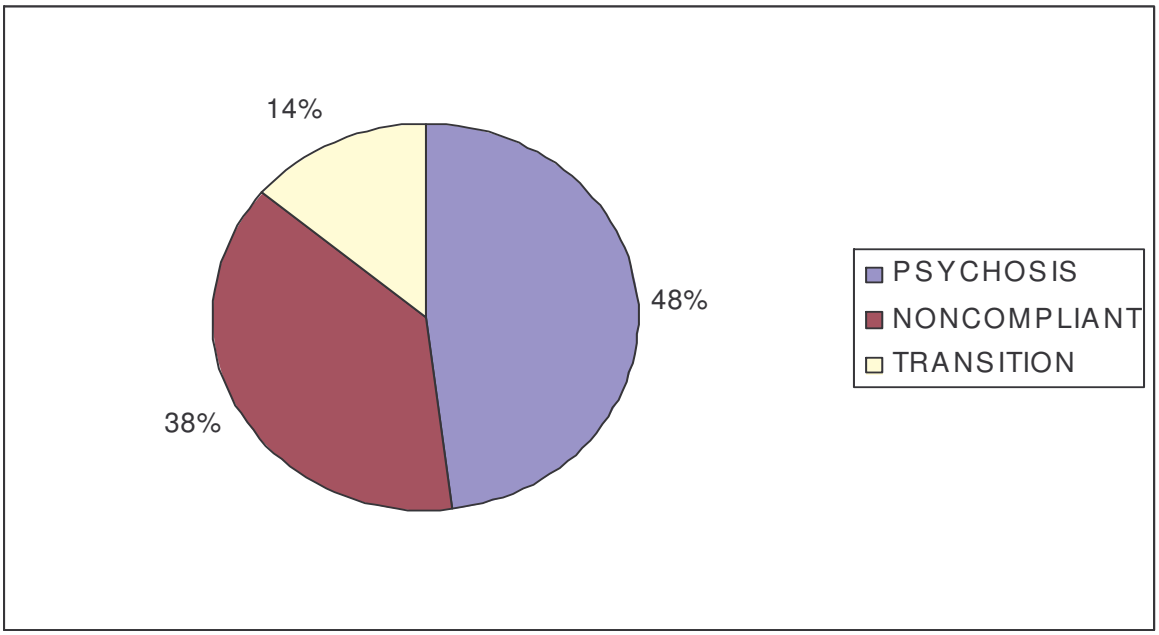
THE RATIONALE FOR COMBINATION MOOD STABILIZER WITH ANTIPSYCHOTIC IN MAINTENANCE TREATMENT

Out of 50 patients still on antipsychotics, 4 patients (6.45%) were on antipsychotics only, 46 patients (74.2%) were still using the combination mood stabilizer and antipsychotic, 24 (48%) of them to control the psychotic symptoms, 19 (38%) due to noncompliance and 7 patients (14%) were in transitional phase to stop antipsychotics. These data are represented in Table 8 and Figure 9.

Table 8: THE RATIONALE FOR COMBINATION MOOD STABILIZER WITH ANTIPSYCHOTIC IN MAINTENANCE TREATMENT

PARAMETER	FREQUENCY	PERCENT
PSYCHOSIS	24	48
NONCOMPLIANCE	19	38
TRANSITION	7	14

Figure 9: THE RATIONALE FOR COMBINATION MOOD STABILIZER WITH ANTIPSYCHOTIC IN MAINTENANCE TREATMENT



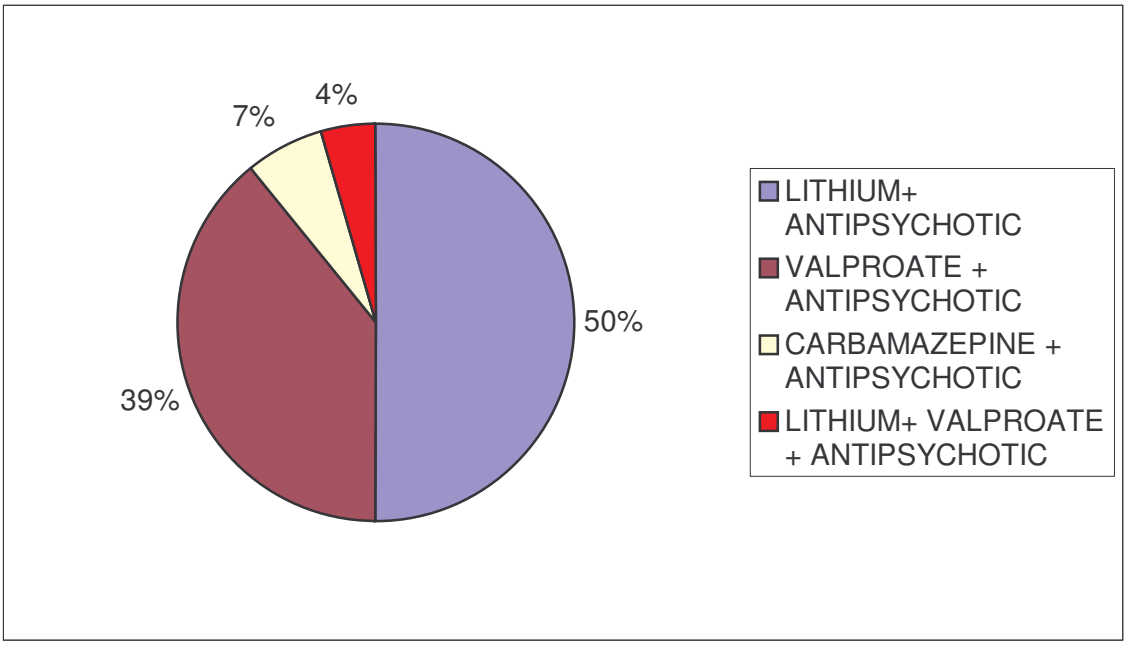
TYPE OF COMBINATION

Out of 46 patients receiving mood stabilizers in combination with antipsychotics, for 23 patients (50%) lithium was prescribed in combination with antipsychotic; 18 patients (39.1%) received valproate in combination with antipsychotic, and 3 patients (6.5%) were prescribed carbamazepine in combination with antipsychotic. In 2 cases (4.35%) two mood stabilizers (lithium and valproate) were prescribed in combination with an atypical antipsychotic. There were no cases of triple mood stabilizers prescribed in combination with antipsychotics.

Table 9: TYPE OF COMBINATION

COMBINATION	FREQUENCY	PERCENT
LITHIUM+ ANTIPSYCHOTIC	23	50
VALPROATE + ANTIPSYCHOTIC	18	39.1
CARBAMAZEPINE + ANTIPSYCHOTIC	3	6.5
LITHIUM+ VALPROATE + ANTIPSYCHOTIC	2	4.35

Figure10: TYPE OF COMBINATION



EVOLUTION OF THE TREATMENT

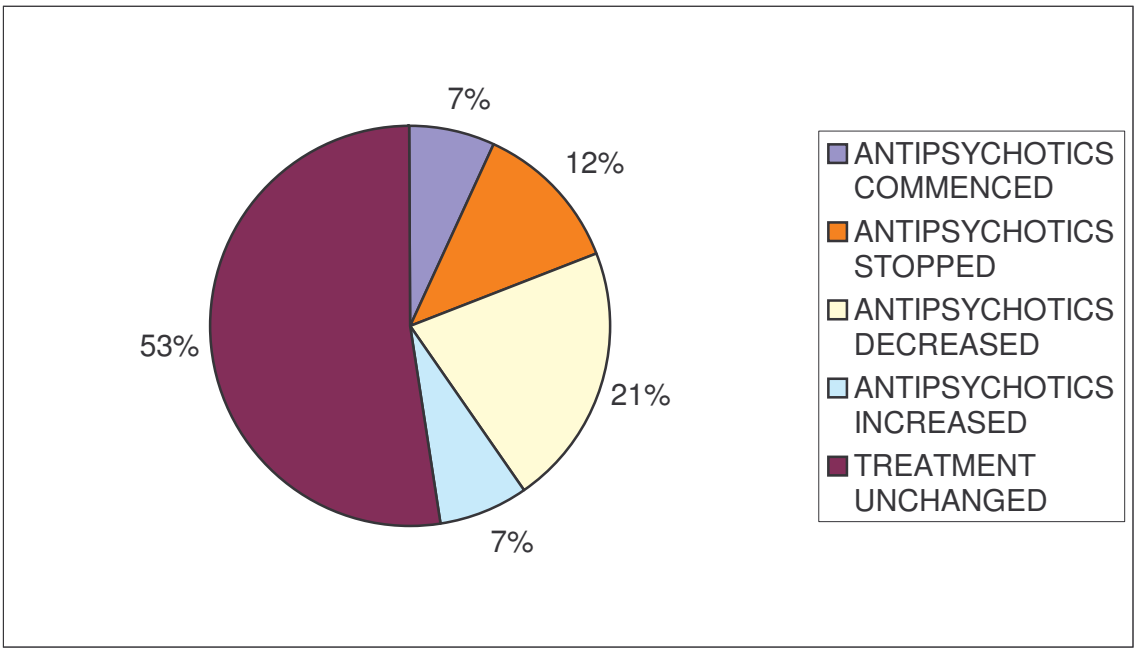
53 patients were referred to the clinic on treatment with antipsychotics. Since then 7 patients (13.2%) had antipsychotics stopped, 12 patients (22.6%) had their antipsychotics decreased. For 4 patients (7.5%) antipsychotics were increased, and in 30 patients (56.6%) the treatment was unchanged.

Of the 9 patients referred only on treatment with mood stabilizers, in 4 cases (7.5%) antipsychotics were added to the treatment. Table 10 and Figure 11 reflect these data.

Table 10: EVOLUTION OF THE TREATMENT

PARAMETER	FREQUENCY	PERCENT
ANTIPSYCHOTICS COMMENCED	4	7.5
ANTIPSYCHOTICS STOPPED	7	13.2
ANTIPSYCHOTICS DECREASED	12	22.6
ANTIPSYCHOTICS INCREASED	4	7.5
TREATMENT UNCHANGED	30	56.6

Figure 11: EVOLUTION OF THE TREATMENT



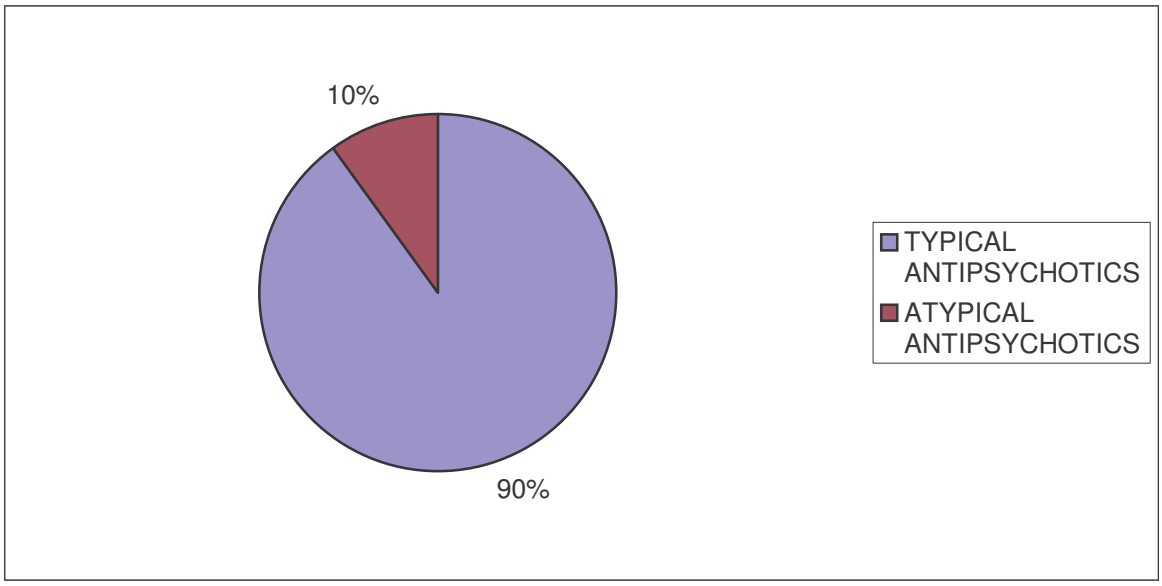
TYPE OF ANTYPSYCHOTIC

Of the 50 patients on maintenance treatment with antipsychotics, 5 (10%) received prescription for atypical antipsychotics.

Table 11: TYPE OF ANTYPSYCHOTIC

TYPE OF ANTIPSYCHOTIC	FREQUENCY	PERCENT
TYPICAL ANTIPSYCHOTICS	45	90
ATYPICAL ANTIPSYCHOTICS	5	10

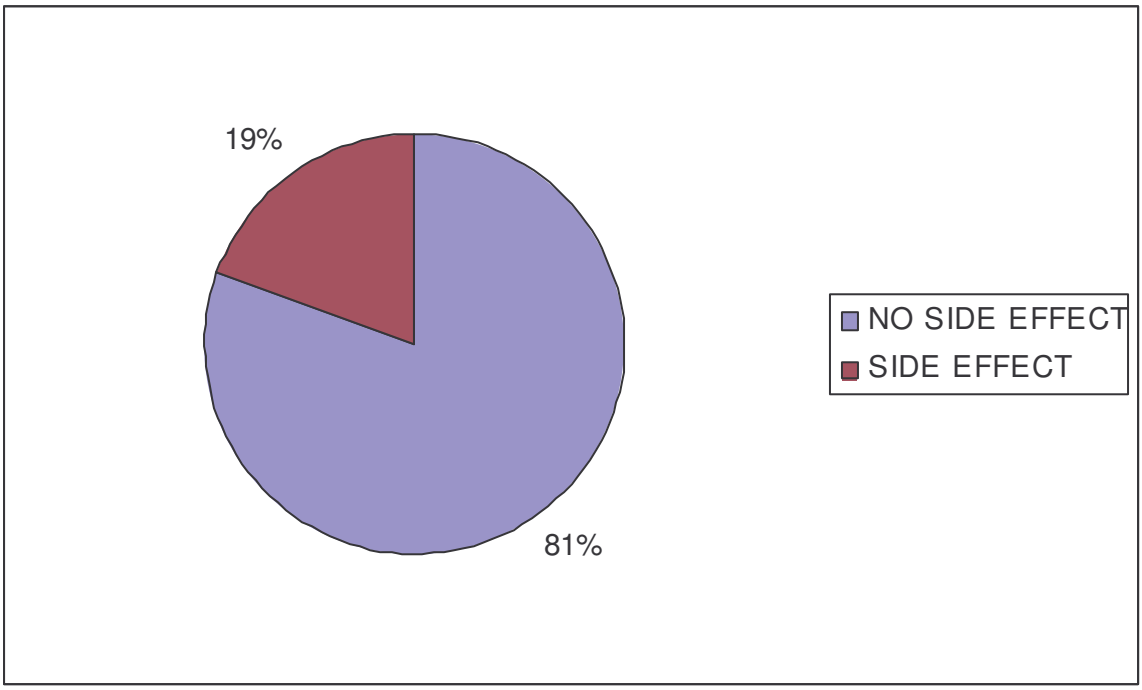
Figure 12: TYPE OF ANTYPSYCHOTIC



DOCUMENTED SIDE EFFECTS TO ANTIPSYCHOTICS

In 50 cases (80.6%) there were no records of the side effects, whereas in 12 patients (19.4%) the side effects of the medication were documented. (Figure 13).

Figure 13: DOCUMENTED SIDE EFFECTS TO ANTIPSYCHOTICS



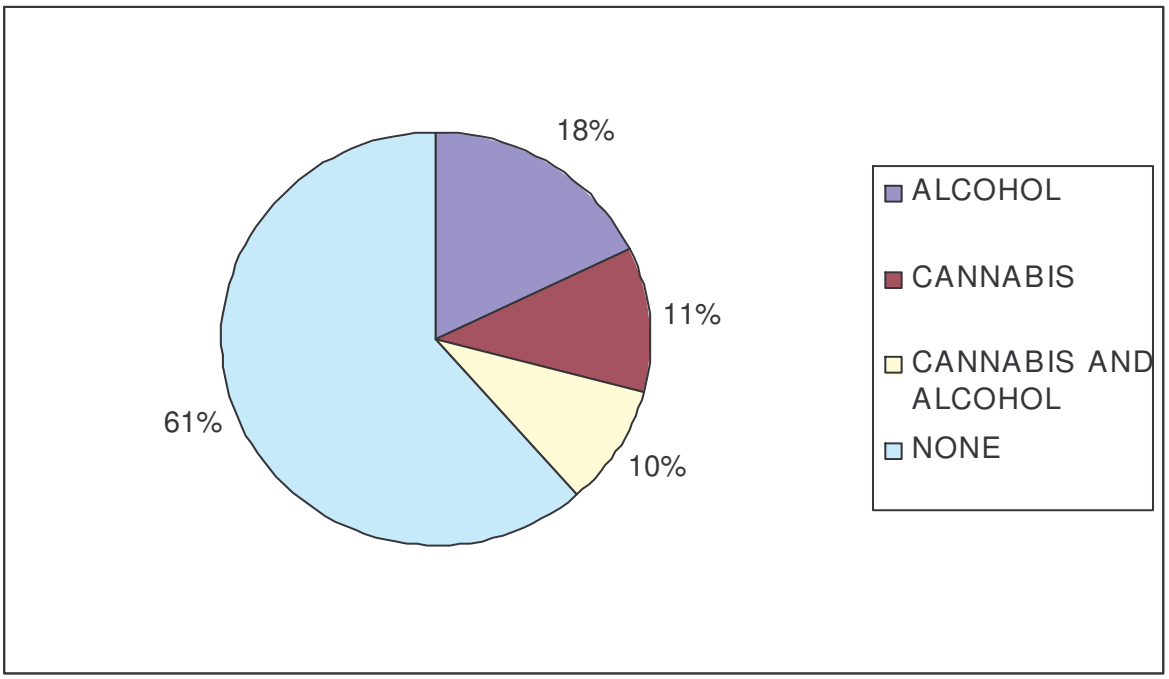
SUBSTANCE ABUSE

When the abuse of substances was analysed 11 patients (17.7%) abused alcohol, 7 patients (11.3%) abused cannabis and 6 patients (9.7%) used both cannabis and alcohol. (Table 12 and Figure 14).

Table 12: SUBSTANCE ABUSE

SUBSTANCE	FREQUENCY	PERCENT
ALCOHOL	11	17.7
CANNABIS	7	11.3
CANNABIS AND ALCOHOL	6	9.7
NONE	38	61.3

Figure 14: SUBSTANCE ABUSE



There was no significant statistical association ($p>0.05$) between alcohol abuse and the prescription of antipsychotics (confidence interval 0.236; 8.826).

The cannabis abuse did not seem to influence significantly the prescription of antipsychotics ($p>0.05$) (confidence interval 0.118; 12.968).

The odds ratio from logistic regression analysis reveals that relative to patients not abusing any substance the need for more medication is increased 6.6 fold when patients abuse polysubstances (simultaneous use of alcohol and cannabis).

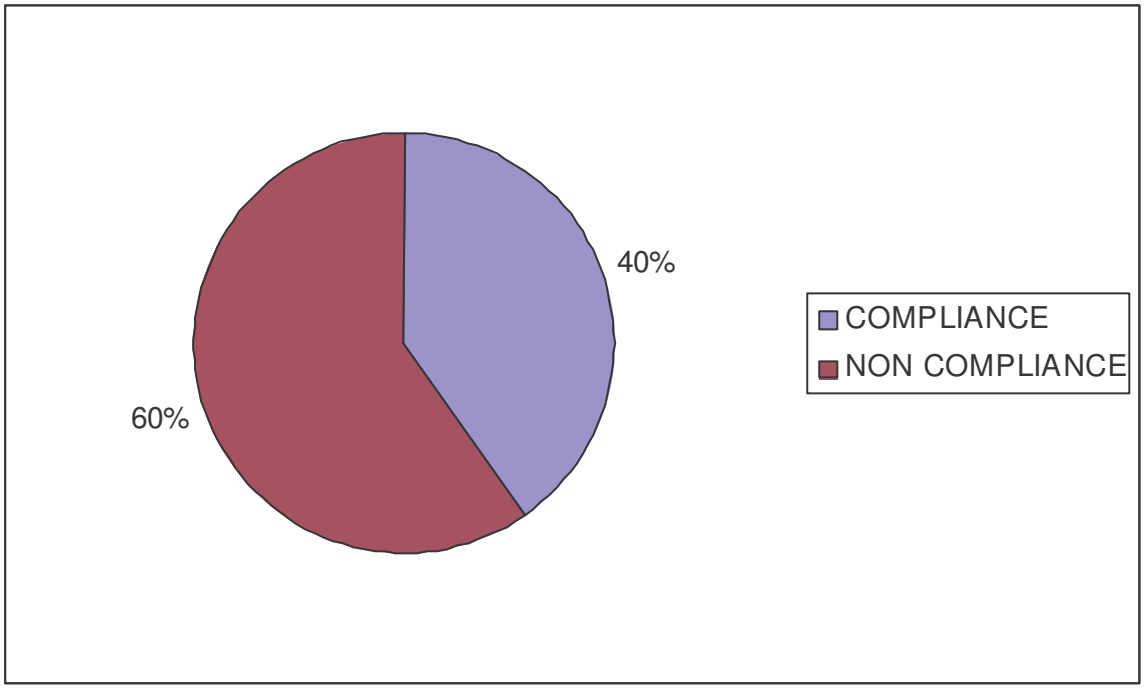
COMPLIANCE

25 patients (40.3%) were compliant with their treatment and 37 patients (59.7%) were noncompliant with their treatment. These data are reflected in Table 14 and Figure 15.

Table 14: COMPLIANCE

PARAMETER	FREQUENCY	PERCENT
COMPLIANCE	25	40.3
NONCOMPLIANCE	37	59.7

Figure 15: COMPLIANCE



There was no significant statistical association ($p>0.05$) between the compliance and the prescription of antipsychotics.

Chapter 4 Discussion

Bipolar disorder is a complex illness. It is a life long episodic disorder, and very disruptive for the patient and family. Repeated episodes lead to progressively deteriorating level of functioning and poor response to treatment.

The complexity and difficulties involved in treating this mental condition are well recognised. The pharmacological options include lithium, valproate, carbamazepine, lamotrigine, topiramate, benzodiazepines.

The use of neuroleptics in bipolar disorder remain controversial because of the increased susceptibility of this group of patients to side effects of neuroleptics.

In this study the demographic data regarding the age and sex of the patients were similar with those reported in the literature.

It was found that 62.9% of the patients were unemployed, these data reflecting the difficulties experienced by the patients to find and /or to maintain the job; similar findings were reported by Harrow in 1990.

85.5% of the examined files contained antipsychotic prescriptions. The majority of the patients referred from the hospitals were on the treatment with antipsychotics. This may reflect the fact that hospitals deal with difficult cases that need more treatment, and / or due to pressure for beds, patients are treated with more medication.

Our study found that 74.1% of the patients were maintained on a combination of mood stabilizer with antipsychotic; these figures were higher than the data reported in the literature. Bowden CL reported that 40% of the patients have poor response to monotherapy and

combination therapy is often necessary (Bowden CL 2004).

The results of this study are consistent with those of previous studies in showing that a high percentage (80.65%) of the patients were on treatment with antipsychotics for longer than 6 months.

The results of this study indicate that combination treatment was used in an attempt to improve the psychotic symptoms and dangerous behaviour in 48 % of the patients. Combination therapy was also used for non-compliance in 38% of the cases.

Studies done by Keck in 1996 and Sernyak in 1997 reported that 68% of the patients started on antipsychotic treatment in the acute phase, continue to receive antipsychotics for long time in the maintenance phase (6 months after the acute phase) (Sernyak MJ 1997, Keck PE 1996). At the time of the study in 35.8% of the patients symptoms improved and their antipsychotics were decreased or stopped.

However 15% of cases needed to restart or to increase the dose of antipsychotics because of a poor response to the treatment with monotherapy with mood stabilizers and /or inadequate dose of antipsychotics.

The 3 patients on combination of two antipsychotics and a mood stabilizer, were in a process of tapering off the oral antipsychotic and to continue with depot antipsychotic and a mood stabilizer (due to poor compliance). The guidelines for management of bipolar disorder suggest that combination of two antipsychotics increases the risk of extrapyramidal side effects and one antipsychotic should be stopped as soon as possible.

In our study lithium and sodium valproate are the mood stabilizers most frequently used in combination with antipsychotics. Lamotrigine is not available in the community and possibly due to drug interactions carbamazepine was used with caution, in 2 severely ill

patients, combination of two mood stabilizers and an antipsychotic was needed to achieve remission; suggesting that these patients have a more severe course of illness and are more treatment resistant.

38% of the patients were on depot antipsychotics due to noncompliance. 4% of patients had typical antipsychotics changed to atypical antipsychotics due to extrapyramidal side effects having developed on the typical antipsychotic.

The use of atypical antipsychotics is associated with a better outcome than the conventional agents. However their cost makes them almost unaffordable for the majority of patients in the 3rd world. In this study only a small percentage (10%) of patients received atypical antipsychotics.

Noncompliance in the maintenance phase of the treatment is a important issue in the management of the patients with bipolar disorder. This study found that the majority of the patients (59.7%) were noncompliant with their treatment.

Those findings were in line with studies done by Keck PE who reported rates of noncompliance from 51% to 64% (Keck PE 1996, 1998). Our study show that 63% of the patients had a level of education less than matric, and this may be a contributing factor to noncompliance.

Poor compliance creates more problems because it is difficult to know if treatment is effective, if doses are adequate and if co-prescription is necessary. Future research is necessary to develop effective strategies to improve the compliance.

Patients with affective disorders exposed to antipsychotics are at increased risk of developing extrapyramidal side effects. In this study 19.4% patients reported side effects of the medication, however in the literature side effects are reported in 79% of the patients using

oral typical antipsychotics and 83% for depot antipsychotics (Jablensky, 2000). The lower figures in our study can be due to underreporting and inadequate documentation (in 80.6% of cases there were no records of the side effects of the medication).

More studies are necessary to clarify this issue.

The substance abuse among bipolar patients is another important problem faced by the therapist. In this study the most commonly used drugs were alcohol and cannabis.

The use of substances among bipolar patients has a negative impact on the patient symptoms (mood lability, psychosis and behavioural problems).

Goldberg (1999) cited in Perlis RH (2005) reported substance misuse in 71% of the patients with bipolar disorder. Our findings were much lower (38.7%) compared with the literature, probably due to underreporting. Alcohol was the most common substance of abuse. No statistical significant correlation was established between individual substance abuse and use of antipsychotics. However this study showed that the need for more medication was increased 6.6 fold in patients with polysubstance abuse compared with the patients not abusing any substance. Future research studies are needed to explore the link between the individual substance and the use of antipsychotics.

The limitations of the study

Due to the nature of the clinic structure diagnosis is made by different doctors servicing the clinics, which means that information gathered was dependent on many doctors.

The group size was small. Of the 95 files with the initial diagnosis of bipolar disorder that were examined, 62 (65.3%) files met the inclusion criteria for this study.

33 files (34.7%) were not used in the study. In 18 files (18.9%) the data were incomplete and were not used in the analysis. In 15 files (15.8 %) initial diagnosis of bipolar disorder was changed and didn't meet inclusion criteria for this study.

Due to geographic differences in treatment patterns, the varying socio-economic status of patient population, caution should be exercised when generalizing our findings to other settings.

These results may not apply to all mood stabilizer and antipsychotic drugs. Due to financial considerations a limited list of mood stabilizer and antipsychotics were available in the community clinic.

Chapter 5 Conclusions

The results of the study suggest that a large number of bipolar patients are only partially responsive to mood stabilizers alone. The patients need maintenance treatment with antipsychotics for longer than 6 months because of persistence of the symptoms.

Adequate pharmacological control of the symptoms is an important component of treatment, but this intervention alone is not sufficient.

More efficient strategies are necessary to educate the people, to improve the compliance and to decrease the use of substances.

There are few national studies aimed at determining the use of combination of mood stabilizer and antipsychotics in maintenance treatment of bipolar disorder. Despite the limitations, this study added more information regarding the number of prescriptions of antipsychotics, in bipolar patients in a community clinic, the rationale of such combination and the correlation between substance abuse and noncompliance and the prescription of antipsychotics.

However these results need to be interpreted with caution.

Larger studies conducted at various settings are needed to investigate the use of combination of mood stabilizer and antipsychotics in the maintenance treatment of bipolar disorder.

Chapter 6 References

1. Academic Highlights (2004) International consensus group on bipolar I depression treatment guidelines Journal of Clinical Psychiatry 65

2. Altamura AC, Salvadori D, et al (2003) Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open label study Journal of Affective Disorders Volume 76, Issues 1-3: 267-271

3. Altshuler L, Suppes T et al (2003) Impact of antidepressants discontinuation after acute bipolar depression remission on rates of depressive relapse at 1 year follow- up American Journal of Psychiatry 160: 1252-1262

4. American Psychiatric Association (2002) Practice Guideline for the treatment of patients with bipolar disorder American Journal of Psychiatry 159 (Suppl 4): 1- 50

5. Angst F, Stassen H, Clayton PJ, Angst J (2002) Mortality of patients with mood disorder: follow –up over 34-38 years Journal of Affective Disorders 68, 2-3: 167-181

6. Aroone LJ, Segal KR (2003) Weight gain in the treatment of mood disorders Journal of Clinical Psychiatry 64 (Suppl 8): 22-29

7. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder (2004) Australian and New Zealand Journal of Psychiatry 38: 280-395

8. Baethge C, Baldessarini RJ, et al (2005) Substance Abuse in First-Episode Bipolar I Disorder: Indications for Early Intervention American Journal of Psychiatry 162: 1008-1010

9. Baldessarini RJ, Tondo L, Hennen J (2003) Lithium treatment and suicide risk in major affective disorders: update and new findings Journal of Clinical Psychiatry 64

(Suppl 5): 44-52

10. Barnes C, Mitchell P (2005) Considerations in the management of bipolar disorder in women Australian and New Zealand Journal of Psychiatry 39: 662-637

11. Berk M et all (2004) Scale matters: the need for a bipolar depression rating Scale Acta Psychiatrica Scandinavica 110 (Suppl 422): 39-45

12. Bouman WP and Pinner G (2002) Use of atypical antipsychotic drugs in old age psychiatry Advances in Psychiatric Treatment 8: 49-58

13. Bowden CL, Brugger AM, Swann AC et al (1994) Efficacy of divalproex, lithium and placebo in the treatment of mania JAMA 271: 918-924

14. Bowden CL (1996) Dosing strategies and time course of response to antimanic drugs Journal of Clinical Psychiatry 57 (Suppl 13): 4-9

15. Bowden CL (1998) Key treatment studies of lithium in manic depressive illness: efficacy and side effects Journal of Clinical Psychiatry 59 (Suppl 6): 13-19

16. Bowden CL, Calabrese JR, (2000) A randomised placebo controlled 12 month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder Archives of General Psychiatry 57: 481-489

17. Bowden CL (2001) Strategies to reduce misdiagnosis of bipolar depression Psychiatric Services 52: 51-55

18. Bowden CL (2004) The effectiveness of divalproate in all forms of mania and the broader bipolar spectrum: many question few answers Journal of Affective Disorder 79 (Suppl 1): 9-14

19. Bowden CL (2004) Making optimal use of combination pharmacotherapy in bipolar Disorder Journal of Clinical Psychiatry 65 (Suppl 15): 21-24

20. Bowden CL (2005) Treatment options for bipolar depression Journal of Clinical Psychiatry 66 (Suppl 1): 3-7

21. Bowden CL, Karren NU (2006) Anticonvulsants in bipolar disorder Australian and New Zealand Journal of Psychiatry 40: 386-393

22. Brunello N (2004) Mood stabilizers: protecting the mood…protecting the brain Journal of Affective Disorders 79, (Suppl1): 15-20

23. Burris KD, Molski TF et al (2002) Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors Journal of Pharmacology and Experimental Therapeutics Vol. 302, Issue 1: 381-389

24. Burt VK, Suri R, Altshuler L et al. (2001) The use of psychotropic medication during breast-feeding American Journal of Psychiatry 158: 1001-1009

25. Calabrese J.R., Bowden C.L, Sachs G.S, Ascher J.A (1999) A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Journal of Clinical Psychiatry 60**:** 79–88

26. Calabrese J, Rappaport DJ, Shelton MD, Kimmel SE (2001) Evolving methodologies in bipolar disorder maintenance research British Journal of Psychiatry 178: S157-S163

27. Calabrese JR et al (2002) Long – term treatment of bipolar disorder with lamotrigine Journal of Clinical Psychiatry 63 (Suppl 10): 18-22

28. Calabrese JR (2002) Bipolar disorders and the effectiveness of novel anticonvulsants Journal of Clinical Psychiatry 63 (Suppl 3): 5-9

29. Calabrese J R. (2003) Latest maintenance data on lamotrigine in bipolar disorder European Neuropsychopharmacology 13: (Suppl 2): 57-66

30. Calabrese JR (2004) Depression mood stabilisation: novel concepts and clinical management European Neuropsychopharmacology 14, (Suppl2): S100-S107

31. Calabrese JR, Elhaj O, Gajwani P, Gao K (2005) Clinical highlights in bipolar depression: focus on atypical antipsychotics Journal of Clinical Psychiatry 66 (Suppl 5): 26-33

32. Calabresi, P, Centonze, D.et al (1999) An in vitro electrophysiological study on the effects of phenytoin, lamotrigine and gabapentin on striatal neurons British Journal of Pharmacology 126**:** 689–696

33. Cipriani A, Pretty H, Hawton K, et al (2005) Lithium use in the prevention of suicidal behaviour and all-cause mortality in patients with mood disorders: a systematic review of randomized trial American Journal of Psychiatry 162: 1805-1819

34. Cookson J (2001) Use of antipsychotic drugs and lithium in mania British Journal of Psychiatry 178: s148-s156

35. Davis LL, Bartolucci A, PettyF (2005) Divalproex in the treatment of bipolar depression: a placebo-controlled study Journal of Affective Disorders Volume 85, Issue 3: 259-266

36. De Leon OA (2001) Antiepileptic drugs for the acute and maintenance treatment of bipolar disorder Harvard Rev Psychiatry 9: 209-222

37. Dharmendra M.S, Eagles J.M. (2003) Factors associated with patients' knowledge of and attitudes towards treatment with lithium Journal of Affective Disorders Volume 75, Issue 1: 29-33

38. Disalver SC, Chen YW, Swann AC et all (1997) Suicidality, panic disorder and psychosis in bipolar depression, depressive- mania and pure-mania Psychiatric Res.73: 47-56

39. Dolder CR, Lacro JP, Dunn LB, and Jeste DV (2002) Antipsychotic medication adherence: Is there a difference between typical and atypical agents? American Journal of Psychiatry 159: 103-108

40. Dunner DL (2003) Drug interactions of lithium and other antimanic/mood stabilizing medications Journal of Clinical Psychiatry; 64 (Suppl 5): 38-43

41. Evins AE (2003) Efficacy of newer anticonvulsants medications in bipolar spectrum mood disorders Journal of Clinical Psychiatry; 64 (Suppl 8): 9-14

42. El-Mallakh RS, Huff MO (2001) Mood stabilizers and ion regulation Harvard Rev Psychiatry 9: 23-32

43. El-Mallakh RS, Karippot A (2002) Use of Antidepressants to Treat Depression in Bipolar Disorder Psychiatry Services 53: 580-584

43. Fawcett JA (2003) Lithium combinations in acute and maintenance treatment of unipolar and bipolar depression Journal of Clinical Psychiatry; 64 (Suppl 5): 32-37

45. Frangou S (2005) Advancing the pharmacological treatment of bipolar depression Advances in Psychiatric Treatment 11: 28-37

46. Freeman TW, Clothier JL, Pazzaglia P et al (1992) A double blind comparison of valproate and lithium in the treatment of acute mania American Journal of Psychiatry 149: 108-111

47. Freeman TW, Stoll AL (1998) Mood stabilizer combinations: a review of safety and efficacy American Journal of Psychiatry 155: 12-21

48. Freeman MA, Freeman SA and McElroy SL. (2002) The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues Journal of Affective Didorders Volume 68, Issue 1: 1-23

49. Frye, M.A., Ketter, T.A (2000) A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. Journal of Clinical Psychopharmacology 20: 607–614.

50. Gadd C (2005) Could valproic acid eradicate HIV from the body? Aids map resources 2005

51. Gao K, Gajwani P, Elhaj O, Calabrese JR (2005) Typical and atypical antipsychotics in bipolar depression Journal of Clinical Psychiatry 66: 1376-1385

52. Gershen S, Soares JC (1997) Current therapeutic profile of Lithium Archive of General Psychiatry 54: 16-22

53. Ghaemi SN, Gaughan S (2000) Novel anticonvulsants: a new generation of mood stabilizers? Harvard Rev Psychiatry 8: 1-7

54. Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang R (2006) Treatment adherence among patients with bipolar or manic disorder taking atypical and typical antipsychotics Journal of Clinical Psychiatry 67: 222-232

55. Gitlin M (2006) Treatment-resistant bipolar disorder Molecular Psychiatry 11: 227–240

56. Goldberg FJ, Garno JL, Leon AC, et al (1999) A history of substances abuse complicates remission from acute mania in bipolar disorder Journal of Clinical Psychiatry 60: 733-740

57. Goldberg FJ (2005) Suicidal ideations and pharmacotherapy among STEP-BD

patients Psychiatry Services 56 (12): 1534-1540

58. Goodwin G.M (1999) Prophylaxis of bipolar disorder: how and who should we treat in the long term? European Neuropsychopharmacology Volume 9 (Suppl 4): S125-S129

59. Goodwin FK (2002) Rationale for long-term treatment of bipolar disorder and evidence for long-term lithium treatment Journal of Clinical Psychiatry 63 (Suppl 10): 5-12

60. Grunze H, Walden J (2002) Relevance of new and newly rediscovered anticonvulsants for atypical forms of bipolar disorder Journal of Affective Disorders 72 (Suppl 1): S15-S21

61. Grunze H, Kasper S, Goodwin G et al (2002) World Federation of Societies of Biological Psychiatry Guidelines for biological treatment of bipolar disorders, part 1: treatment of bipolar depression World Journal of Biological Psychiatry: 115-124

62. Grunze H, (2005) Revaluating therapies for Bipolar Depression Journal of Clinical Psychiatry 66 (Suppl 5): 17-24

63. Guo JJ, Keck PE, et al (2006) Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: a retrospective, population – based, case-control study Journal of Clinical Psychiatry 67: 1055-1061

64. Harrow M, Goldberg JF, Grossman LS, (1990) et al: Outcome in manic disorders: a naturalistic follow-up study Archives of General Psychiatry 47: 665–671

65. Hebert AA (2001) Cutaneous reactions to anticonvulsant medications Journal of Clinical Psychiatry 62 (Suppl 14): 22-26

66. Herman E (2004) Lamotrigine: a depression mood stabilizer European Neuropsychopharmacology Volume 14, (Suppl 2): S89-S93

67. Hilty MD, Brady KT, Hales RE (1999) A Review of Bipolar Disorder Among Adults Psychiatric Services 50: 201-213

68. Hirschfeld RMA, Keck PE, Jr. Kramer M, Karcher K, et al (2004) Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial American Journal of Psychiatry 161: 1057-1065

69. Hoier EH, Preben BO Mortensen, Olensen AV (2000) Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973-1993 The British Journal of Psychiatry 176: 76-82

70. Hyman SE, Arana GW, Rosenbaum JF (1995) Handbook of psychiatric drug therapy 3 rd edition: 93-123

71. Ikonomov OC, Manji HK (1999) Molecular Mechanisms Underlying Mood Stabilization in Manic-Depressive Illness: The Phenotype Challenge American Journal of Psychiatry 156: 1506-1514

72. International consensus group on bipolar depression treatment guidelines (2004) Journal of Clinical Psychiatry 65

73. Isojarvi JI, Laatikainen TJ, Pakarinen AJ et al. (1993) Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy New England Journal of Medicine 329: 1383-1388

74. Jablensky A, McGrath JJ, Herrman H, et al (2000) Psychotic disorders in urban areas: an overview of the Study on Low Prevalence Disorders. Australian and New Zealand Journal of Psychiatry, 34: 221-236

75. Jefferson J, W (1990) Lithium present and future Journal of Clinical Psychiatry 51 (Suppl 8): 4-8

76. Judd LL, Akiskal HS (2003) The prevalence and disability of bipolar spectrum disorder in US population: re-analysis of the ECA database taking into account sub-threshold cases Journal of Affective Disorder 73: 123-131

77. Kane JM (1998) Role of neuroleptics in manic depressive illness The Journal of Clinical Psychiatry 49(Suppl 11): 12-13

78. Kaplan and Sadock's Comprehensive textbook of psychiatry 7 th edition (2004)

79. Kapur S, Remington G (2001) Atypical antipsychotics: New directions and new challenges in the treatment of schizophrenia Annual Review of Medicine

80. Kapur S, Remington G (2001) Dopamine D_2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient Biological Psychiatry 50, Issue 11: 873-883

81. Keck PE, McElroy SL, Tugrul KC et al (1993) Valproate oral loading in the treatment of acute mania Journal of Clinical Psychiatry 54: 305-308

82. Keck PE, McElroy SL 1996 Outcome in the pharmacological treatment of bipolar disorder Journal of Clinical Psychopharmacology 16/ No 2 (Suppl 1): S 15 –S 22

83. Keck PE, Jr, McElroy SD (2002) Carbamazepine and valproate in the maintenance treatment of bipolar disorder Journal of Clinical Psychiatry 63 (Suppl 10): 13-18

84. Keck PE, Jr., Marcus R, et al (2003) A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania American Journal of Psychiatry 160: 1651-1658

85. Keck PE, Jr (2005) The role of second-generation antipsychotic monotherapy in the rapid control of acute bipolar mania Journal of Clinical Psychiatry 66 (Suppl 3): 5-11

86. Keck PE (2005) Bipolar depression: a new role for atypical antipsychotics? Bipolar Disorders 7 (Suppl 4): 34-40

87. Ketter TA (2002) Predictors of treatment response in bipolar disorders: evidence from clinical and brain imaging studies Journal of Clinical Psychiatry 63 (Suppl 3): 21-25

88. Ketter T. A, Manji H. K, Post R. M. 2003. Potential Mechanisms of Action of Lamotrigine in the Treatment of Bipolar Disorders Journal of Clinical Psychopharmacology 23(5): 484-495

89. Ketter TA (2004) New medication treatment options for bipolar disorders Acta Psychiatrica Scandinavica 110 (Suppl 422): 18-33

90. Jones HM and Pilowsky LS, (2002) Dopamine and antipsychotic drug action revisited The British Journal of Psychiatry (2002) 181: 271-275

91. Kupfer DJ (2006) Course of illness and illness outcome in bipolar depression Journal of Clinical Psychiatry 67: 1140-1151

92. Lehrman G et al (2005) Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. Lancet 366: 549-555

93. Leverich GS, Altshuler LL, Frye MA et al (2006) Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline and bupropion as adjuncts to mood stabilizers American Journal of Psychiatry 163: 232- 239

94. Leysen JE, Janssen PMS et al (1994) Risperidone: a novel antipsychotic with

balanced serotonin- dopamine antagonism, receptor occupancy profile and pharmacological activity Journal of Clinical Psychiatry 55 (Suppl 2): 5-12

95. Licht RW (1998) Drug treatment of mania: A critical review Acta Psychiatrica Scandinavica 97: 387-397

96. Maj M, et all (1998) Long -term outcome of lithium prophilaxy in bipolar disorder American Journal of Psychiatry 155: 30-35

97. Manji, H.2001 K., Moore, G. J. & Chen, G. (2001) Bipolar disorder: leads from the molecular and cellular mechanisms of action of mood stabilisers British Journal of Psychiatry, 178 (Suppl. 41): S107 -S119

98. Marangell LB (2006) Treatment resistant bipolar depression and emerging therapies Journal of Clinical Psychiatry 67: 1140-1151

99. McElroy SL, Keck PE, Stanton SP et al (1996) A randomised comparison of Divalproex oral loading versus Haloperidol in the initial treatment of acute psychotic mania Journal of Clinical Psychiatry 57: 142-146

100. McElroy SL, Altshuler LL, Suppes T, et all (2001) Axis I psychiatric comorbidity and its relationship to historical illness variables in 228 patients with bipolar disorder American Journal of Psychiatry 158: 420-426

101. McIntyre RS (2002) Psychotropic drugs and adverse events in the treatment of bipolar disorders revised Journal of Clinical Psychiatry 63 (Suppl 3): 15-20

102. McIntyre RS, Konarski JZ (2005) Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder Journal of Clinical Psychiatry 66 (Suppl 3): 28-36

103. Moller HJ, Nasrallah HA (2003) Treatment of bipolar disorder Journal of Clinical Psychiatry; 64 (Suppl 6): 9-17

104. Montgomery SA, Schatzberg AF (2000) Pharmacotherapy of depression and mixed states in bipolar disorder Journal of Affective Disorders Volume 59, (Suppl 1): S39-S56

105. Montes J M, Saiz-Ruiz J et al (2005) Lamotrigine for the treatment of bipolar spectrum disorder: a chart review Journal of Affective Disorders Volume 86, Issue 1: 69-73

106. Mula M, Trimble MR, et al (2003) Topiramate and Psychiatric Adverse Events in Patients with Epilepsy Epilepsia Volume 44 Page 659

107. Muzina DJ, Calabrese JR (2005) Maintenance therapies in bipolar disorder: focus on randomised controlled trials Australian and New Zealand Journal of Psychiatry 39: 652-661

108. Nemeroff CB (2000) Fifty years of lithium use in treatment of bipolar disorder Journal of Clinical Psychiatry 61(Suppl 9): 3-7

109. Nemeroff CB (2003) Safety of available agents used to treat bipolar disorder: focus on weight gain Journal of Clinical Psychiatry 64: 532-539

110. Nilsson A (1999) Lithium therapy and suicide risk Journal of Clinical Psychiatry 60; (Suppl 2): 85-88

111. O'Donovan C, Kusumakar V, Graves GR, Bird DC (2002) Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder J Journal of Clinical Psychiatry 63: 322-330

112. Patel MX, David AS (2005) Why aren't depot antipsychotics prescribed more often and what can be done about it? Psychiatric Treatment 11: 203-211

113. Perlis RH (2005) The role of pharmacologic treatment guidelines for bipolar

disorder Journal of Clinical Psychiatry 66(Suppl 3): 37-47

114. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L (2000) Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 41:13–18

115. Pope M, Scott J (2003) Do clinicians understand why individuals stop taking lithium? Journal of Affective Disorders Volume 74, Issue 3: 287-291

116. Post RM (2005) The impact of bipolar depression. Journal of Clinical Psychiatry 66 (Suppl 5): 5-9

117. Post RM, Leverich GS, Altshuler LL, et al. (2003) An overview of recent findings Of the Stanley Foundation Bipolar Network, pt 1. Bipolar Disorder 5; 310-319

118. Post RM, Frye MA, (1998) Beyond lithium in the treatment of bipolar illness. Neuropsychopharmacology 19: 206–219

119. Post RM, Leverich GS (1992) Lithium discontinuation-induced refractoriness: preliminary observations American Journal of Psychiatry 149: 1727-1729

120. Post RM, Leverich GS, Rosoff AS, Altshuler LL (1990) Carbamazepine prophylaxis in refractory affective disorders: a focus in long- term follow- up Journal of Clinical Psychopharmacology 10: 318-327

121. Ragson NL, Altshuler LL, Gudeman D et al. (2000) Medication status and polycystic ovary syndrome in women with bipolar disorder: Journal of Clinical Psychiatry 61: 173-178

122. Routy JP (2005) Valproic acid: a potential role in treating latent HIV infection. Lancet 366: 523-524.

123. Sachs GS, Grossman F, Ghaemi SN, et al (2002) Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double- blind, placebo controlled comparison of efficacy and safety American Journal of Psychiatry 159: 1146-1154

124. Sachs GS and Rush AJ (2003) Response, Remission, and Recovery in Bipolar Disorders: What are the realistic treatment goals? Journal of Clinical Psychiatry 64 (Suppl 6): 18-22

125. Sackeim HA, Prudic J, et al (2000) A prospective, randomised, double- blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities Archive of General Psychiatry 57: 425-434

126. Salloum IM, Cornelius JR, Daley DC, et al. (2005) Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism Archive of General Psychiatry 62: 37-45

127. Saksa JR, Baker CB, Woods SW (2004) Mood-stabilizer-maintained, remitted bipolar patients: taper and discontinuation of adjunctive antipsychotic medication General Hospital Psychiatry 3: 233-236

128. Sernyak MJ, Godleski LS, Griffin RA, et al (1997) Chronic neuroleptic exposure in bipolar outpatients Journal of Clinical Psychiatry 58: 193-195

129. Schaffer A, Cairney J et al (2006) Use of treatment services and pharmacotherapy for bipolar disorder in a general population-based mental health survey Journal of Clinical Psychiatry 67: 386-393

130. Schatzberg AF (2004) Employing pharmacologic treatment of bipolar disorder

to greatest effect Journal of Clinical Psychiatry 65(Suppl 15): 15-20

131. Sajatovic M, Brescan DW, Perez DE et al (2001) Quetiapine alone and added to a mood stabilizer for serious mood disorders Journal of Clinical Psychiatry 62: 728-732

132. Schou Mogens (2001) Lithium treatment at 52 Journal of Affective Disorders Volume 67, Issues 1-3: 21-32

133. Shastry BS (2005) Bipolar disorder: an update Neurochemistry International Volume 46, Issue 4: 273-279

134. Small JG, Klopper MH, Milstein V Carbamazepine compared with lithium in the treatment of mania Archive of General Psychiatry 48: 89-93

135. Stefan H. Feuerstein T.J. (2006) Novel anticonvulsant drugs Pharmacology & Therapeutics Article in Press

136. Strakowsky SM, et all (1996) Suicidality among patients with mixed and manic bipolar disorder American Journal of Psychiatry 153: 674-676

137. Suppes T (2002) review of the use of topiramate for treatment of bipolar disorders Journal of Psychopharmacology 22: 599-609

138. Suppes T, Kelly DI, Perla JM, (2005) Challenges in the management of bipolar depression Journal of Clinical Psychiatry 66 (Suppl 5): 11-16

139. Suppes T et al. (2005) Texas implementation of medication algorithms Journal of Clinical Psychiatry 66 (Suppl 7): 870- 886

140. Swann AC, Bowden CL, Morris D, et al. (1997) Depression during mania: treatment response to lithium or divalproex. Archives of General Psychiatry; 54: 37-42

141. Swann AC (2001) Major system toxicities and side effects of anticonvulsants Journal of Clinical Psychiatry 62(Suppl 14): 16-21

142. Swann AC (2005) Long term treatment in bipolar disorder Journal of Clinical Psychiatry 66 (Suppl 1): 7-12

143. Swann AC (2006) What is Bipolar disorder? American Journal of Psychiatry 163: 177-179

144. Texas implementation of medication algorithms (2005) Journal of Clinical Psychiatry 66: 875-886

145. Tohen M, Waternaux CM, Tsuang MT (1990) Outcome in mania: a 4 year prospective follow up of 75 patients utilizing survival analysis Archives of General Psychiatry 47: 1106 –1111

146. Tohen M, Zarate CA Jr (1998) Antipsychotic agents and bipolar disorder Journal of Clinical Psychiatry 59 (Suppl 1): 38-48

147. Tohen M, Zhang F, Taylor CC et al (2001) A meta-analysis of the use of typical antipsychotic agents in bipolar disorder Journal of Affective Disorders Volume 65, Issue: 85-93

148. Tohen M, Chengappa KNR, Suppes T, et al (2002) Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy Archives of General Psychiatry 59: 62-69

149. Tohen M., E. Vieta, J. Calabrese, T.A. Ketter, G. Sachs, C. Bowden, P.B. et al. (2003) Efficacy of olanzapine and olanzapine–fluoxetine combination in the treatment of bipolar I depression, Archives of General Psychiatry 60: 1079–1088

150. Tohen M, Calabrese J, Bowden C., et al (2003) Olanzapine ‘s efficacy for relapse prevention in bipolar disorder: a randomised double – blind placebo- controlled 12 month clinical trial European Neuropsychopharmacology 13 (Suppl 4): S212- 213

151. Tohen M, Chengappa KNR, Suppes T, et al (2004) Relapse prevention in bipolar I disorder: 18 month comparison of olanzapine plus mood stabilizer versus mood stabilizer alone British Journal of Psychiatry 184: 337-345

152. Tohen M, Waldemar Greil P.H, Calabrese JR et al (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: A 12-month, randomized, double-blind, controlled clinical trial American Journal of Psychiatry 162: 1281 - 1290

153. Vasudev K, Goswami U, Kohli K, (2000) Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder Psychopharmacology 150: 15-23

154. Vieta E, Goikolea JM, Corbella B et al (2001) Risperidone safety and efficacy in the treatment of bipolar and schizoaffective disorders: results from a 6 month, multicenter, open study Journal of Clinical Psychiatry 62: 818-825

155. Vieta E, Goikolea JM (2005) Atypical antipsychotics: newer options for mania and maintenance therapy Bipolar Disorders 7 (Suppl 4): 21-33

156. Zarate C, Tohen M (2004) Double blind comparison of the continued use of antipsychotics treatment versus its discontinuation in remitted manic patients American Psychiatric Association 161: 169-171

157. Walburn J, Gray R et al (2001) Systematic review of patient and nurse attitudes to depot antipsychotic medication British Journal of Psychiatry 179: 300-307

158. White HS (2003) Mechanism of action of newer anticonvulsants Journal of Clinical Psychiatry 64 (Suppl 8): 5-8

159. Wirshing DA, Boyd JA, Meng LR (2002) The effects of novel antipsychotics

on glucose and lipid levels Journal of Clinical Psychiatry 63: 856-865

160. Xiaohua Li, Ketter TA, and Frye MA. (2002) Synaptic, intracellular, and neuroprotective mechanisms of anticonvulsants: are they relevant for the treatment and course of bipolar disorders? Journal of Affective Disorders Volume 69, Issues 1-3: 1-14

161. Yatham LN (2005) Atypical antipsychotics in bipolar depression: potential mechanisms of action Journal of Clinical Psychiatry 66 (Suppl 5): 40-48

162. Yatham LN (2004) Newer anticonvulsants in the treatment of bipolar disorder Journal of Clinical Psychiatry 65 (Suppl 10): 28-35

163. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A (2003) Mood stabilisers plus risperidone or placebo in the treatment of acute mania. British Journal of Psychiatry 182: 141-147

164. Yatham LN (2002) The role of novel antipsychotics in bipolar disorders Journal of Clinical Psychiatry 63 (Suppl 3): 10-14

165. Yerevanian BI, Koek RJ, Mintz J (2002) Lithium, anticonvulsants and suicidal behaviour in bipolar patients Journal of Affective Disorders 73: 223- 228

166. Yonkers KA, Wisner KL, Stowe Z et all (2004) Management of bipolar disorder during pregnancy and postpartum period American Journal of Psychiatry 161: 608-620

Appendix I

DSM-IV Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1 inflated self-esteem or grandiosity

2 decreased need for sleep (e.g. feels rested after only 3 hours of sleep)

3 more talkative than usual or pressure to keep talking

4 flight of ideas or subjective experience that thoughts are racing

5 distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)

6 increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

7 excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a mixed episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g. medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.

Appendix II

DSM-IV Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1 depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).

Note: in children and adolescents, can be irritable mood.

2 markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)

3 significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: in children, consider failure to make expected weight gains.

4 insomnia or hypersomnia nearly every day

5 psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6 fatigue or loss of energy nearly every day

7 feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8 diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9 recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.